Dissertation

Molecular design and engineering for affinity separations
of polar systems using isothermal titration calorimetry and
molecular modeling.

by Lisette M. J. Sprakel

MOLECULAR DESIGN AND ENGINEERING
FOR AFFINITY SEPARATIONS OF POLAR
SYSTEMS USING ISOTHERMAL TITRATION
CALORIMETRY AND MOLECULAR MODELING

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Lisette Maria Johanna Sprakel
born on the 12th of March 1990
in Apeldoorn, the Netherlands

This Dissertation has been approved by:
Prof. dr. ir. B Schuur (Supervisor)
Prof. dr. S.R.A. Kersten (Co-Supervisor)

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7500 AE Enschede
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Chairman	Prof. dr. J.L. Herek	University of Twente
Supervisor	Prof. dr. ir. B Schuur	University of Twente
Co-Supervisor	Prof. dr. S.R.A. Kersten	University of Twente
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You can design and create, and build the most wonderful place in the world. But it takes people to make the dream a reality.

Walt Disney

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To all my friends, family and loved ones.

Fortunately, *they* create all the beautiful, exciting and meaningful moments in my life, without which this book would have been completed two years earlier.

The background is a complex, low-poly geometric pattern composed of numerous triangles in various shades of orange, yellow, and red. The triangles vary in size and orientation, creating a textured, crystalline effect. The overall color palette is warm and vibrant, ranging from deep orange to bright yellow.

Il

Introduction

1. General introduction

The climate targets of the European Union (EU) for the year 2030 include, amongst other targets, a decrease of greenhouse gas emissions of 40 % and an improvement in energy efficiency of 27 %.¹ Since in 2016 roughly 25 % of the total energy used in the EU was used for industrial purposes,² reducing the industrial energy demand is necessary to reach the goals for 2030. Industrial separation processes account for 50 % of the total energy consumed in industry and globally, their share of the energy consumption is up to 15 %.³ In bio refineries separation processes even account for up to 80 % of the energy consumption and the processes contain various mixtures that are to be separated. These mixtures may either be dilute aqueous streams or complex multi-component mixtures with valuable components that are difficult to separate.⁴ Thus, for significant reductions in energy consumptions alternatives to the energy intensive distillation process should be further developed, for example for the separation of trace contaminants from water, as suggested by Sholl and Lively.³ Not only from an energy point of view there is an incentive to improve industrial processes, also the demand for green chemistry is increasing. For the implementation of green chemistry in the sector of chemical manufacturing industrial wide collaboration is required to be successful. Moreover, several challenges need to be faced regarding implementation in cost-effective and safe technologies.⁵

The use of renewable feedstock and the design for energy efficiency are two of the 12 principles of green chemistry that were already published in 1998.⁶ For many bio-based plastics and other chemicals in the pharmaceutical, food and chemical industry,⁷⁻¹⁰ carboxylic acids are raw materials and building blocks in the production and as a consequence there is a growing desire to produce these acids through fermentation. The incentive to produce carboxylic acids via green routes and fermentation is also growing as greenhouse gas emissions are a strongly negative side-effect of the petrochemical based process and currently most volatile (C_2 - C_4) carboxylic acids are produced based on these non-renewable petrochemical sources.¹¹ Acids such as lactic acid and succinic acid are already mainly produced through fermentation processes.⁸⁻¹⁰ Other acids can also be obtained from biomass hydrolysates, and are typically present in dilute aqueous streams, e.g. levulinic acid,¹² 2,5-furandicarboxylic acid (FDCA) that can be used for production of polyethylene furanoate (PEF) as an alternative to polyethylene terephthalate (PET)¹³ and biobased adipic acid for production of nylon.¹⁴

Acids produced by fermentation are present in aqueous streams. Also in other industrial (waste) streams either valuable polar components or contaminants are present in diluted aqueous streams that need to be removed or recycled. For example, volatile fatty acids can be obtained from fermented wastewater.^{15,16} It is estimated that 9 Mton acetate, 5 Mton butyrate and 6 Mton propionate could be recovered annually from wastewater of the dairy industry.⁷ As the total global market demand for the C₂-C₄ acids is predicted to be 18 Mton in 2020 (97 % of acetic acid, 0.5 % butyric acid and 2.5 % propionic acid),⁷ this is a strong opportunity. An example of separation of contaminants is that low concentrations of pyridines are to be removed from industrial streams because of their toxicity.^{17,18}

Thus, separation techniques are required to separate these components that have in common that they are all polar and are all present in low concentrations in aqueous streams. Distillation of streams containing large water fractions is inefficient as it would require evaporation of large amounts of water. Furthermore, some acids may even decompose at elevated temperatures. Separation of polar components by affinity separations can also be of interest in non-aqueous streams in industry, e.g. for mixtures with very low relative volatility or thermal instability, as in those cases distillation is intrinsically not feasible.^{19,20}

Affinity separations are promising alternatives to ordinary distillation in these cases, as they improve or enable the separation by adding an affinity agent. The general scheme for affinity agent based separation processes is shown in Figure 1, where it can be seen that next to the initial separation column there is a second column in which the regeneration of the affinity agent takes place. Because this regeneration is an important step for the feasibility of the process, it should always be taken into account in the design of affinity separation processes. An optimal affinity agent induces a large distribution of solutes (K_D) in the first step and a low K_D in the regeneration step.

Figure 1 Affinity separation process where the solvent S is added in the first process step to improve the separation of A and C . In a second regeneration step the solvent S is separated from component A in order to recycle the solvent.

To evaluate and compare separation processes, the ratio of the concentrations of A in the product stream of the overall process, including the separation step and the regeneration of the affinity agent, and the feed stream is defined as the concentration factor CF in eq (1).

$$CF = \frac{[A]_{\text{product}}}{[A]_{\text{feed}}} \quad (1)$$

Examples of affinity separation processes are adsorption, where target molecules are adsorbed from a feed stream onto a (solid) surface, and extraction, where solutes are transferred between two immiscible liquid phases. Next to implementing extraction based on two liquid phases as liquid-liquid extraction (LLX), it can be implemented in a vapor-liquid distillation process as extractive distillation (XD), depending on the specific separation that is required. Both LLX and adsorption are industrially applied for acid recovery from diluted fermentation broths and waste streams.²¹⁻²³

1.1 Liquid-liquid extraction (LLX)

LLX can be an efficient, economical and environmentally friendly method for separating acids.²³⁻²⁵ The process can also be schematically described by Figure 1 and consists of a forward extraction column and a regeneration column, which can be either a distillation column in the case of volatile acids that do not decompose²⁶⁻²⁹ or a back-extraction column in which for

example a swing in temperature is applied to regenerate the solvent.³⁰ The distribution ratio K_D of an acid HA is defined as the ratio of concentration of acid in the organic solvent phase $[\overline{\text{HA}}]$ and aqueous phase $[\text{HA}]$, see eq (2). The selectivity of a solvent S_a towards component a relative to b is then defined as the ratio of their distribution coefficients, see eq (3).

$$K_D = \frac{[\overline{\text{HA}}]}{[\text{HA}]} \quad (2)$$

$$S_a = \frac{K_{D,a}}{K_{D,b}} \quad (3)$$

Instead of applying physical solvents such as ethers, esters, aliphatic or aromatic hydrocarbons, alcohols, and ketones,^{31,32} LLX can be performed with composite solvents that generally show higher distribution ratios of the acids. These binary solvents are composed of an extractant that interacts directly with the acid, and a diluent providing the solvation of the complexes.^{28,33,34} The state-of-the-art technology is a binary solvent of trioctylamine and a diluent,³⁴⁻³⁶ showing a high efficiency.³⁷ The diluent in these binary solvents plays an important role, not only by adjusting the physical properties of the solvent, but also by improving the solvation of the extractant-acid complexes.^{38,39}

1.2 Extractive distillation (XD)

Extractive distillation processes are promising when application of conventional distillation is limited as a result of non-ideal behavior of the mixture components, in the case of an azeotrope or when they are close-boiling.²⁰ In these cases XD can be performed by adding a solvent, in most cases high-boiling, to the distillation column in order to increase the relative volatility of the mixture components, see the schematic overview in Figure 2. Consequently, the energy usage of the process is decreased. Figure 2 also shows the solvent recovery column in which product A is obtained and solvent S is recovered and recycled to the XD column.

Figure 2 Extractive distillation of feed composed of A and B with solvent S.

In an XD column vapor and liquid flows are contacted with each other and with the aid of a solvent the mixture is separated. The effectiveness of the process and choice of solvent is determined by the vapor-liquid-equilibrium (VLE) behavior and the composition of the liquids and vapors at the temperatures and pressures of the process. From the composition of the phases the relative volatility α can be calculated using eq (4) (P_i^{sat} is the saturated vapor pressure of a component at a given temperature, y_i is the vapor mole fraction and x_i is the liquid mole fraction) and the existence of an azeotrope can be determined. The value of α that is still sufficient for a conventional distillation process is considered to be $\alpha > 1.1 - 1.4$, depending on the specific case.^{20,40} Even for a larger relative volatility ($1.3 < \alpha < 3$) of the binary mixture a reduction in energy consumption may be induced by applying XD instead of conventional distillation.⁴¹

$$\alpha = \frac{\frac{y_i}{x_i}}{\frac{y_j}{x_j}} = \frac{\gamma_i P_i^{\text{sat}}}{\gamma_j P_j^{\text{sat}}} = \frac{y_i(1 - x_i)}{x_i(1 - y_i)} \quad (4)$$

For systems where $\alpha < 1.1$ and not sufficient for ordinary distillation or in case an azeotrope is present, an appropriate solvent in an extractive distillation process has a higher affinity for the least volatile mixture component. Through interaction with the mixture the appropriate solvent increases the relative volatility and, if applicable, possibly also ‘break’ the azeotrope, see Figure 3.

Figure 3 Theoretical solvent effect on vapor-liquid equilibrium of system with minimum-boiling azeotrope (dashed line that crosses line $y = x$) or low relative volatility (dash dot line). The arrow indicates the solvent effect.

The solvent selectivity, see eq (5),²⁰ can be written as the ratios of the activity coefficients of both components with and without the presence of the solvent, assuming that the presence of the solvent in the liquid phase does change the boiling point of this phase, but has no (significant) influence on the saturated vapor pressures of the components. Because in most cases high-boiling solvents are applied, the liquid phase is where the interactions between the solvent and mixture components occur.

$$S_{ij} = \frac{(\alpha_{ij})_S}{\alpha_{ij}} = \frac{\left(\frac{\gamma_i P_i^{\text{sat}}}{\gamma_j P_j^{\text{sat}}} \right)_S}{\frac{\gamma_i P_i^{\text{sat}}}{\gamma_j P_j^{\text{sat}}}} \cong \frac{\left(\frac{\gamma_i}{\gamma_j} \right)_S}{\frac{\gamma_i}{\gamma_j}} \quad (5)$$

1.2.1 Application of extractive distillation

In the case of an azeotrope, α equals 1, which means that the ratio of activity coefficients is inversely proportional to the ratio of the saturated vapor pressures (eq (4)). Since the close-boiling mixtures applied in this research will have a similar vapor pressure, azeotropes can already form at small deviations from ideality.²⁰

There are two major types of azeotropes, i.e. heterogeneous azeotropes in which two distinct liquid phases are formed (as a result of both activity coefficients being significantly larger than 1) for which additional process

equipment is required and homogeneous azeotropes consisting of one liquid phase. Homogeneous azeotropes can be subdivided into minimum boiling azeotropes and maximum boiling azeotropes, that each require a specific type of interaction with the solvent that is applied in XD. Minimum boiling azeotropes are formed in mixtures with positive deviations from Raoult's law (i.e. both activity coefficients greater than or equal to 1) and the ratio of activity coefficients is larger than the ratio of saturated vapor pressures. These azeotropes require a solvent that interacts less non-ideal with the high-boiling component than it repels the low-boiling component (or interacts less strong with the low-boiling component than it attracts the high-boiling component).²⁰

When there is no azeotrope in the case of a close-boiling mixture, the separation may still be complicated due to α being close to unity. In those cases, XD with a solvent that has a higher affinity for one of the mixture components can improve the separation process. Pseudo-binary VLE data show the compositions of the liquid and vapor phases in the system based on only the fractions of the mixture components, not the solvent, and can be measured experimentally. From these data activity coefficients and the α in the presence of the solvent can be calculated.

1.3 Key issues in affinity separation processes

1.3.1 Solvent selection

The development of new solvents and new types of solvents is an ongoing process. In the last few decades the solvent class of ionic liquids (ILs) was developed and received a lot of attention.⁴²⁻⁴⁵ More recently there is focus on a solvent classes where different components are mixed in one solvent, e.g. deep eutectic solvents (DESs)^{46,47} and also aqueous two phase systems (ATPSs).⁴⁸⁻⁵⁰ Solvents that are tunable by CO₂ or other external factors have also been developed.⁵¹ An extensive review on solvent classes and solvent developments for acid extractions is given in Chapter 4 of this thesis.

With the increasing number of available solvents, there is a widespread attention in literature for solvent selection criteria and methods. The first requirements a solvent should fulfill are related to practical considerations, such as availability, viscosity, density, toxicity, miscibility, interfacial tension, wetting characteristics, (minimal) solubility in the feed stream, reactivity and thermal stability.^{20,40,52,53} Next to these considerations, the solvent should have sufficient capacity and regeneration should be feasible. In case of XD, next to an increase of relative volatility of the binary mixture, sufficient relative volatility with the solute and a low heat

of vaporization is required, and no azeotropes should be formed with the mixture components.^{20,40,52,53} A sufficient difference in boiling point between solvent and components also implies that the solvent is present in the liquid phase, which is more effective as it can influence activity coefficients in that phase.²⁰ In case of LLX, the solvent should show a miscibility gap with water, which is strongly related to the solvent polarity, and the solvent should have sufficient selectivity and capacity. For the regenerability of the solvent mainly the boiling point and heat of vaporization are determining as solvents are mostly recovered by distillation. In the design of an LLX process, the choice of the dispersed phase is also related to solvent selection, as well as the coalescence behavior of the solvent.⁵⁴

For XD initial solvent selection can be based on functional groups and expected interactions or empirical data,⁵⁵ which is generally followed by predictions based on infinite dilution activity coefficients that are calculated with for example UNIFAC or COSMO-RS.^{53,56,57} For LLX, there are also numerous methods for solvent selection,^{54,58-60} which were initially more empirical but became more based on data banks or group-contribution and quantum-chemical methods such as UNIFAC and COSMO-RS.^{54,61} More and more, the regeneration of the solvent is included in the solvent selection procedure.^{59,62-64}

1.3.2 Solvent regeneration

Although LLX processes may require less energy input for the separation, additional energy is required in the regeneration. This results in a trade-off between the extraction step and the regeneration step. High capacity solvents with low selectivity may require more energy in the regeneration step, as raffinate impurities are usually recovered as the distillate, whereas high selectivity and low capacity solvents may result in larger solvent-to-feed ratios, recycles and therefore increased cost of equipment.⁶⁵ For LLX processes, the most simple and straightforward method of solvent recovery is by distilling or evaporating either the solute or the solvent. However, in the case of thermally unstable components, other techniques are required, such as chemical regeneration in which often byproducts are formed, or regeneration based on a swing in temperature or diluent.³⁰ Most of the characteristics of an ideal solvent are related to the regenerability. For example, a solvent is more easily regenerable when it has a low solubility for the carrier and also shows a low solubility in the carrier. Solvents can be screened based on activity coefficients, as large activity coefficients of the solvent in the carrier phase are favored for low leaching, and low activity coefficients for the solute in the solvent for a high capacity.⁴⁰ For XD processes, generally the solvent is distilled in the regeneration step, thus the main solvent specifications required are a boiling point sufficiently above those of the mixture components and that no azeotrope is formed.²⁰

1.4 Scope and outline of this thesis

The prediction of solvent effects is a challenging task. Although several scales and parameterizations based on solvent properties are available to ease solvent selection,⁶⁶⁻⁶⁸ these do not cover the whole range of solvents and mixtures in separation processes. The direct prediction of solvent effects based on activity coefficients or group contribution methods does also not always lead to the right solvent as the selectivity may be concentration dependent and regeneration of solvent is not included. For the close-boiling polar mixtures that are central to this thesis, and in which specific and strong interactions, azeotropes and non-ideality are all common, these predictions of solvent effects are even more challenging.

Ideally, solvent selection not only focuses on the initial separation step, but also on the regeneration step. Moreover, the procedure for prediction of solvent effects and testing of solvents should be simple and time-efficient, and preferably also allow for the design of new solvents. The selection procedure can include several techniques, both theoretical and experimental, as long as extensive experimental work is avoided. To develop such a procedure, a fundamental understanding of the mechanisms and interactions involved in LLX and XD is required. Therefore, mechanisms, interactions and the effect of extractant and solvent composition were studied in this thesis using isothermal titration calorimetry (ITC, see Chapter 2), in combination with VLE/LLE measurements and supported by molecular modeling (MM, see Chapter 3) calculations. Based on the improved insights and understanding of mechanisms predictive methods were developed.

This thesis consists of two parts that have in common that they each deal with affinity separations of close-boiling polar compounds and that ITC and MM are applied to study phenomena and mechanisms involved in these processes. The first part (Chapters 4-7) focusses on LLX of acids and the second part (Chapters 8-9) the work focusses on XD processes.

Chapter 2 presents a thorough analysis of the accuracy of ITC applied in the molar concentration domain that is applicable to LLX, as concentrations applied in LLX are up to a factor thousand higher than those applied in the field of biochemistry and biotechnology where ITC is commonly applied. A single and a sequential reaction model were compared for their applicability in acid-base interactions in LLX, and standard deviations for the thermodynamic parameters were determined. In **Chapter 3**, the available methods and calculation options for MM with Spartan'16 Parallel software are discussed.

The part of this thesis focusing on liquid-liquid extraction starts with **Chapter 4**, in which solvents applied in LLX are reviewed. For each of the three groups, i.e. nitrogen based extractants, phosphorous based extractants and ionic liquids, effects of extractant type and solvent composition are studied and related to the extraction mechanism. Strategies for regeneration of the solvent are evaluated based on a typical process in which a diluent-swing based process appeared to be most feasible.

To improve the understanding of mechanisms involved in LLX and study implications thereof on the molecular structure of suitable extractants, ITC is applied - supported by MM - on various acid-base interactions directly related to LLX in Chapter 5 and 6. **Chapter 5** focusses on the role of the diluent in the extraction mechanism based on two cases. In the first case the interaction between acetic acid and tertiary amines and phosphorous based extractants is studied in various diluents. The second case involves the weaker acid phenol, also in interactions with tertiary amines and phosphorous based extractants. The method of ITC is validated with liquid-liquid equilibrium (LLE) experiments and supported by MM. In **Chapter 6** the focus lies on the interplay between the molecular structure of the extractant and the temperature sensitivity of the complexation reaction. One case of interaction of acetic acid with tertiary amines and aminopyridines was studied, as well as a case of interaction of 4-cyanopyridine with different types of substituted phenols. The phenomenon of enthalpy-entropy compensation was observed for different sets of extractants and implications thereof on the design of solvent molecules are given.

The effect of a swing in diluent on the complexation reaction was studied in **Chapter 7**, for the specific case of LLX of succinic acid with solvents composed of either trioctylamine (TOA) or trioctylphosphine oxide (TOPO). A temperature-swing based process and diluent-swing based processes where either a part of the (active) diluent is evaporated or an anti-solvent (either a liquid or a gas) was added before the regeneration column were compared. A cost evaluation was performed using Aspen Plus in which capital costs and the required energy input for operation were included.

As prediction of VLE is not always straightforward, especially when strong interactions or azeotropes are present in the mixtures, defining heuristics for a first selection of solvents would be beneficial. In an attempt to find such heuristics for solvent selection, **Chapter 8** studies on the effect of solvents for three different mixtures of close-boiling polar compounds, i.e. a mixture of diethylmethylaniline and diisopropylether, a mixture of valeric acid and its isomer isovaleric acid, and a mixture of 2-butanol and 2-butanone.

To avoid extensive experimental screening of solvents for application in XD processes, a method was developed in which MM and ITC are combined to predict the solvent effect on the relative volatility. **Chapter 9** focusses on the application of this method based on calculated and measured interaction energies. The method is applied to three different separation cases: a) a mixture of octanoic acid and levulinic acid, b) the mixture of diethylmethanamine and diisopropylether already used in Chapter 8, and c) the mixture of 2-butanol and 2-butanone also used in Chapter 8.

Chapter 10 contains the general conclusions based on the work presented in this thesis and also contains recommendations and directions for further research. An outlook regarding the opportunities for affinity separations of close-boiling polar compounds by LLX and XD forms the final part of this chapter.

References

- (1) European-Council. 2030 Climate and energy policy framework; 2014.
- (2) Eurostat, European Council. Energy statistics - an overview; 2018.
- (3) Sholl, D. S.; Lively, R. P. *Nature* 2016, *532*, 435-437.
- (4) Kiss, A. A.; Lange, J.-P.; Schuur, B.; Brilman, D. W. F.; van der Ham, A. G. J.; Kersten, S. R. A. *Biomass Bioenerg* 2016, *95*, 296-309.
- (5) Giraud, R. J.; Williams, P. A.; Sehgal, A.; Ponnusamy, E.; Phillips, A. K.; Manley, J. B. *ACS Sust Chem Eng* 2014, *2*, 2237-2242.
- (6) Anastas, P. T.; Warner, J. C. *Green chemistry : theory and practice*; Oxford University Press: Oxford [England] ;, 1998.
- (7) Atasoy, M.; Owusu-Agyeman, I.; Plaza, E.; Cetecioglu, Z. *Bioresour Technol* 2018, *268*, 773-786.
- (8) Gao, C.; Ma, C.; Xu, P. *Biotechnol Adv* 2011, *29*, 930-939.
- (9) John, R. P.; G.S, A.; Nampoothiri, K. M.; Pandey, A. *Biotechnol Adv* 2009, *27*, 145-152.
- (10) Ghaffar, T.; Irshad, M.; Anwar, Z.; Aqil, T.; Zulifqar, Z.; Tariq, A.; Kamran, M.; Ehsan, N.; Mehmood, S. *J Radiat Res Appl Sci* 2014, *7*, 222-229.
- (11) Le Berre, C.; Serp, P.; Kalck, P.; Torrence, G. P. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA, 2000.
- (12) Brouwer, T.; Blahusiak, M.; Babic, K.; Schuur, B. *Sep Purif Technol* 2017, *185*, 186-195.
- (13) Nakajima, H.; Dijkstra, P.; Loos, K. *Polymers* 2017, *9*, 523.
- (14) Skoog, E.; Shin, J. H.; Saez-Jimenez, V.; Mapelli, V.; Olsson, L. *Biotechnol Adv* 2018, *36*, 2248-2263.
- (15) Reyhanitash, E.; Brouwer, T.; Kersten, S. R. A.; van der Ham, A. G. J.; Schuur, B. *Chem Eng Res Des* 2018, *137*, 510-533.
- (16) Reyhanitash, E.; Zaalberg, B.; Kersten, S. R. A.; Schuur, B. *Sep Purif Technol* 2016, *161*, 61-68.
- (17) Gadipelly, C.; Pérez-González, A.; Yadav, G. D.; Ortiz, I.; Ibáñez, R.; Rathod, V. K.; Marathe, K. V. *Ind Eng Chem Res* 2014, *53*, 11571-11592.
- (18) Lim, J. C. L.; Lee, K. E. *Nat Environm Pollut Technol* 2017, *16*, 591-597.
- (19) Blahušiak, M.; Kiss, A. A.; Kersten, S. R. A.; Schuur, B. *Energy* 2016, *116*, 20-31.
- (20) Doherty, M. F.; Knapp, J. P. *Kirk-Othmer Encyclopedia of Chemical Technology*, 2004.
- (21) Hano, T.; Matsumoto, M.; Ohtake, T.; Sasaki, K.; Hori, F.; Kawano, Y. *J Chem Eng Jpn* 1990, *23*, 734-738.
- (22) López-Garzón, C. S.; Straathof, A. J. J. *Biotechnol Adv* 2014, *32*,

- (23) Shan, X.; Qin, W.; Dai, Y. *Chem Eng Sci* 2006, *61*, 2574-2581.
- (24) Wardell, J. M.; King, C. J. *J Chem Eng Data* 1978, *23*, 144-148.
- (25) Li, Z.; Qin, W.; Dai, Y. *J Chem Eng Data* 2002, *47*, 843-848.
- (26) Hong, Y.; Hong, W.; Han, D. *Biot Bioproc Eng* 2001, *6*, 386-394.
- (27) Ricker, N. L.; Pittman, E. F.; King, C. J. *J Sep Process Technol* 1980, *1*, 23-30.
- (28) Wasewar, K. L. *Int J Chem Eng Appl* 2012, *3*, 249-255.
- (29) Shah, V. H.; Pham, V.; Larsen, P.; Biswas, S.; Frank, T. *Ind Eng Chem Res* 2016, *55*, 1731-1739.
- (30) Tamada, J.; King, C. *Ind Eng Chem Res* 1990, *29*, 1333-1338.
- (31) Lo, T. C.; Baird, M. H. I.; Hanson, C. *Handbook of solvent extraction*; Wiley: New York :, 1983.
- (32) Wasewar, K. L.; Keshav, A.; Seema. *Int J Res Rev Appl Sci* 2010, *3*, 290-302.
- (33) Tamada, J. A.; Kertes, A. S.; King, C. J. *Ind Eng Chem Res* 1990, *29*, 1319-1326.
- (34) Marti, M. E. *Sep Sci Technol* 2016, 1-11.
- (35) Rasrendra, C. B.; Girisuta, B.; van de Bovenkamp, H. H.; Winkelman, J. G. M.; Leijenhurst, E. J.; Venderbosch, R. H.; Windt, M.; Meier, D.; Heeres, H. J. *Chem Eng J* 2011, *176-177*, 244-252.
- (36) Uslu, H.; Datta, D.; Bamufleh, H. S. *J Mol Liq* 2015, *212*, 430-435.
- (37) Eyal, A. M.; Canari, R. *Ind Eng Chem Res* 1995, *34*, 1789-1798.
- (38) Tung, L. A.; King, C. J. *Ind Eng Chem Res* 1994, *33*, 3217-3223.
- (39) Wasewar, K. L.; Shende, D.; Keshav, A. *Ind Eng Chem Res* 2011, *50*, 1003-1011.
- (40) Seader, J. D.; Henley, E. J.; Roper, D. K. *Separation process principles: chemical and biochemical operations*; 3rd ed. ed.; Wiley: Hoboken, N.J, 2011.
- (41) Blahušiak, M.; Kiss, A. A.; Babic, K.; Kersten, S. R. A.; Bargeman, G.; Schuur, B. *Sep Purif Technol* 2018, *194*, 301-318.
- (42) Marták, J.; Schlosser, Š. *Sep Purif Technol* 2007, *57*, 483-494.
- (43) Oliveira, F. S.; Araujo, J. M. M.; Ferreira, R.; Rebelo, L. P. N.; Marrucho, I. M. *Sep Purif Technol* 2012, *85*, 137-146.
- (44) Yang, Q.; Xing, H.; Su, B.; Bao, Z.; Wang, J.; Yang, Y.; Ren, Q. *AIChE J* 2013, *59*, 1657-1667.
- (45) Blahušiak, M.; Schlosser, S. *J Chem Thermodyn* 2014, *72*, 54-64.
- (46) Liu, Y.; Friesen, J. B.; McAlpine, J. B.; Lankin, D. C.; Chen, S.-N.; Pauli, G. F. *J Nat Prod* 2018, *81*, 679-690.
- (47) Warrag, S. E. E.; Peters, C. J.; Kroon, M. C. *Curr Opin Green and Sust Chem* 2017, *5*, 55-60.
- (48) Freire, M. G.; Claudio, A. F. M.; Araujo, J. M. M.; Coutinho, J. A.

- P.; Marrucho, I. M.; Lopes, J. N. C.; Rebelo, L. P. N. *Chem Soc Rev* 2012, *41*, 4966-4995.
- (49) Matthieu, G.; Nicolas, P.; Nicolas, S.; Eric, C.; Farouk, T.; P., C. J. A.; Isabelle, B. *Angew Chem Int Ed* 2018, *57*, 1563-1566.
- (50) Farias, F. O.; Passos, H.; Sanglard, M. G.; Igarashi-Mafra, L.; Coutinho, J. A.; Mafra, M. R. *Sep Purif Technol* 2018, *200*, 84-93.
- (51) Clarke, C. J.; Tu, W.-C.; Levers, O.; Bröhl, A.; Hallett, J. P. *Chem Rev* 2018, *118*, 747-800.
- (52) Jongmans, M. T. G.; Londoño, A.; Mamilla, S. B.; Praght, H. J.; Aaldering, K. T. J.; Bargeman, G.; Nieuwhof, M. R.; Kate, A. t.; Verwer, P.; Kiss, A. A.; van Strien, C. J. G.; Schuur, B.; de Haan, A. B. *Sep Purif Technol* 2012, *98*, 206-215.
- (53) Lei, Z.; Li, C.; Chen, B. Extractive Distillation: A Review. *Sep Purif Rev* 2003, *32*, 121-213.
- (54) Müller, E.; Berger, R.; Blass, E.; Sluyts, D.; Pfennig, A. *Ullmann's Encyclopedia of Industrial Chemistry*.
- (55) Robbins, L. A. Liquid-liquid extraction: a pretreatment process for wastewater. *Chem Eng Prog* 1980, *76*, 58-61.
- (56) Kossack, S.; Kraemer, K.; Gani, R.; Marquardt, W. *Chem Eng Res Des* 2008, *86*, 781-792.
- (57) Lei, Z.; Dai, C.; Zhu, J.; Chen, B. *AIChE J* 2014, *60*, 3312-3329.
- (58) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Robert McElroy, C.; Sherwood, J. *Sust Chem Proc* 2016, *4*, 7.
- (59) Schuur, B. *Chem Pap* 2015, *69*, 245-253.
- (60) Bonet, J.; Plesu, V.; Bonet-Ruiz, A.-E.; Tuluc, A.; Iancu, P.; Tohaneanu, M. C.; Llorens, J. *Clean Technol Envir* 2015, *17*, 1227-1238.
- (61) Birajdar, S. D.; Padmanabhan, S.; Rajagopalan, S. *J Chem Eng Data* 2014, *59*, 2456-2463.
- (62) Shah, V. H.; Pham, V.; Larsen, P.; Biswas, S.; Frank, T. *Ind Eng Chem Res* 2016, *55*, 1731-1739.
- (63) Demesa, A. G.; Laari, A.; Tirronen, E.; Turunen, I. *Chem Eng Res Des* 2015, *93*, 531-540.
- (64) Steltenpohl, P.; Graczová, E. *Acta Chem Slov* 2014, *7*, 129.
- (65) Rousseau, R. W. *Handbook of separation process technology*; John Wiley and Sons, 1987.
- (66) Christian Laurence; Gal, J.-F. *Lewis Basicity and Affinity Scales*; John Wiley & Sons, Ltd, 2009.
- (67) Taft, R. W.; Abboud, J.-L. M.; Kamlet, M. J.; Abraham, M. H. *J Solution Chem* 1985, *14*, 153-186.
- (68) Meyer, P.; Maurer, G. *Ind Eng Chem Res* 1995, *34*, 373-381.

2

Accuracy analysis of isothermal titration calorimetry (ITC) for measurement of thermal activity in liquid-liquid extraction

Abstract

The applicability and accuracy of isothermal titration calorimetry (ITC) to investigate intermolecular interactions in a high concentration domain applicable to liquid-liquid extraction (LLX) was studied for acid-base interactions. More accurate fits can be obtained using a sequential binding mechanism compared to a single reaction model, at the risk of finding a local minimum. Experiments with 0.24 M TOA resulted in a residue of fit of 4.3 % for the single reaction model, with a standard deviation σ of 1.6 % in the stoichiometry parameter n , 12 % in the complexation constant $K_{n,1}$ and 2.5 % in the enthalpy $\Delta H_{n,1}$. For the sequential model, σ was higher, 11 % in $K_{1,1}$, 26 % in $K_{n+1,1}$ and 12 % in $\Delta H_{n+1,1}$. This study clearly showed that at higher concentrations (order of mol/L), accurate parameter estimation is possible and parameter values are concentration dependent. It is thus important to do ITC at the application concentration.

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2.1 Introduction

Isothermal titration calorimetry (ITC), a technique to measure thermal effects of intermolecular interactions, has been used in several fields, most of them related to biomolecular research or biochemistry.¹⁻⁹ Protein related interactions have been studied in the majority of the published work,¹⁰⁻¹⁴ followed by synthetic compounds, lipids/micelles, nucleic acids and carbohydrates.² Although ITC was already applied in the 1970s to study interactions and hydrogen bonding between (substituted) phenols and pyridine or picoline,¹⁵⁻¹⁸ wide application of ITC to study binding interactions started with the publication of Freire et al.¹⁹ in 1990, in which they introduced ITC as an accurate method for this purpose. Ghai et al.²⁰ published in 2012 the last review in a yearly series covering both ITC techniques and applied methods and data analysis. Between 2011-2015, the developments mainly comprise of interpretation and analysis of ITC data, focusing on important assumptions and possible errors using both single binding and multiple binding models.² Although most of the work published on ITC focuses on binding of biological macromolecules, Falconer et al.² also reviewed research on synthetic molecules with more defined and less complex interaction sites with e.g. π - π interactions, cation- π interactions or anion- π interactions.² All interactions were measured at low concentrations ranging from micromoles per liter up to a few millimoles per liter.

In essence, in all reported application fields of ITC, it is key to apply complementary techniques to analyze the nature of the interactions responsible for the thermal effects measured in ITC to fully interpret the data, e.g. interactions between proteins and nanoparticles,^{11,12} where structural changes of proteins are of importance to study toxicity and to understand the effect of nanoparticles on the proteins. By using ITC in combination with other analytical methods (e.g. dynamic light scattering (DLS), zeta-potential measurement, small-angle X-ray scattering (SAXS), fluorescence spectroscopy, dynamic force spectroscopy, quartz crystal microgravimetry), conformational changes in the protein can be studied.^{11,12} The interactions of proteins with nanoparticles are often a combination of effects, such as hydrogen bonds, Van der Waals interactions and electrostatic interactions.^{11,12} Fox et al.¹³ used ITC in combination with X-ray crystallography to show that the interaction mechanism of anions with the binding pocket of an anhydrase protein is based on ion-pair formation. The combination of ITC with complementary techniques to study the molecular nature of the effects that are directly measured by ITC was also suggested by Loh et al.²¹ for surfactant aggregation and micelle formation.

Aggregation and micelle formation are also important interactions when ionic liquids (ILs) are considered,¹⁴ and the stability of the proteins in the presence of ILs could be determined using ITC. However, the thermodynamic models used for fitting of the data of ITC are not fully developed for this field, due to a complex system of agglomerates that is present in these systems. Similar challenges occur for the study of ion-coupled transport through membranes, in which the membrane proteins are highly dynamic. Next to the dynamic nature, complex allosteric interactions may occur.^{22,23} Allosteric effects are the responses of enzymes to interactions at sites other than their active site, changing their structure,²⁴ and adjusting their binding ability. Positive cooperative allosteric effects facilitate binding of more components,²⁴ while negative cooperativity decreases the ability to bind more components.²⁴ Freiburger et al.²⁵ developed an approach based on ITC, NMR and circular dichroism by which the mechanisms of allosteric effects of dimeric enzymes could be studied in detail, focusing on simultaneous changes in the conformation, folding and binding of the enzymes, and they suggest to always combine ITC with supplementary techniques such as NMR or circular dichroism spectroscopy.²⁶ For the fitting model, it has been suggested to obtain data over a range of temperatures to improve accuracy. There is analogy between the allosteric effects in proteins and the interactions of small molecules and complexes in liquid-liquid extraction, since in both cases, multiple effects are responsible for the measured heat effects in ITC, and also for liquid extractions it is possible that binding of one molecule to an extractant affects the binding of a second molecule to the complex. Therefore, also for the systems with much higher concentrations, as studied for liquid-liquid extraction (LLX), it is to aid the model development with complementary techniques. Here, well known systems have been selected for which the types of interaction have been reported.^{27,28}

ITC analysis for higher concentration domains was shown by Cuypers et al.,^{29,30} who studied interactions of phenols and thiophenols with phosphine oxide and phosphate extractants,²⁹ and N-oxides.³⁰ The concentrations applied by Cuypers et al.^{29,30} were approximately 1 mM for the phenols and 10 mM for the phosphine oxides,²⁹ and no sensitivity or accuracy analysis was performed. The use of ITC in this field enabled direct analysis of the interactions, whereas interactions between extractants and solutes otherwise are typically indirectly derived, and model parameters are obtained from a fit on data from measurements in heterogeneous systems. The advantage of a direct analysis of the interactions in the organic phase is that the mechanism of interaction can be studied precisely instead of studying the net effect of a combination of interactions. Other research

focusing on the mechanism of extraction focused on IR spectroscopy and NMR analysis.^{28,31-33} However, based on these techniques a quantitative analysis of the different equilibria in the organic phase is challenging. For these purposes ITC is a promising complementary technique.

In this study, using acetic acid (HAc) and tri-*n*-octyl amine (TOA) as a well-known extraction system,^{34,35} ITC was studied at even higher concentrations to improve the shape of the isotherms, and the fitting accuracy of parameters such as binding constants was determined for an extractant concentration of 0.12 - 0.48 M in the sample cell and an acid concentration of 9 - 18 M in the titrant. These concentrations result in complex formation relevant for LLX applications. Due to the small size of the complexes formed in these systems, and their geometrical degrees of freedom, numerous types of complexes may be formed, in contrary to enzyme - ligand interactions that are geometrically typically highly defined. As a result of the geometrical degrees of freedom for small complexes, also interactions of multiple molecules with the complex are possible, not necessarily identical to the interaction of a first molecule with the extractant. It is essential to study these interaction effects in the concentration domain corresponding to the application.

In the theory section, the models and conditions used in literature focusing on ITC are discussed, as well as their applicability to describe solvent-solute interactions in liquid-liquid extraction. The accuracy under typical conditions for liquid-liquid extraction was studied with series of experiments at different sample concentrations and for varying experimental variables such as injection volume (5 - 20 μ L) and titrant concentrations (9 - 18 M). A phenomenological description of isotherms obtained from ITC of the acid-base interactions is combined with a quantitative evaluation of the accuracy and reproducibility of ITC and the influence of experimental conditions.

2.2 Materials and methods

2.2.1 Chemicals

All chemicals were used without further purification and commercially obtained from Sigma Aldrich (acetic acid (>99.7 %), trioctylamine (98 %), 1-octanol (>99 %), heptane (99 %), methylisobutylketon (MIBK, 99 %)), and from VWR International (toluene (>99.5 %)).

2.2.2 Isothermal titration calorimetry (ITC)

The ITC experiments were performed using a TA Instruments TAM III Microcalorimeter operated based on dynamic correction. Experiments with 0.12 M and 0.24 M TOA in toluene were carried out in a 4 mL sample vial, the experiment with 0.48 M TOA in toluene in a 1 mL sample vial.

A reference cell was used in each experiment containing water with a heat capacity equal to the contents of the sample cell. The syringe is connected to the sample cell through a cannula and was filled with 300 μL of titrant. A stainless steel stirrer was operated at 1.33 Hz. There are two types of injection, i.e. a continuous injection of titrant and a series of periodical injections. For the experiments with periodical injections an injection interval of at least 60 minutes was applied. All experiments were performed at 20 $^{\circ}\text{C}$, and the first injection of 3 μL was not taken into account for data fitting, to account for diffusive loss of titrant.³⁶ The experiments are corrected for the energy of dilution of the titrant, calculated based on a blank measurement, see the Appendix.

Three types of experiments, listed in Table 1, were each performed six times, a) titration of pure acetic acid (HAc) into 0.48 M trioctylamine (TOA) in toluene, b) titration of pure acetic acid into 0.24 M TOA in toluene and c) titration of 50 vol% acetic acid in toluene into 0.12 M TOA in toluene. The sample concentrations were chosen based on the Wiseman c-value,³⁷ and the injection volume scheme to maximize accuracy, see the Appendix. At the end of the experiment, the final ratio of acid titrant concentration $[\text{A}]_{\text{tot,final}}$ (free acid and complexed acid) in the sample cell over the total amine concentration $[\text{B}]_{\text{tot,final}}$ (free and complexed) in the sample cell is defined as $R_m = \left(\frac{[\text{A}]_{\text{tot}}}{[\text{B}]_{\text{tot}}} \right)_{\text{final}}$. $[\text{B}]_{\text{tot,final}}$ is different from $[\text{B}]_0$ because of the change in volume.

Table 1 Overview of experiments each performed six times for the reproducibility test of ITC. Acetic acid (HAc) is titrated into TOA dissolved in toluene at 20 $^{\circ}\text{C}$.

	Titrant	[TOA]	Injections	R_m
A	Pure HAc	0.48 M	2 x 3 μL , 5 x 5 μL , 15 x 10 μL , 13 x 15 μL	7.3
B	Pure HAc	0.24 M	3 μL , 5 x 5 μL , 15 x 10 μL , 7 x 15 μL	7.5
C	50 vol% HAc in toluene	0.12 M	3 μL , 2 x 5 μL , 11 x 10 μL	9.5

2.3 Theory

This section gives an overview of the methods and errors of ITC analysis that have been reported in literature, presents the calculation method for the thermodynamic parameters, and discusses different reaction mechanisms and models of fitting.

2.3.1 Fitting of ITC data

The fitting models described in literature on ITC data fitting include a 1:1 complexation,^{36,38} a single set of identical sites yielding a similar fit to 1:1 complexation,^{29,39} or sequential binding of the ligands to the complex.⁴⁰ Some authors used customized scripts,⁴¹ including also agglomeration of specific complexes or the effect of competing ligands. In this work, only basic models based on a single set of identical sites (with the possibility to vary the stoichiometry) and based on sequential binding will be compared for the fitting of acid-amine complexation in toluene.

The sequential reaction model starts with the formation of (1,1)-complexes according to eq (1) and the equilibrium constant of this complex formation $K_{1,1}$ is defined in eq (2).

$$K_{1,1} = \frac{[AB]}{[A][B]} \quad (2)$$

From these two parameters, both ΔG and ΔS can be calculated using eq (3) and (4).

$$\Delta G_{1,1} = -RT \ln K_{1,1} \quad (3)$$

$$\Delta G_{1,1} = \Delta H_{1,1} - T\Delta S_{1,1} \quad (4)$$

For higher stoichiometries, extra equations can be added to the system of eq (1)-(2). For a second molecule of A interacting with the complex AB to form the complex A_2B , the reaction equation and equilibrium constant are shown in eq (5)-(6).

$$K_{2,1} = \frac{[A_2B]}{[A][AB]} \quad (6)$$

By fitting these equations to the heat release of the ITC experiment, not only $\Delta H_{1,1}$ and $K_{1,1}$ can be obtained but also $\Delta H_{2,1}$ and $K_{2,1}$. In the Appendix,

the theoretical ITC-curves are displayed for a single reaction model with 1:1 stoichiometry (eq (1)-(2)) and for a reaction system based on two reaction equations (eq (1), (2), (5) and (6)). For a varying stoichiometry n in the second reaction, the reaction mechanism can also consist of multiple equations, i.e. next to eq (2), the sequential series of equations defined by the constant in eq (7) are fit, and at least a clear double S-curve is needed for a decent fit (see the Appendix Figure A1b). For the fitting procedure, initial guess values were taken that are typical for hydrogen bonding and proton exchange (i.e. $K_{1,1} = 10$, $\Delta H_{1,1} = -30$ kJ/mol, $K_{n+1,1} = 100$, $\Delta H_{n+1,1} = -18$ kJ/mol and $n = 1.6$). In this reaction, n molecules of A interact with the AB-complex.

$$K_{n+1,1} = \frac{[A_{n+1}B]}{[A]^n [AB]} = \frac{[A_{n+1}B]}{[A]^{n+1} K_{1,1} [B]} \quad (7)$$

Fitting ITC data to this kind of multiple site models has been reported by Brautigam⁴² (details in the Appendix), and similar to his findings, also for acid extractions a model may be used based on two different types of interaction. In the case of inactive diluents, complexes with a higher stoichiometry are formed where only one acid interacts directly with the base,²⁸ and the subsequent acids add to the complex through hydrogen bonding. For this sequential binding, the interaction between the first acid with the base is different, but all other interactions are considered equal in energy, i.e. $\Delta H_{1,1}$ and $\Delta H_{n+1,1}$, respectively. The corresponding equilibrium constants and enthalpies of complexation are the fit parameters of this model next to the stoichiometry n .

Since models with multiple reactions require extensive fitting procedures and large sets of data, a simpler model could be advantageous. A potential model is a single reaction model based on a single set of identical sites. In this model, an average stoichiometry is used for the fitting and it is assumed that the interaction of each compound is equal. The reaction equation is similar to the one in eq (1), however for this system an average stoichiometry is used, see eq (8) with corresponding equilibrium constant in eq (9). In this model only one molecule of B reacts with n molecules of A. The stoichiometry coefficient n does not occur as an exponent of the concentration of A, because this would imply a sequential reaction mechanism.

$$K_{n,1} = \frac{[A_n B]}{[nA][B]} \quad (9)$$

2.3.2 Error in the parameters

Under ideal conditions, the main source of error is the error in volume and this results in a statistical error of approximately 1 % for ΔH and K . In actual experiments in an ITC machine errors of around 1 % for ΔH and 5 % for K were found.⁴³ Based on a comparison of results from different laboratories the calculated error in ITC experiments appeared to be even larger. Errors were reported⁴³ in both ΔG and ΔH of 3-4 kJ/mol and since ΔS is derived from these parameters, the error is 6-8 kJ/mol in $T\Delta S$, where in this case typical values for ΔG are around -50 kJ/mol, for ΔH between +20 kJ/mol and -20 kJ/mol and $T\Delta S$ around 50 kJ/mol.⁴³ There are very large differences in the reported accuracy of the parameters obtained, e.g. very large errors for thiophenol were found as result of a low heat of injection for specific compounds.²⁹ The error in ΔG is often not mentioned, but it should be smaller than the error in ΔH because ΔG is logarithmically dependent on K , see eq (3).³⁶

For the models applied in this study, i.e. the single reaction model of eq (8) and (9), and the sequential reaction model of eq (1), (2) and (7), the total heat released after each injection Q_{tot} was calculated with eq (10) and (11), respectively. In these equations V_{tot} is the total volume of sample and titrant present in the sample cell.

$$Q_{\text{tot}} = V_{\text{tot}} \left([A_n B] (n) \Delta H_{n,1} \right) \quad (10)$$

$$Q_{\text{tot}} = V_{\text{tot}} \left([AB] \Delta H_{1,1} + [A_{n+1} B] (\Delta H_{1,1} + n \Delta H_{n+1,1}) \right) \quad (11)$$

To compare the fitting statistics with the theoretical sensitivity of ΔH , K and n for errors in experimental data under the conditions applied in this study, an analysis was performed making use of a Monte Carlo simulation. An ideal set of data points was generated based on fixed values for the parameters K , ΔH and n , for the sequential reaction model and a normally distributed random error with a standard deviation of 1 % in the heat of injection was added as noise. From eq (10)-(11), it can be concluded that a simulated random error in other variables such as the sample volume or injected volume will also directly result in an error in the heat of injection. Data sets were simulated based on the following assumptions: initial volume (V_{tot}) is 2.72 mL, amount of extractant (n_{base}) is $6.6 \cdot 10^{-4}$ mol (corresponding to an initial concentration of 0.24 M), $K_{1,1} = 12$, $\Delta H_{1,1} = -28$ kJ/mol, $K_{n+1,1} = 118$, $\Delta H_{n+1,1} = -15$ kJ/mol and $n = 1.6$. These values are similar to parameters obtained from a fit on experimental data.

2.4 Results and discussion

Two injection procedures for ITC experiments have been studied, i.e. through a series of periodical injections, including a study of the accuracy of the derived parameters and the effect of measurement data on the parameter fitting, and through continuous injection, which may reduce analysis time.

2.4.1 Periodical injection

In a typical ITC experiment with periodical injection, in which pure acetic acid was titrated to a mixture of 0.24 M TOA in toluene, the first six injection volumes were smaller (injection 1: 3 μL , injection 2-6: 5 μL) than the following injections (10-15 μL) to obtain a higher data density in these regions of the S-curve, which eases the fitting of the experimental data. The direct experimental results for this experiment are shown in Figure 1.

Figure 1 Raw data for ITC analysis of titration of pure acetic acid into 0.24 M TOA in toluene at 20 °C.

In Figure 1, initially the signals with the same injection volume (injection 2-6) have a comparable signal. The very first point shows a small signal, even if the smaller volume of 3 μL instead of 5 μL is taken into account. It is common that the first point is off, and this is due to loss of the titrant by diffusion.³⁶ The signal is positive, which means that the interaction is exothermic and up to 20 kJ/mol acid is released, which is a value that is in agreement with literature on amine-carboxylic acid interactions.^{27,34} Above a molar ratio of approximately two, the intensity of the heat release reduces, until after a ratio of more than 5.5 only the enthalpy of mixing is measured.

2.4.1.1 Blank measurements

Next to extractant-solute interactions, also the heat of interaction with the diluent might affect the results, and to investigate on the thermal effects due to diluent interactions, blank measurements for titration of acetic acid into several diluents have been performed, shown in Figure 2. For some of the diluents, such as toluene, there is a strong change in the heat of injection in the first few injections. For other diluents, such as 1-octanol, the heat of injection is similar for all injections (excluding the first data point). The heat effects are a combination of the heat of dilution of the titrant and the heat of dilution of the diluent. If a diluent is very apolar and inactive, e.g. heptane or toluene, the (endothermic) heat effect of the first few injections of the highly polar and active acid can be very strong, which is primarily due to breaking of hydrogen bonds between the acid molecules that are diluted into an apolar environment. With addition of the acid, the environment becomes more polar and the heat effect of future additions decreases. For the active diluent 1-octanol, the heat effect of most injections is similar, and upon injection of acid there are no significant net hydrogen bonding effects, due to the hydrogen bonding ability of 1-octanol. For all parameter fits, ITC raw data were corrected with the blank measurement data to correct for the heat effects due to diluent effects, assuming that the heat of dilution is equal for pure diluent and for the solvent mixtures used in the actual experiments.⁴³

Figure 2 Blank experiments for titrating acetic acid into the pure diluent (no extractant) at 20 °C, for ◇ heptane, ▼ MIBK, ■ 1-octanol (50 vol% acid), ▲ toluene and ● 1-octanol (pure acid).

2.4.1.2 Diluent effects

Before quantitatively discussing the fitting results for one type of diluent, a set of experiments with different diluents is presented here and the shapes of the integrated and diluent effect corrected experimental ITC results are compared phenomenologically. Among the results in Figure 3a is the curve corresponding to the experiment with acetic acid and TOA in toluene that was shown in Figure 1, as well as an experiment with MIBK and one with heptane. For the diluent toluene, the heat released as a result of the first few injections is large compared to the following injections. The graph shows a double S-shape, also shown in Figure A1b, implying that the enthalpy of complexation of the first acid is larger negative than that of the second and following acids. For all three diluents the intensity of the heat release reduced after a stoichiometry of approximately 2. The MIBK-graph shows a low energy release as a result of the first few injections, which then increases first before reducing again at stoichiometry > 2 , indicating that here the presence of the first acid promotes the subsequent acid - complex binding. For heptane there is no remarkable high or low heat released for the first injections and the graph shows a plateau.

Figure 3b shows the results when 1-octanol was applied as the diluent. In this case, the energy released in the first injections is higher and the energy release already reduces at a stoichiometry > 1 . This indicates that interaction with the first acid is stronger and that the (1,1)-complex is the main complex formed. This is a result of competition between 1-octanol and acetic acid for binding with the extractant molecule.²⁸

Figure 3 Differences in the shape of isotherm (S-curve) for titration of pure acetic acid to 0.24 M TOA at 20 °C in **a)** ■ toluene, △ MIBK and ○ heptane, and **b)** ● 1-octanol.

To compare the two types of models, it was attempted to fit the characteristic result obtained with toluene both with the single reaction model using an average stoichiometry (eq (8) and (9)), and with the sequential reaction model (eq (1), (2) and (7)). The best-fit isotherms are shown in Figure 4. For the major part of the curves, both models fit (almost) similar and the residuals of the fits are 3.2 % for the sequential model and 4.8 % for the single reaction model. However, especially at the first part of the curves, the sequential reaction model gives a much better fit for the experimental data, see Figure 4. The lower heat release in the first injections for MIBK may be a result of a similar enthalpy of complexation for the first and following acids and a lower complexation constant of the first complex in MIBK, see Table A1 in the Appendix for details on the fit parameters. For heptane, the plateau indicates similar enthalpies of complexation for the acids interacting with the amine in combination with a moderate $K_{1,1}$. Because of the plateau, the single reaction model is a better fit for heptane compared to toluene and MIBK.

Without going further in depth on why these diluents induce these differences, it is clear that these differences are important for the proper fitting of the thermodynamic parameters to the experimental data. For a proper fit with the model based on a single set of identical sites, either very similar values for the complexation enthalpy of the different acids are required, or a 1:1 stoichiometry of the complexation. When larger complexes are formed with different enthalpies of complexation of the acids the sequential binding model is more applicable.

Figure 4 Fit of experimental data obtained with titration of acetic acid to 0.24 M TOA in toluene at 20 °C. The model lines represent the sequential reaction model (dotted line) and the single reaction model (dash-dot line) described in eq (1), (2) and (7), and eq (8) and (9), respectively. The parameters obtained from the data fit are shown in Table A1 in the Appendix.

2.4.1.3 Accuracy of parameters from ITC experiments

To investigate the accuracy and reproducibility of ITC experiments and to study the effect of the concentration of the titrant and the concentration of extractant in the sample mixture, the experiments from Table 1 were each performed six times. For each of the experiments, the parameters were fit to the experimental data, and then the average values of the parameters and their corresponding standard deviation were calculated. Because the K-values are dependent on n, (eq (9)) they cannot be directly compared with each other and the resulting averages should only be used for determining the sensitivity of the parameter on experimental errors. The parameter values as well as the fitting statistics for the single reaction model are given in Table 2, and in Table 3 the results for the sequential reaction model with the same experimental data are given. For both models, the stoichiometry of the amine is assumed to be $m = 1$, because overloading of a single amine is expected.^{27,28} A very important observation from Table 2 and Table 3 is that the values of the equilibrium constants are dependent on the concentration of amine. This is a logical result, since the amine affects the properties of the solution (e.g. polarity, availability of hydrogen bond donating and accepting groups), and it shows that it is very important to

study interactions at the same concentration as those used in the practical application such as LLX. The standard deviation of $K_{n,1}$ and $\Delta H_{n,1}$ is lower using the third experimental method with a lower concentration of 0.12 M TOA. This is most likely a result of the lower concentration of acid in the titrant, allowing for a larger number of injections and larger injection volumes per mole of titrant and therefore less error in injection volume. For fitting of the stoichiometry n , the first method with 0.24 M TOA shows a lower standard deviation, however, the relative standard deviation in $\Delta H_{n,1}$ and n is for all three methods less than 3.5 %. With a relative standard deviation of up to 13 %, the accuracy in $K_{n,1}$ is lower.

Table 2 Calculated values for $K_{n,1}$, n , $\Delta H_{n,1}$ and fit residue for fitting of the experimental data for three experimental datasets (see Table 1) with the single reaction model of eq (8), (9) and (10).

Dataset		$K_{n,1}$	n	$\Delta H_{n,1}$ (kJ/mol)	Residue of fit (%)
Pure HAc to 0.48 M TOA in toluene	average	23.6	2.96	-19.8	4.3 %
	standard deviation	3.11	0.1	0.65	1.3 %
	relative standard deviation (%)	13	3.5	3.3	
Pure HAc to 0.24 M TOA in toluene	average	35.6	2.8	-20.8	4.3 %
	standard deviation	4.39	0.045	0.52	1.1 %
	relative standard deviation (%)	12	1.6	2.5	
50 vol% HAc to 0.12 M TOA in toluene	average	38.8	2.79	-22.7	4.4 %
	standard deviation	0.5	0.09	0.17	0.4 %
	relative standard deviation (%)	1.29	3.34	0.76	

Table 3 Calculated values for $K_{1,1}$, $\Delta H_{1,1}$, $K_{n+1,1}$, $\Delta H_{n+1,1}$, n and fit residue for fitting of the experimental data for three experimental datasets (see Table 1) with the sequential reaction model of eq (1), (2), (7) and (11).

Dataset		$K_{1,1}$	$\Delta H_{1,1}$ (kJ/mol)	$K_{n+1,1}$	$\Delta H_{n+1,1}$ (kJ/mol)	n	Residue of fit (%)
Pure HAc to 0.48 M TOA in toluene	average	16.7	-25.3	53.8	-18.3	1.73	5.6 %
	standard deviation	6.14	1.26	15.4	0.93	0.08	1.5 %
	relative standard deviation (%)	37	5	29	5.1	4.7	
Pure HAc to 0.24 M TOA in toluene	average	12.7	-30	97	-15.6	1.58	3.6 %
	standard deviation	1.46	1.25	25.2	1.95	0.02	0.9 %
	relative standard deviation (%)	11	4.2	26	12	1.4	
50 vol% HAc to 0.12 M TOA in toluene	average	18.5	-34.6	168	-14.9	1.59	4.1 %
	standard deviation	1.1	0.94	38	1.83	0.03	1.3 %
	relative standard deviation (%)	6	2.7	23	12	1.9	

Also, $K_{1,1}$ shows a very high standard deviation of 37 % when 0.48 M TOA is used, compared to 11 % for the method with 0.24 M TOA and 6.0 % for the method with 0.12 M TOA. Apparently, fitting of the first K-value is more difficult at the higher concentration of TOA or the lower number of injections, which can also be seen in the low (relative) standard deviation in both K-values (6.0 % in $K_{1,1}$ and 23 % in $K_{n+1,1}$) in the case of 0.12 M TOA. Next to the effect of more injections or a larger injection volume with 50 % acetic acid, at a lower concentration of TOA the maximum slope of the titration curve is less steep, allowing for more data points in the steep part of the curve, which may decrease the error in the obtained -parameters. For the other two methods, the relative standard deviations in $K_{n+1,1}$ are also large, with 26 % for 0.24 M TOA and 29 % for 0.48 M TOA. Similar to the results in Table 2, the relative standard deviation in the values of n and $\Delta H_{1,1}$ are very low, especially in the case of 0.12 M TOA (1.9 % in n and 2.7 % in $\Delta H_{1,1}$) and 0.24 M TOA (1.4 % in n and 4.2 % in $\Delta H_{1,1}$), and with 0.48 M TOA at 4.7 % in n and 5.0 % in $\Delta H_{1,1}$ still acceptable.

When the results of the single reaction model are compared with those of the sequential reaction model, it can be seen that overall the residue of fit of both models are comparable and have reasonable values, < 10 %. However, it should be mentioned that as shown in Figure 4, the much better fit of the sequential reaction model in the first part of the curve does not strongly affect the overall residue of fit. Nevertheless, to properly describe

this phenomenological effect, the sequential reaction model is much better suited. For the second method with 0.48 M TOA, the residue of fit and the standard deviation of the K-values are larger for the sequential reaction model. This increased fitting error is probably due to the lower n_{inj} that was applied in this method. For one of the experiments with 0.24 M TOA, the 95 % confidence intervals of the parameter fit were also determined. For $\Delta H_{1,1}$ (-28.8 kJ/mol) the interval ranged from -33.7 kJ/mol to -24.0 kJ/mol, for $K_{1,1}$ (11.7) the interval was only very small and ranged from 11.70 to 11.71. For the parameters of the second reaction the intervals were larger, for $\Delta H_{n+1,1}$ (-16.8 kJ/mol) the interval ranged from -21.0 to -12.6 kJ/mol, for $K_{n+1,1}$ (96.7) the interval ranged from 76.4 to 117 and for n (1.55) the interval ranged from 1.45 to 1.64.

When the three experimental methods are compared for the sequential binding model based on their c-value and number of injections n_{inj} , see Table 4, it can be seen that all the c-values are in the ‘ideal’ range between 10-100. Comparing the methods and assuming that increasing the TOA concentration does not strongly increase the measurement accuracy, there is no clear advantage of the increased n_{inj} or c-value for fitting of the single reaction model. However, for the sequential reaction model, the fit residues are smaller when a higher number of injections was applied in the analysis. The increased number of injections increases the data density, thereby enabling a better parameter fit.

Table 4 c-values and number of injections for the three experimental data sets applied (see Table 1).

	Titrant	[TOA]	c-value	n_{inj}	Residue single reaction fit (%)	Residue sequential reaction fit (%)
A	Pure HAc	0.48 M	34	14	4.3 %	5.6 %
B	Pure HAc	0.24 M	24	28	4.3 %	3.6 %
C	50 vol% HAc in toluene	0.12 M	13	34	4.4 %	4.1 %

2.4.1.4 Comparing the errors based on experimental data fitting with theoretical errors based on simulation

To determine the theoretical effect of errors in the measurement data on the fitting of the parameters, Monte Carlo simulations were run with series of simulated data. For simulations on the sequential reaction model a noise with a standard deviation of 1 % was added to simulated data, and these data were used to fit the model parameters, see Table 5 (top row). Detailed and additional results for a lower concentration of extractant are shown in the Appendix. The K-values are more sensitive to errors in the experimental

data than the other parameters. However, comparing with the original values for the parameters, it appears that a local minimum is reached. The possibility of a local minimum for the parameter fit was also suggested by Brautigam⁴² and Le et al.,⁴⁴ which means that the fit depends on the initial values ($K_{1,1} = 10$, $\Delta H_{1,1} = -30$ kJ/mol, $K_{n+1,1} = 80$, $\Delta H_{n+1,1} = -12$ kJ/mol and $n = 1.8$). Because of this local minimum, the data fitting was repeated using the original values for the parameters as initial values, see Table 5 (bottom row). This does result in average values of the parameters that are around the original values, and smaller standard deviations in the parameters of 0.5 - 2 %. The single reaction model results are presented in the Appendix, and do not show dependency of initial estimates. Comparing the theoretical fit accuracy based on the Monte Carlo simulation on simulated data (Table 5) with the fit on experimental data (Table 3), shows that the fitting on experimental data results in significantly less accurate parameter fits. This indicates that either the error in the heat measured is significantly larger, also possibly not normally distributed, or other errors (e.g. volume, concentration) play a significant role.

Table 5 Parameter fit for $K_{1,1}$, $\Delta H_{1,1}$, $K_{n+1,1}$, $\Delta H_{n+1,1}$, n and fit residue for fitting 170 series of simulated data with the sequential reaction model of eq (1), (2) and (7) for a 0.24 M TOA system.

Dataset		$K_{1,1}$	$\Delta H_{1,1}$ (kJ/mol)	$K_{n+1,1}$	$\Delta H_{n+1,1}$ (kJ/mol)	n	Residue of fit (%)
Simulated dataset $\sigma = 0.01$	Average	7.92	-32.6	162	-11.4	1.65	2.8 %
	standard deviation	0.44	0.72	22	0.56	0.05	2.0 %
	relative standard deviation (%)	5.6	2.2	14	4.9	3	
Simulated dataset $\sigma = 0.01$ <i>Original values used as initial value</i>	Average	12	-28	118	-15	1.6	0.90 %
	standard deviation	0.12	0.142	2.5	0.13	0.010	0.20 %
	relative standard deviation (%)	0.99	0.51	2.1	0.87	0.62	

To study the dependency of the derived parameters on each other, the value for n was fixed and data fitting was performed using only the other two parameters as variables. The initial values applied were the same as those mentioned above for the results in the top row of Table 5. Although the residue of the fit increased from 2.8 (top row of Table 5) to 3.2 %, the only parameter that changed significantly in average value and confidence interval is $K_{n+1,1}$. The value decreased to 121 with a new 95 % confidence interval from 115 to 128. Apparently only $K_{n+1,1}$ is dependent on n and these parameters are able to (partially) compensate each other in the fitting.

2.4.2 Continuous injection

Next to injecting periodically, continuous injection of the titrant into the sample cell is also possible.⁴⁵ A comparison between periodical injection and continuous injection is shown in Figure 5. It can be seen that the experiment with heat-flow correction results in a large noise in the curve. When dynamic correction was applied in the ITC experiment, the noise was significantly reduced. The problem with continuous injection appears to be the delay in the signal. For the faster injection ($0.27\ \mu\text{mol/s}$, dotted line) the curve is moved to the right compared to the periodical injection, where there is enough time to reach equilibrium at each point. For the slower injection ($0.12\ \mu\text{mol/s}$, dashed line) this effect is only seen in the first part of the curve (where the heat of injection has a larger negative value). Decreasing the rate of injection even further, would lead to better results but this also increases the experiment time to a longer time than when periodical injections are applied, thereby making the application of continuous injection less advantageous.

Figure 5 ITC-curve comparing the method of continuous injection (lines) with periodical injection (titration) (black squares). Titration of acetic acid to $0.24\ \text{M}$ TOA in water-saturated 1-octanol at $20\ ^\circ\text{C}$. Continuous injection was performed using dynamic correction at $0.12\ \mu\text{mol/s}$ (dashed line) and $0.27\ \mu\text{mol/s}$ (dotted line), and using heat flow correction at $0.27\ \mu\text{mol/s}$ (continuous grey line).

2.4.3 Comparison with reported ITC accuracy in literature

In this work, the accuracy of parameter fitting for the acid-base interactions in the concentration range applicable to liquid-liquid extraction was determined. To put these results into perspective, Table A5 in the Appendix shows experimental specifications and a summary of the accuracy reported in this work in combination with results published for other applications. Although the concentrations applied in this work are higher, the standard deviation obtained in the parameters for the single reaction model are comparable to those reported in other sources for one set of site models and 1:1 reaction models.^{29,36,38,39,46} No other source reported on the exact same sequential model. Brautigam,⁴² however, reported a noise level of about 1 % for a two and three-site model, which is more accurate compared to the standard deviation for $\Delta H_{1,1}$ in this work. Also, for a three site model Freyer et al.⁴⁰ reported an error of 0.5 - 6 % for ΔH which is similar to the standard deviation in this work and they reported an error of 7 - 10 % for K , which is more accurate.

2.5 Conclusion

The use of ITC to analyze interactions in high concentration domains was studied for acid-base interactions relevant for liquid-liquid extraction. The parameter estimation accuracy was evaluated for acetic acid complexation with TOA in toluene. Because it was found that the complexation constants are extractant concentration dependent, it is key that ITC analysis is performed at the concentration that is also applied in the liquid-liquid extraction process. Furthermore, based on a phenomenological study, it was concluded that a sequential reaction model is more suitable to fit ITC-results for acid-base titration than a single reaction model. For the sequential reaction model, the parameters ΔH , K and n were derived from a fit on experimental periodical injection data with standard deviations of respectively 2.7 - 12 %, 6.0 - 37 %, and 1.4 - 4.7 %. Fitting of such multi-parameter models was found to be sensitive to local minima, indicating the importance of good initial guess values. In order to benchmark the accuracy of the parameter fit on experimental data, also Monte Carlo simulations were done for simulated data to which a 1 % noise was added. From these results, it was found that the error in the parameters based on fitting on real experimental data is larger than the theoretical 0.5 - 2.1 %, but still allows for accurate parameter estimation. The accuracy of the derived parameters is the highest when a periodical injection is applied in combination with a lower concentration of TOA and a higher number of injections. Continuous injection posed no improvement compared to periodical injection due to a delay in the obtained power signal that requires a low rate of injection of titrant and therefore longer measurement time than the periodical injection, instead of the anticipated shorter time.

References

- (1) Kabiri, M.; Unsworth, L. D. *Biomacromolecules* 2014, *15*, 3463-3473.
- (2) Falconer, R. J. *J Mol Recognit* 2016, *29*, 504-515.
- (3) Tsvetkov, P. O.; Barbier, P.; Breuzard, G.; Peyrot, V.; Devred, F. *Methods Cell Biol* 2013, *115*, 283-302.
- (4) Damian, L. *Methods Mol Biol* 2013, *1008*, 103-118.
- (5) Demarse, N. A.; Killian, M. C.; Hansen, L. D.; Quinn, C. F. *Methods Mol Biol* 2013, *978*, 21-30.
- (6) Aweda, T. A.; Meares, C. F. *Methods* 2012, *56*, 145-153.
- (7) Roselin, L. S.; Lin, M.-S.; Lin, P.-H.; Chang, Y.; Chen, W.-Y. *Biotechnol J* 2010, *5*, 85-98.
- (8) Wilcox, D. E. *Inorg Chim Acta* 2008, *361*, 857-867.
- (9) Ladbury, J. E.; Chowdhry, B. Z. *Chem Biol* 1996, *3*, 791-801.
- (10) Liang, Y. *Acta Biochim Biophys Sin* 2008, *40*, 565-576.
- (11) Huang, R.; Lau, B. L. T. *BBA-Gen Subjects* 2016, *1860*, 945-956.
- (12) Omanovic-Miklicanin, E.; Manfield, I.; Wilkins, T. *J Therm Anal Calorim* 2017, *127*, 605-613.
- (13) Fox, J. M.; Kang, K.; Sherman, W.; Héroux, A.; Sastry, G. M.; Baghbanzadeh, M.; Lockett, M. R.; Whitesides, G. M. *J Am Chem Soc* 2015, *137*, 3859-3866.
- (14) Bharmoria, P.; Kumar, A. *BBA-Gen Subjects* 2016, *1860*, 1017-1025.
- (15) Beezer, A. E.; Hawksworth, W. A.; Orban, M.; Tyrrell, H. J. V. *J Chem Soc Farad T 1: Phys Chem in Cond Phas* 1977, *73*, 1326-1333.
- (16) Barton, S. S.; Kraft, J. P.; Owens, T. R.; Skinner, L. J. *J Chem Soc Perk T* 1972, 339-341.
- (17) Zaretskii, M. I. *Chem Heterocyc Compd* 1997, *33*, 1-16.
- (18) Arnett, E. M.; Joris, L.; Mitchell, E.; Murty, T. S. S. R.; Gorrie, T. M.; Schleyer, P. v. R. *J Am Chem Soc* 1970, *92*, 2365-2377.
- (19) Freire, E.; Mayorga, O. L.; Straume, M. *Anal Chem* 1990, *62*, 950A-959A.
- (20) Ghai, R.; Falconer, R. J.; Collins, B. M. *J Mol Recognit* 2012, *25*, 32-52.
- (21) Loh, W.; Brinatti, C.; Tam, K. C. *BBA-Gen Subjects* 2016, *1860*, 999-1016.
- (22) Boudker, O.; Oh, S. *Methods* 2015, *76*, 171-182.
- (23) Draczkowski, P.; Matosiuk, D.; Jozwiak, K. *J Pharm Biomed Anal* 2014, *87*, 313-325.
- (24) Traut, T. *Allosteric regulatory enzymes*; Springer: New York, 2008.
- (25) Freiburger, L. A.; Baettig, O. M.; Sprules, T.; Berghuis, A. M.; Auclair, K.; Mittermaier, A. K. *Nat Struct Mol Biol* 2011, *18*, 288-294.
- (26) Freiburger, L.; Auclair, K.; Mittermaier, A. *Methods* 2015, *76*, 149-161.
- (27) Tamada, J.; King, C. *Ind Eng Chem Res* 1990, *29*, 1333-1338.
- (28) Tamada, J. A.; King, C. J. *Ind Eng Chem Res* 1990, *29*, 1327-1333.
- (29) Cuypers, R.; Burghoff, B.; Marcelis, A. T. M.; Sudhölter, E. J. R.; de Haan, A. B.; Zuillhof, H. *J Phys Chem A* 2008, *112*, 11714-11723.

- (30) Cuypers, R.; Murali, S.; Marcelis, A. T. M.; Sudhoelter, E. J. R.; Zuillhof, H. *ChemPhysChem* 2010, *11*, 3465-3473.
- (31) Ziegenfu, H.; Maurer, G. *Fluid Phase Equilib* 1994, *102*, 211-255.
- (32) Ingale, M. N.; Mahajani, V. V. *Separ Technol* 1994, *4*, 123-126.
- (33) Scheler, C.; Popovic, M.; Iannotti, E.; Mueller, R.; Bajpai, R. *Appl. Biochem. Biotech.* 1996, *57*, 29.
- (34) Marti, M. E. *Sep Sci Technol* 2016, 1-11.
- (35) Rasrendra, C. B.; Girisuta, B.; van de Bovenkamp, H. H.; Winkelman, J. G. M.; Leijenhorst, E. J.; Venderbosch, R. H.; Windt, M.; Meier, D.; Heeres, H. J. *Chem Eng J* 2011, *176-177*, 244-252.
- (36) Boyce, S. E.; Tellinghuisen, J.; Chodera, J. D. *bioRxiv, Biochem* 2015, 23796/23791-23796/23797.
- (37) Wiseman, T.; Williston, S.; Brandts, J. F.; Lin, L.-N. *Anal Biochem* 1989, *179*, 131-137.
- (38) Tellinghuisen, J. *Anal Bioche.* 2005, *343*, 106-115.
- (39) Wang, M.-L.; Lin, Y.-I.; Liu, B.-L. *Solvent Extr Ion Exch* 1997, *15*, 605-629.
- (40) Freyer, M. W.; Lewis, E. A. *Method. Cell Biol.*; Academic Press, 2008, pp 79-113.
- (41) Tellinghuisen, J. *Anal Biochem* 2012, *424*, 211-220.
- (42) Brautigam, C. A. *Methods* 2015, *76*, 124-136.
- (43) Schalley, C. A. *Analytical methods in supramolecular chemistry*; Wiley: Weinheim :, 2007.
- (44) Le, V. H.; Buscaglia, R.; Chaires, J. B.; Lewis, E. A. *Anal Biochem* 2013, *434*, 233-241.
- (45) Markova, N.; Hallén, D. *Anal Biochem* 2004, *331*, 77-88.
- (46) Saha, S.; Roy, A.; Roy, K.; Roy, M. N. *Sci Rep* 2016, *6*, 35764.
- (47) Tellinghuisen, J. *Anal Biochem* 2005, *343*, 106-115.
- (48) Tellinghuisen, J. *Anal Biochem* 2012, *424*, 211-220.
- (49) Freyer, M. W.; Lewis, E. A. *Methods in Cell Biology*; Academic Press, 2008, pp 79-113.
- (50) Wiseman, T.; Williston, S.; Brandts, J. F.; Lin, L.-N. *Anal Biochem* 1989, *179*, 131-137.
- (51) Turnbull, W. B.; Daranas, A. H. *J Am Chem Soc* 2003, *125*, 14859-14866.
- (52) Liu, Y.; Sturtevant, J. M. *Biophys Chem* 1997, *64*, 121-126.
- (53) Le, V. H.; Buscaglia, R.; Chaires, J. B.; Lewis, E. A. *Anal Biochem* 2013, *434*, 233-241.
- (54) Freiburger, L. A.; Baettig, O. M.; Sprules, T.; Berghuis, A. M.; Auclair, K.; Mittermaier, A. K. *Nat Struct Mol Biol* 2011, *18*, 288-294.
- (55) Keller, S.; Vargas, C.; Zhao, H.; Piszczek, G.; Brautigam, C. A.; Schuck, P. *Anal Chem* 2012, *84*, 5066-5073.
- (56) Wieprecht, T.; Beyermann, M.; Seelig, J. *Biochemistry* 1999, *38*, 10377-10387.
- (57) Saha, S.; Roy, A.; Roy, K.; Roy, M. N. *Sci Rep* 2016, *6*, 35764.

Appendix

Minimizing the error in experimental ITC results

To obtain the most accurate results with ITC, the experimental parameters that can be varied are the number of injections n_{inj} , the injection volume V_{inj} , the concentration of samples or extractant in the measuring cell $[B]$, the titrant concentration in the syringe $[A]_{syr}$ and the final ratio of titrant concentration over sample concentration in the sample cell after the experiment $R_m = \left(\frac{[A]_{tot}}{[B]_{tot, final}} \right)$. Increasing the number of injections does not always reduce the error, since volume errors are important for volumes under 7 μ L and injection energies may become too small.⁴⁷ In contrast to earlier published values of $n_{inj} = 30$, now values around $n_{inj} = 10 - 15$ are recommended,^{36,43,48} taking into account that the integrated heat of injection should be above 10 cal, or 42 μ J.⁴⁹ The error in titrant concentration can also be very significant.³⁶ The number of injections is limited by the syringe volume, sample cell volume, titrant concentration $[A]_{syr}$ and initial concentration in the measuring cell $[B]_0$, where in general $[A]_{syr}/[B]_0$ should be between 20-50.⁴⁹ These concentrations can be related to the equilibrium constant. Wiseman introduced a c -value to describe the shape of the binding isotherms of ITC and optimize experimental conditions, such as the concentration in the sample cell $[B]$. The definition of the Wiseman c -value is shown in eq (A1), where K is the equilibrium constant.⁵⁰

$$c = [B]Kn \quad (A1)$$

Several guidelines can be found for the value of c , where c should in general be between 1 and 1000,³⁶ and more ideally between 10-100.⁴⁹ For too low c -values the calculation of n and ΔH becomes problematic, whereas for too high c -values the calculation of K is problematic. When the stoichiometry is known, experiments with $c < 10$ can also be very accurate.⁵¹ Although multiple values for c are reported, successful analysis can be performed even at $c < 1$ when the titration range is increased from the normal $R_m = 2$, to $R_m = (6.4/c^{0.2} + 13/c)$ with $R_m \geq 1.1$.^{36,43,48} According to Tellinghuisen⁴⁸ successful analysis is less determined by the c -value itself than by the total detectable heat and the maximal conversion of the complexation reaction. Another advice is to remove the first (small) injection from the data points, to account for diffusive titrant loss.^{36,48} In the fitting of the data, a correction by a constant value can be applied to account for drift.⁴³

For the experiments with 0.12 M TOA a higher value for R_m was chosen because the slope of the S-curve in the last part of the curve was steeper than for the other two types of experiments. Because of the higher sample concentration, for the experiments with 0.48 M TOA a smaller sample vial was used to allow for sufficient R_m . The disadvantage of a smaller total

volume is that the number of injections could not further be increased significantly without making concessions that could lead to a too small injection volume.

Furthermore, important assumptions that are used in ITC analysis are that binding is reversible and equilibrium is reached between injections. It is therefore important to ensure that the signal is back to the baseline before the next injection. Also the heat of dilution of the ligand and (macro) molecule influences the measurements, for this blanks should be performed of titrating ligand into the buffer solution and of the buffer solution in the macromolecule.² It should be taken into account that performing blanks uses the assumption that the heat of dilution is equal for dilution into the pure diluent and into the solvent mixture.⁴³ Lastly, ΔH is not (necessarily) constant with temperature, so experiments at different temperatures might be required.⁵²

Diluent effects

The parameter fitting of the experimental data in Figure 3 is performed using MATLAB by a least squares minimization of the error between experimental and calculated data based on the model equations. The results are shown in Table A1. It can be seen that in the case of toluene for the sequential reaction model $\Delta H_{1,1}$ is higher than $\Delta H_{n+1,1}$, indicating that indeed the interaction with the first acid is stronger than with the following acids in the diluent toluene. In the case of 1-octanol it is clear that the (1,1)-complex is the main complex formed as $K_{1,1}$ is high and $K_{n+1,1}$ is very low for the sequential reaction model. This can also be concluded from the low stoichiometry $n = 1.2$ in the fit of the single reaction model for 1-octanol.

Table A1 Parameter fit for the ΔH , K , and n -values for interaction of acetic acid with 0.24 M TOA in toluene, MIBK, heptane and 1-octanol at 20 °C, with both the sequential reaction model (top) and single reaction model (bottom), described in eq (1), (2) and (7), and eq (8) and (9), respectively. Isotherms are shown in Figure 3.

Sequential reaction model	$K_{1,1}$	$\Delta H_{1,1}$ (kJ/mol)	$K_{n+1,1}$	$\Delta H_{n+1,1}$ (kJ/mol)	n	Residue (%)
Toluene	-32.4	10.7	-13	141	1.6	3.2 %
MIBK	-22.2	5.6	-20.4	47.5	1.5	4.5 %
Heptane	-17.9	22.5	-20.9	45.4	1.9	5.7 %
1-octanol	-28.8	90.7	-27.6	0.8	0.8	2.2 %
Single reaction model	$K_{n,1}$	$\Delta H_{n,1}$ (kJ/mol)			n	Residue (%)
Toluene	-20.6	37.7			2.8	4.8 %
MIBK	-16.7	28.4			3.4	4.0 %
heptane	-15.4	25.8			3.8	4.1 %
1-octanol	-31.8	28.7			1.2	8.9 %

Theoretical ITC curves for single site model and dual site model

Figure A1a shows a theoretical isotherm for a system based on the one reaction formation of the 1:1 complex (see eq (1) and (2)). Figure A1b shows a theoretical isotherm for a reaction system based on two reaction equations (see eq (1), (2), (5) and (6)) where the enthalpy of complexation is larger for the interaction of the first ligand than for the second ligand. In this isotherm a double S-shape is visible.

Figure A1 Shape of theoretical isotherms for **a)** a single reaction model with 1:1 stoichiometry (0.83 M extractant, 17.5 M titrant, $K = 30$, $\Delta H = -35$ kJ/mol) and **b)** a sequential reaction model with 1:1 and 2:1 stoichiometry of the complexes (0.59 M extractant, 17.5 M titrant, $K_{1,1} = 1.0 \cdot 10^4$, $\Delta H_{1,1} = -35$ kJ/mol, $K_{2,1} = 200$, $\Delta H_{2,1} = -18$ kJ/mol).

Lessons from literature for fitting of multiple site models

Brautigam⁴² studied the fitting of isothermal data based on a two-site and a three-site model. In general both the two-site and three-site binding model show good results. For the fitting a clear biphasic (clear S-shape) isotherm was required for the two-site model and three distinct phases were required for the three-site model.⁴² Monte Carlo analysis of the fitting of such a three-sites model was performed by Freyer et al.⁴⁹ Three K-values and three ΔH -values were fit from a virtual set of 1000 simulated experiments in which a noise of approximately 1 μ J was applied with injection heat ranging up to 170 μ J. The average error in the resulting parameters was between 0.5 - 6 % for ΔH and 7 - 10 % for K. When the fitting of the different parameters is compared, in this case the results were better for ΔH and n than for K.⁴⁹

Fitting an increased number of parameters may not always yield a single solution to the parameter fit,⁴² and an appropriate starting position for fitting is necessary to optimally determine the best-fit solution.⁵³

Care should be taken to avoid local minima when fitting multiple site models, which may be done through restricting the parameters to realistic values, but should be performed very carefully. Fitting of a monophasic isotherm with the three-site binding scenario for the reveal of two parameters was successfully performed using strongly constrained parameters.⁴² Another

option to improve fitting is a global fit on the basis of multiple experimental data sets to derive one set of thermodynamic parameters. This is what Freiburger et al.⁵⁴ did in the analysis of ITC data on folding and unfolding of allosteric enzymes based on a sequential two-site binding model. A global fit was applied for different temperatures and combined with the van 't Hoff equation, to improve accuracy.⁵⁴

Fitting statistics of singlereaction model.

Fitting statistics were also determined for the single reaction model. For the single reaction model it was assumed that $K_{n,m} = 45$, $\Delta H = -20$ kJ/mol, $n = 2.8$ and $m = 1$. For the single reaction model the parameter fit was independent of initial guess values, see the results in Table A2. The standard deviation in the parameter $K_{n,1}$ is 2.4 %, this implies that $K_{n,1}$ is more sensitive to deviations in the data than the other parameters, with a relative standard deviation of 0.24 % in n and 0.39 % in $\Delta H_{n,1}$. However, even in this case the deviation in the parameter $K_{n,1}$ is not excessively larger than the standard deviation of 1 % in the data that was fit. The same procedure was performed for simulated datasets with a normalized error in the initial volume, in the amount of moles of extractant present and in the concentration in the syringe. This resulted in similar standard deviations in the parameter fits as those shown in Table A2, so the parameter fit is not extra sensitive to any of these factors. Compared to the parameter fit analysis based on experimental results, see Table 3, the results based on simulated data with a 1 % normalized error show significantly lower relative standard deviations. This supports the hypotheses that the error in the heat measured is either larger, not normally distributed or that other factors induce significant errors.

Table A2 Parameter fit for $K_{n,1}$, n , $\Delta H_{n,1}$ and fit residue for fitting 1000 series of simulated data with the single reaction model of eq (8)-(10).

Dataset		$K_{n,1}$	n	$\Delta H_{n,1}$ (kJ/mol)	Residue of fit (%)
Simulated dataset $\sigma = 0.01$	average	45.03	2.8	-20	0.80 %
	standard deviation	1.1	0.007	0.077	0.10 %
	relative standard deviation (%)	2.4	0.24	0.39	

Effect of extractant concentration on data fitting

The Monte Carlo analysis was also performed at a lower concentration of extractant than that applied in in Table A2 and Table 5. For these simulated data sets the amount of extractant (n_{base}) was $3.3 \cdot 10^{-4}$ mol, corresponding to an initial sample concentration of 0.12 M TOA. The results are shown in

Table A3 for the single reaction model and in Table A4 for the sequential reaction model. Compared to the fitting for the 0.24 M TOA model of in Table A2 and Table 5, the results are very similar regarding both standard deviation and residue of fit, with the only exception that for the sequential model in Table A3 the standard deviation in the residue of the fit is lower as a result of the lower extractant concentration. This may be an effect of the less strong steep part of the isotherm at the lower concentration. Comparing the relative standard deviations of Table A3 and Table A4 with the experimental results of the 0.12 M TOA system (see Table 2 and Table 3), it can be seen that for this system the differences are smaller for both reaction models, implying that the experimental error is reduced in the 0.12 M TOA system with the 50 % acetic acid titrant.

Table A3 Parameter fit for $K_{n,1}$, n , $\Delta H_{n,1}$ and fit residue for fitting 1000 series of simulated data with the single reaction model of eq (8)-(10) for an initial extractant concentration of 0.12 M.

Dataset		$K_{n,1}$	n	$\Delta H_{n,1}$ (kJ/mol)	Residue of fit (%)
Simulated dataset $\sigma = 0.01$	average	44.99	2.8	-20	0.80%
	standard deviation	0.98	0.009	0.098	0.10%
	relative standard deviation (%)	2.2	0.32	0.49	

Table A4 Parameter fit for $K_{1,1}$, $\Delta H_{1,1}$, $K_{n+1,1}$, $\Delta H_{n+1,1}$, n and fit residue for fitting 170 series of simulated data with the sequential reaction model of eq (1), (2), (7) and (11) for an initial extractant concentration of 0.12 M.

Dataset		$K_{1,1}$	$\Delta H_{1,1}$ (kJ/mol)	$K_{n+1,1}$	$\Delta H_{n+1,1}$ (kJ/mol)	n	Residue of fit (%)
Simulated dataset $\sigma = 0.01$	average	9.2	-31.7	229	-11.2	1.7	2.10%
	standard deviation	0.53	0.95	22	0.6	0.02	0.30%
	relative standard deviation (%)	5.8	3	9.7	5.4	1.3	
Simulated dataset $\sigma = 0.01$ <i>Original values used as initial value</i>	average	12	-28	118	-15	1.6	0.80%
	standard deviation	0.14	0.17	3.3	0.14	0.011	0.20%
	relative standard deviation (%)	1.1	0.61	2.8	0.95	0.66	

Comparison with reported ITC accuracy in literature

Table A5 shows experimental specifications and a summary of the accuracy reported in this work in combination with results published for other applications. In most of the systems in Table A5, either Origin or the Omega software that was delivered with the Microcal machines was applied. Other (free) software for ITC data analysis are NITPIC and SEDPHAT.² NITPIC is a software program to process ITC data, that can fit parameters based on multiple models and also calculates the errors in the experimental data.⁵⁵ SEDPHAT can apply several binding models and statistical tools in combination with global fitting of parameters.⁴²

Table A5 *Fitting procedures and accuracy reported for parameters obtained from ITC experiments.*

System	Energy	[B]	[A]	K	Error	Fitting	Machine	Ref
Acetic acid with TOA in toluene	Up to 20 kJ/mol	0.12 - 0.48 M, (c = 13-34)	9 - 18 M	25-40	Standard deviation, single reaction: 1.3-13 % in K, 1.6-3.5 % in n, 0.76-3.3 % in ΔH , sequential reaction: 6.0-37 % in $K_{-1,1'}$, 2.7-5.0 % in $\Delta H_{-1,1'}$, 23-29 % in $K_{n+1,1'}$, 5.1-12 % in $\Delta H_{n+1,1'}$ and 1.4-4.7 % in n	Least squares, MATLAB	TAM III	This work
Ba ²⁺ with 18-Crown-6	Up to 40 kJ/mol	1.0 mM	~42 mM		Statistic error 0.2 % in ΔH ($\Delta H = 42$ kJ/mol), <0.1 % in K ($K = 10^7$ M)	Least squares, 1:1 complexes, Origin		47
(Thio)phenols with phosphine oxide and phosphate	Up to 16 kJ/mol	1-10 mM	10-100 mM	10 ² - 10 ⁴	1-10 % in n, 8-46 % in K, 4-14 % in ΔH , 0-6 % in ΔG , 4-30 % in T ΔS	Origin software, one-set-of-sites	Microcal VP - ITC	29
Carboxybenzenesulfonamide CBS and bovine CAII		10 μ M (c = 10)	720 μ M		Relative standard error of ± 3 % in K and 1 % in ΔH , interlaboratory statistical error of ~20 %	Origin least squares, 1:1 complexes	GE/MicroCal VP-ITC	36
Simulated data and data of bio-molecular interaction	Up to 42 kJ/mol	190 μ M	4500 μ M	10 ⁷	Noise level 0.42 kJ/mol	Two-site, three site, SEDPHAT	Malvern VP-ITC	43
Peptide-lipid	Up to 80 kJ/mol	20mM	200 μ M	10 ³ - 10 ⁵	2-10 % in ΔH	Customized model	Microcal MC2	56
Cyclodextrin-heptanoate system;	Up to 13 kJ/mol	9.76mM	160.4 mM	~10 ³	0.3-0.7 % in n, 1.3-2.7 % in K and 0.4-1 % in ΔH	Omega software, one-set-of-sites	Microcal Omega	52
Heptanoic acid - heptylamine system				~10 ⁻³	0.3-1.1 % in n, 1.7-5.0 % in K and 0.5-1.5 % in ΔH	Omega software, one-set-of-sites	Microcal Omega	52
Inclusion of cyclodextrin and nicotinic/ascorbic acid	Up to 4 kJ/mol	50 μ M	500 μ M	~10 ⁻³	1-4 % in n, 9-10 % in K, and 5-7 % in ΔH	Origin 7.0, Microcal, one-site	Microcal VP-ITC	57
Monte-Carlo analysis of simulated data	Up to 45 kJ/mol			10 ⁴ - 10 ⁷	0.5 - 6 % for ΔH and 7-10 % in K	Three-sites		49
General		~0.1 mM			5 % in K with 90 % conversion, for $10 < K < 10^8$ 1/M, when $q_{\text{det}}/\text{sigma}_{\text{tot}}$ ($\sigma =$ standard deviation in q) ~ 700)			48
General					Error of 3 kJ/mol in ΔG and ΔH , error in ΔS of 20-30 J/mol/K			42

3

Molecular modeling for interactions in
affinity separations

Abstract

The potential of application of molecular modeling (MM) for studies on intermolecular interactions relevant for the fields of liquid-liquid extraction and extractive distillation was examined. This resulted in an overview of the various theoretical models, basis sets and solvation models that are available and reported in literature. In this chapter, these models are briefly discussed and compared for acid-base interactions using Wavefunction Spartan'16 Parallel software. Direct interaction energies as well as energy profiles with varying intermolecular distances were computed. Diluent effects and the effect of water molecules were modeled using different theoretical models to compare the model results. Hartree-Fock (HF) and more advanced and accurate quantum chemical calculations based on density functional theory (DFT) were applied for energy minimization calculations. The more advanced and accurate calculations have as a disadvantage that they are also more computationally intensive. From the comparison of the results, the use of HF was justified because it was found to give similar results as calculations based on DFT. An important finding was that geometry optimizations can result in local minima instead of global minima, which can be addressed by applying a series of initial geometries. For a more realistic representation of the interactions water molecules need to be added to the model.

3.1 Introduction

Originally, modeling for process and chemical engineering focused on the macro-scale, but in the last decades there has been more focus on modeling at smaller scales and even molecular-based scales.¹⁻⁷ Incentives for this development include the need for more defined material characteristics, required increased efficiency of processes, required control over reactions, specific product development up to a molecular scale and environmental restrictions.⁸ A better understanding of processes, interactions and reactions at the molecular scale is of significant aid in these cases.

Nowadays, the entire range of modeling from the molecular geometry optimization using molecular modeling tools, via simulations of groups of molecules with molecular dynamics simulations, up to macro scale modeling of unit operations is available for chemical engineers. Even though the macroscopic models are derived from fundamental physical phenomena, the macroscopic models based on equations of state, and activity coefficient models are typically of (semi-)empirical nature describing phase equilibria. The molecular modeling simulations and molecular dynamics simulations are *ab initio* or semi-empirical methods based on fundamental physical properties of the atoms and molecules in the system. Where molecular modeling is typically done with single molecules and small groups of molecules, molecular dynamics simulations describe larger ensembles of molecules. For molecular dynamics, software packages such as GROMACS, LAMMPS and AMBER are used that describe virtual ‘boxes of molecules’ to study for example extractant agglomeration behavior, third phase formation and the behavior of molecules at the interface.^{1,2,9} As these molecular dynamics simulations are based on force field methods, properties such as the molecular charges, molecular conformations and geometry and proton charges need to be defined upfront or predicted with quantum-mechanical molecular modeling software.⁴ Results can also be (partially) validated through modeling of binary mixtures and verifying this with experimental miscibility data.⁹ Molecular modeling (MM) includes all concepts related to the development and application of theories (both physical and chemical) that are needed for predicting phenomena at a molecular scale. Several properties can be predicted and computed based on MM, including thermodynamic, mechanical and transport properties and information on the morphology and geometry of molecules and complexes.⁸ Combining and coupling of different scales of modeling from molecular scale to macro or process scale can be very powerful to address chemical engineering phenomena.⁸

The combination of molecular dynamics simulation of the larger scale extraction system coupled with MM calculations at the molecular scale

was, for example, successfully applied for nitric acid extraction by amides, with GROMACS software coupled to Gaussian09 for the charges on the extractant, by which aggregates of the amides were shown and phenomena like co-extraction could be explained.⁴ Also, for extraction of uranyl by tributylphosphate (TBP), LAMMPS molecular dynamics package was successfully applied, for which the state of the proton was chosen upfront.¹⁰ When interface phenomena were studied with ABMER10 software for the same system, molecular charges and conformations were obtained from Gaussian09 at DFT or HF level.³ LAMMPS based on calculations with molecular models was also used for the study on e.g. interaction of trinitrophenol by a secondary amine;¹¹ extraction mechanisms of picric acid by a secondary amine, where interatomic interaction potential and conformational energy calculated with GAMESS;⁵ and structure and aggregation for interactions of an ionic liquid (IL) with polar covalent molecules in solvents, to obtain insight on the molecular scale and relate the results to experimental data.⁶ Lastly, AMBER03 was applied for the study of interactions and equilibria of tryptophan and ILs, where the ILs were calculated with GROMACS coupled with Gaussian for DFT calculations of the molecules.⁷ Molecular dynamic simulations are computationally intensive and the required input for these simulations is more extensive, requiring a deeper understanding and expertise. The aim of this work is to examine and develop a fast and easily applicable method that can also be applied by a process engineer on a standard personal computer. Less computationally intensive MM simulations with single molecules or small sets are for practical reasons expected to be more suitable for this purpose, but possibly at the cost of accuracy and therefore their applicability and accuracy for predictions and interpretation of molecular interactions was studied.

With MM the interactions, geometry and energies at the molecular level can be calculated and predicted to determine and validate mechanisms of interactions in complex formation.^{12,13} MM was also applied in the solvent screening of liquid-liquid extraction (LLX) processes, e.g. for extraction of metals,¹³ phenol^{14,15} and lactic acid.¹⁶ With MM also improved understanding of the effect of molecular structure on the thermodynamics of the complexation equilibrium and the structure of the formed complexes can be obtained.¹² MM is however mainly applied to compute the complexation enthalpy related to extraction and thereby for example design and select solvents, or study their interaction mechanisms.¹³⁻¹⁶ The aim of the work in this thesis is to apply MM as a tool in combination with other methods such as isothermal titration calorimetry (ITC) and measurement of liquid-liquid and vapor-liquid equilibria to study molecular interactions related

to LLX and extractive distillation (XD) processes. The goal is to not only improve understanding of the interactions and mechanisms involved, but also to study and predict solvent effects on the separation processes based on calculated interaction energies.

When molecular modeling methods based on semi-empirical or *ab initio* methods cannot be applied, e.g. in the case of large (sets of) molecules, there is still a possibility to model the behavior. In this case molecular mechanics can be applied, i.e. methods totally avoiding quantum mechanics, electron densities and the wave function, that are instead based on classical physics. The main advantage is the calculation speed and low computational force required for these methods. In these models it is assumed that the nucleus and the electrons around the nucleus are perfect spheres and intermolecular bonds are treated as springs. Molecular mechanics methods compute the potential energy based on classical physics equations, in which all constants are to be experimentally obtained or obtained from *ab initio* calculations. Sets of parameters and functions that are used are called force fields, which are based on databases of compounds for the parametrization. The class of molecules used for the parametrization determines the success in a specific application, which is a strong disadvantage. The equations and calculated potential function can only be used for comparison of configurations, not for electronic properties and they do not have an absolute result that can be interpreted.^{17,18}

3.2 From Schrödinger equation to *ab initio* calculations

The molecular modeling within quantum chemistry is in principle all based on the time-independent Schrödinger equation. Since solving this equation exactly is (practically) impossible for multiple particle systems, several approximations and assumptions are generally made in order to be able to approximate the solutions to this equation. Figure 1 gives a schematic overview of these assumptions and approximations. The first assumption is the Born-Oppenheimer approximation that assumes that electrons move in a field of fixed nuclei. This results in the electronic Schrödinger equation. This equation can provide the potential energy surface from which equilibrium geometries and vibrational energies can be obtained.¹⁷

The electronic Schrödinger equation and the molecular orbitals can be solved exactly for one-electron systems (hydrogen, He⁺). For multiple electron systems, other approximations are applied to solve the electronic Schrödinger equation, these approximations lead to the Hartree-Fock wave function.¹⁹⁻²¹ First of all, it is assumed that each electron's motion can be

described with an orbital, or single particle function. This implies that all Hamiltonians are separable and the total electronic wave function is the product of the separate wave functions of particles. This is in line with the identical nature of electrons. Secondly, it is assumed that each electron moves independently but does feel Coulomb repulsion based on its average position. Thus the particles are independent in a mean field. This implies that there is an effective potential, that is spherically symmetric and an average over the positions of all electrons.¹⁷⁻¹⁹

Schrödinger equation

- Born-Oppenheimer approximation: electrons move in a field of fixed nuclei

Electronic Schrödinger equation

- Potential energy surface, equilibrium geometry, vibrational energy
- Only solved exactly for one-particle system

- Electrons move independently and experience average Coulomb repulsion (mean field)
- Each electron's motion described with single particle function
- Total electronic wavefunction is product of separate wavefunctions

Hartree-Fock wavefunction

- Also for multiple particle systems

- Slater determinant applied to satisfy anti-symmetry
- Molecular orbitals from linear combinations of basis functions
- Iterations to minimize Hartree-Fock Energy (variational method)

Variational solution ($\geq$ exact) for energy

***Figure 1** Assumptions and approximations leading to the solutions obtained with the Hartree-Fock method.*

A problem is that the antisymmetry principle is not satisfied by the Hartree product of separate wave functions. The antisymmetry principle is the postulate that electrons are described by antisymmetric wave functions regarding interchange of the coordinates of an electron pair, thereby also imposing the Pauli exclusion principle. Therefore, a Slater determinant based on one spin orbital per electron is used to satisfy the antisymmetry and thereby also the Pauli principle. For energy calculations the Hartree-Fock wave function is used in the form of a Slater determinant. The next step is to obtain the molecular orbitals (numerically) by integration over a grid or as a linear combination of basis functions. A set of basis functions is called a basis set, which is used in the Hartree-Fock method to represent the electronic wave function with the aim to transform the partial differential equations of the model into algebraic equations for the atomic orbitals that can be solved numerically. Iterations with initial orbitals are required to solve the equations by minimizing the Hartree-Fock Energy. This principle of iterations and minimizing the energy from linear combination of a set of basis functions is called the variational method, leading to the variational

solution that is equal or greater than the exact energy. It is important to realize that these obtained orbitals for multiple electron systems are mathematical and thus only approximate reality.¹⁷⁻¹⁹

3.3 Software and calculations

Wavefunction Spartan'16 Parallel, in this thesis referred to as 'Spartan', is a software package for molecular modeling calculations that can perform the calculations based on different theoretical models in combination with various basis sets and solvation models. This section provides a short overview of the calculation options within Spartan. The basis of the software is a graphical interface in which the molecules and structures can be built after which MM calculations can be performed. Spartan software is equipped with the Spartan Spectra and Properties Database (SSPD) in which for an extensive collection of molecules the pre-calculated optimized structures, energies, molecular properties and various spectra are stored.

3.3.1 Theoretical models available in Spartan

There are six types of theoretical models that can be applied in Spartan. The simplest model is the molecular mechanics model that models molecules based on classical mechanics. Then the semi-empirical models follow that are based on the Hartree-Fock (HF) model but combine this with a series of approximations required to solve the quantum chemical equations and additional parameters from experimental data.⁸ In all semi-empirical models empirically determined (additional) parameters are applied. Within quantum chemistry *ab initio* methods are fully based on quantum mechanics, the wave function and physical constants. The Hartree-Fock model itself is an *ab initio* model with a quantum chemical nature, as described in section 3.2. Density Functional Theory (DFT) models are often considered to be *ab initio* in nature, where instead of the traditional method based on the wave function, the electronic system is calculated with an electronic density equation by which the computational complexity is strongly reduced. Figure 2 shows an overview of the characteristics and options for the theoretical models.

Recently developed ω B97X DFT methods,²² that generally outperform other and older equations (e.g. the popular B3LYP), make use of a systematically optimized function for the density function and one additional parameter in a second optimization step. These methods depend on the electron density behavior around the evaluation point, i.e. the location of the particle, instead of only the behavior at the evaluation point. ω B97 is the name of the specific long range function and the X indicates the use of an additional short-range correction parameter. For the method ω B97X-D, the '-D' indicates that

an additional empirical correction is added for dispersion.²³ This method is a so called Range Separated Hybrid Generalized Gradient Approximation (RSH - GGA), in which additional functions for the potential are applied.²³ Other and more advanced models are MP2 (*ab initio*, the simplest version of the Møller-Plesset involving the exact Hamiltonian instead of only the Hartree-Fock Hamiltonian) and T1 (combining Hartree-Fock geometries, and an approximation of the MP2 energy calculation based on an empirical correction).⁸

Isodesmic reactions are reactions where the formal bond count remains equal, such as proton transfer. For these isodesmic reactions, Hartree-Fock was found to be able to calculate the relative energy (i.e. compared to a different geometry, structural arrangement or the energy of the individual reactants) within reasonable accuracy compared to higher level calculations. Furthermore, HF is capable of accurately calculating conformational energy differences compared to experimental data (for the absolute energy HF is insufficient).^{18,24,25} For isodesmic reactions relative energy calculations may result in larger errors when DFT is applied, whereas for non-isodesmic reactions that involve net bond making or breaking MP2 or density functional models are required. In MP2 and DFT models additional wave functions are applied to complement the Hamiltonian of the Hartree-Fock model.^{18,24,25} All possible methods have in common that they are not able to (fully) describe the intermolecular interactions and potential functions, which is in general accounted for by applying force fields in the molecular modeling of chemical process conditions, that also have their limitations in applicability and are only available for selected cases.⁸

Figure 2 Overview of characteristics and options for the calculation methods.

3.3.2 Basis sets

There are several basis sets available within Spartan. Choosing more advanced models with more equations can improve results but also increases computation time. The simplest basis set available is the STO-3G basis set (based on Slater Type Orbitals (STO), where each of the basis functions is a contraction of three primitive Gaussian type orbitals (3G) to save computational costs¹⁷). The basis set 6-31G* contains more flexibility and polarization functions for all atoms except hydrogen and is a compromise between calculation speed and accuracy of the calculation. This is the most commonly applied basis set available in Spartan. The 6-31G* basis set implies that six functions are used for the description of each core atomic orbital and groups of three and one functions describe each of the valence-shell atomic orbitals (the s and three p orbitals). Furthermore the '*' indicates that d-type polarization functions are included for all non-hydrogen atoms (and '**' would refer to p-type polarization functions that can be applied for hydrogen atoms).⁸

Increasing the level of the basis sets can add other functions to the calculations such as polarization or diffuse functions.²⁴ For geometry calculations where no transition metals are involved the advantages of larger basis sets than 6-31G* for Hartree-Fock models are small.⁸ All calculations performed within Spartan are based on equations and models that are applicable to components in the gas phase. To calculate the energies for other conditions additional solvation models are available to add the energies for solvation to the gas phase energies. These solvation models will be described in section 3.3.3.

3.3.3 Solvation models

Within Spartan there are several options to incorporate solvation. In the default option the Conductor like Polarizable Continuum Model (C-PCM) is applied. Because this is a continuum model no specific interactions between solvent and solute are taken into account and no energy for solvation is reported. Other options for solvation are the SM5.4 model and MMFFaq model (a solvation method based on the Merck Molecular Force Field) derived from the semi-empirical SM5.4 model that is able to calculate the energy for solvation in water. These models are fast since the solvation energy is added after geometry optimization. SM8 and SM12 are solvation models that can also incorporate solvation in a set of organic solvents using the 6-31G* basis set, for these models it is also technically possible to optimize the geometry but this might be problematic due to the discontinuous nature of derivatives in the field used for modeling the electronic system.²⁴

3.3.4 Energy

The values for energy calculated by Spartan represent the total energy, which is the heat of the reaction that would form the molecules from a set of nuclei and electrons.²⁵ As these values are very large, in most cases the relative energy of the set of molecules is reported with respect to its reactants. For the Hartree-Fock model it is assumed that electrons move independently, which results in calculated values for the total energy that are too large. This can result in Hartree-Fock reaction energies that are less negative than experimental energies.²⁵ For DFT and MP2 models this is not the case.

Figure 3 Example of molecules built in Spartan'16 Parallel, with **a)** tripropylamine, **b)** acetic acid and **c)** the hydrogen bonded (dashed line) complex of tripropylamine and acetic acid.

3.3.5 Calculation tasks

After constructing the molecule in an initial geometry in Spartan, see for example Figure 3, the software can be used to perform several tasks. In most cases, first a geometry optimization is performed. Depending on the desired level of calculation, this should be performed first at a lower level before calculating at the desired level. There is a possibility of finding a local minimum in the geometry optimization. For this reason multiple starting geometries can be applied to compare the energy levels of the resulting geometries. Geometry optimization can also be performed applying solvation. After the geometry optimization the energy of the molecule(s) can be calculated. By comparing the energy of reactants and products the reaction enthalpy can be calculated. For the system in Figure 3, the calculated energy of the product in Figure 3c can be compared with those of Figure 3a and b.

3.3.6 Energy profiles

Energy profiles can also be calculated with Spartan, in which the distance between two molecules is constrained at a series of values and at each distance the geometry is optimized and the energy is calculated. For molecules that attract each other, an energy profile is shown in Figure 4. For a large distance between the molecules there is no interaction, which is in this case defined as an energy of 0. Reducing the distance results in attractive forces between the molecules, caused by a decrease in potential energy. At a certain point the molecules are too close and the potential energy is increasing, resulting finally in repulsive intermolecular forces. The depth of the energy-minimum indicates the bond-energy of the interaction between the two molecules.

Figure 4 Typical energy profile of two interacting molecules as a function of their intermolecular distance.

Figure 5 Spartan'16 Parallel model of tripropylamine (top left) and acetic acid (bottom right). The green flag indicates the constrained distance between both molecules.

3.4 Molecular modeling in the field of acid-base interactions for liquid-liquid extraction

3.4.1 Effect of chain length of the amine on interactions in complexes

The higher the level of calculation that is applied, the longer the computation time. In general, for geometry optimizations (except for transition metals) and conformational energy differences in organic compounds the calculation level of Hartree-Fock is sufficient.¹⁸ However, for specific cases, results may be improved by applying higher calculation levels such as DFT. Another option, as errors in the geometry only have a small effect on the thermochemical calculations, is to apply a lower level equilibrium geometry in the higher level thermochemical calculation. To reduce the computational time, techniques based on optimizing the initial geometry, reducing the degrees of freedom in the molecule and starting the calculation from a lower level are applied.^{18,25} Often also the chain lengths of molecules can be reduced to save computation time,²⁶ since the first methyl groups in a carbon chain are expected to affect the interaction more than the last methyl groups of a chain. The first methyl groups of a carbon chain in a tertiary amine have most likely also a strong influence on the angle of the nitrogen atom and it is thus better to apply tripropylamine (TPA) instead of ammonia or trimethylamine as a simplified amine. To validate this assumption, several calculations were performed and compared for a system of acetic acid and either trimethylamine (TMA), triethylamine (TEA), tripropylamine (TPA) or trioctylamine (TOA) using the DFT ω B97X-D 6-31G* level of calculation.²² For each of the cases, 2 local minima were found for the geometry (and energy) of the system, see Table 1. The first minimum is found at a smaller distance between the proton of the acid molecule and nitrogen atom of the amine, with which a larger interaction energy is associated. For further interpretation of the two minima that are calculated, see Chapter 5 of this thesis. Comparing the different tertiary amines, it is clear that all energies are in the same range and there is no clear trend with increasing or decreasing carbon chain length. For TPA two different geometries were applied (each related to a local minimum), one with a more round geometry (directly from Spartan's SSPD library based on equilibrium geometries, see Figure 3a) and one with a more open or flat geometry (see Figure 3c) that is also found in (larger) complexes, *vide infra*. These differences between the geometry of the tertiary amine alone and in a complex with the acids in larger complexes will be studied next.

Table 1 Interaction energy (kJ/mol) of complexation of acetic acid and tertiary amine, calculated with DFT ω B97X-D 6-31G* and CPCM with a 'polar solvent'.

Amine	1 st minimum	2 nd minimum
TMA	-61.76	-56.1
TEA	-68.39	-61.88
TPA	-54.91	-46.25
TPA* (open geometry. <i>vide infra</i>)	-60.84	-54.74
TOA	-67.22	-61.46

In larger complexes with TOA, the first acid is interacting with a direct bond between the acid and the amine, corresponding to an interaction energy of 74 kJ/mol. The next two acids are interacting with the first acid, corresponding to an interaction energy 65 kJ/mol. The 4th and the 5th acid are sequentially bonded to the 2nd and 3rd acid with an interaction energy of 48 kJ/mol. This means that the interaction energy per acid decreases upon binding of more acids. The bond length of the interaction between TOA and the first acid decreases from 1.081 to 1.051 upon interaction with more acids, indicating a stronger bond. At the same time the bond length from the oxygen atom to the proton increases, indicating a weaker bond between the acid anion and the proton. For interaction calculations of acetic acid with TOA, there is a difference in the interaction energy of the acids compared to TPA based calculations. For the first acid the interaction energy with TPA equals 53 kJ/mol, for the 2nd and 3rd acid 60 kJ/mol and for the 4th and 5th acid 43 kJ/mol. The calculated interaction energy with the 2nd up to 5th acid is similar to the case of TOA. For the first acid the energy is lower, because the calculated energy level of the TPA in the complex is relatively high as a result of a more open geometry that TPA has in the complex compared to TPA without a complex. This difference between TPA and TOA results from the molecule size and chain lengths in the final complex. When the interaction energy with the first acid is calculated based on the open geometry of TPA, an energy of 80 kJ/mol is found, similar to that calculated for TOA. This indicates that for the modeling of this acid-amine system TPA can be applied instead of TOA, if the open geometry is used.

3.4.2 Density functional theory (DFT) versus Hartree-Fock (HF) level of calculation

The energy profiles of the interaction between TPA and acetic acid for both the HF and the DFT model are shown in Figure 6a for solvation in 1-octanol and in Figure 6b for solvation in toluene. It can be seen that although there are some differences between the two levels of calculation, overall the interaction pattern is very similar. Analyzing the differences accurately, it can be seen that the negative interaction energy is smaller (the energy minimum is less negative) when the HF model is applied compared to the DFT model, which is the result from the assumption that electrons move independently. Comparing the two levels of calculation, differences can be observed, e.g. for 1-octanol (Figure 6a) two minima are visible in all calculations, although more pronounced in DFT calculations. The difference between the minimum at a distance of proton transfer (1 Å) and hydrogen bonding (2 Å) (see Chapter 5) is however less pronounced than with HF. Also in the rest of the energy profile the spreading of the calculated points is larger. For toluene (Figure 6b) DFT does not show an energy minimum at 1 Å and only at 2 Å, whereas the HF based calculations do show a local minimum at 1 Å, although it is very small relative to the absolute minimum at 2 Å. Nevertheless, when the differences between 1-octanol and toluene are compared for both models (excluding some outlying data points) the results are similar, i.e. for interaction in toluene the energy is lower at an intermolecular distance of 2 Å and for interaction in 1-octanol the energy is lower at an intermolecular distance of 1 Å. Thus, both levels of calculation show the main difference between 1-octanol and toluene, i.e. in 1-octanol proton transfer is the more pronounced mechanism of interaction. This implies that the effect of the diluent can be studied using both theoretical models. The modeling with the HF model is advantageous, because of lower computational intensity. When comparing the solvation models CPCM and SM8 in Figure 6 only small differences are visible, especially in the case of toluene (Figure 6b). For 1-octanol (Figure 6a) there is a difference in the absolute value of the energy, not in the profile.

a

b

Figure 6 Energy profiles for interaction of tripropylamine (TPA) and acetic acid calculated with Spartan'16 Parallel using different levels of calculation and solvation models in **a)** in 1-octanol and **b)** in toluene ($\square$ HF 6-31G* level with SM8 solvation, $\blacksquare$ HF 6-31G* level with CPCM solvation, $\circ$ DFT- ω B97X-D 6-31G* level with SM8 solvation and $\bullet$ DFT- ω B97X-D 6-31G* level with CPCM solvation). The dotted lines are added to guide the eye.

3.4.3 Effect of water

In (most) liquid-liquid extraction processes from aqueous solutions, water molecules are also present in the organic phase as a result of physical extraction or co-extraction²⁷ and these water molecules can also interact with the acid-base complexes. The effect of the presence of water molecules in the molecular modeling calculations was simulated for several systems of interacting acetic acid with a tertiary amine, with five water molecules around the interacting molecules in each of the calculations. For a system comprising of TMA and acetic acid the characteristic proton transfer shows a deeper energy valley in the presence of the water molecules, see Figure 7a. (HF 6-31G*, CPCM 1-octanol). This is most likely a result of stabilization of the acid-amine complex in the presence of water molecules. Similar results of a larger energy valley in the presence of water molecules were obtained for the same system of TMA and acetic acid in the CPCM solvation of water. Figure 7a also shows the results for the same system (with and without five additional water molecules) with SM8 solvation. The calculations without additional water molecules are also in this case comparable with those for CPCM solvation. However, when computing the model including five additional water molecules, the geometry optimization with SM8 appears to be problematic as no optimized geometry was found for this case (Figure 7a). The SM8 model is known for cases in which geometry optimizations are problematic (see also section 3.2.3).

a

b

Figure 7 Energy profiles calculated with Spartan'16 Parallel HF 6-31G* level with and without additional water molecules using different solvation models for 1-octanol for interaction of acetic acid and **a**) trimethylamine (TMA) and **b**) tripropylamine (TPA) (□ five water molecules and SM8 solvation, ■ no water and SM8 solvation, ○ five water molecules and CPCM solvation and ● no water and CPCM solvation). The lines are added to guide the eye.

Modeling of the interaction between tripropylamine (TPA) and acetic acid was also performed with SM8 and CPCM solvation (both at HF level) with and without water molecules present in the molecular structure. Because of the increased chain length of TPA compared to TMA, the degrees of freedom are increased, geometry optimization is more problematic and the computational time is significantly increased. Molecular modeling of the TPA - acetic acid interaction was also performed at the CPCM level, see Figure 7b in which results similar to those for TMA (see Figure 7a) are shown, i.e. the energy valley for the model with five additional water molecules is deeper compared to that for the model without the water molecules. Note that the absolute values for the interaction energy, i.e. the depth of the energy valley, are different for TMA and TPA. An attempt was made to also model the TPA based system with SM8 solvation. For the model without additional water molecules a clear energy profile was obtained (see Figure 7b) that is similar to that in Figure 7a. However, for computation with additional water molecules at SM8 level indeed a more problematic geometry optimization occurred. For this system, either no optimized geometry was obtained at all or the water molecules were not interacting with the acid-base complex in the optimized geometry and are located at increased intermolecular distance compared to the initial geometry. Thus, for this system no energy profile was obtained. Apparently this system of in total 7 molecules is too complex to obtain a converged geometry and energy calculation with MM at the HF level of calculation with SM8 solvation using a normal PC. The existence of local minima in the system energy upon varying the geometry or position of any of the identical water molecules can also impede convergence. Either a lower level of calculation should be accepted, less water molecules should be incorporated or more computational strength is required. Another option is to model the acid-amine complex with MM and then apply molecular dynamics calculations for the interactions with additional water molecules.

3.4.4. Diluent effect on acid-base interactions studied with molecular modeling

The effect of diluent on the complexation of a tertiary amine and acetic acid was also studied using molecular modeling, see Figure 8. For all solvents there are two local minima in the total energy of the complex with varying distance between the amine and acid. For 1-octanol the optimum configuration is at the typical distance of proton transfer, the energy minimum might even be lower when water molecules are incorporated in the modeled complex. For all other diluents the total energy of the

complex is lower with a typical intermolecular distance that corresponds to only hydrogen bonding, indicating that preferred state of the complex. This stronger interaction between acid and amine in 1-octanol can directly be related to the process of liquid-liquid extraction, as 1-octanol is a diluent that strongly increases the acid distribution compared to other diluents.²⁸

Figure 8 Effect of diluent on the energy profile for varying the distance between TOA and acetic acid, calculated with the HF 6-31G* wavefunction with SM8 solvation in the active protic solvents ● 1-octanol, ▲ chloroform; in the hydrogen bond accepting solvents ◆ ethyl acetate and ▼ MIBK; and in the inactive solvents △ toluene and □ heptane, using Wavefunction Spartan'16 Parallel. The lines are added to guide the eye.

3.5 Molecular modeling for solvent interactions in the field of extractive distillation

Next to application in the field of liquid-liquid extraction, molecular modeling can also be applied for interactions related to extractive distillation processes. However, in the field of extractive distillation simulations and predictions of the macro scale solvent effects are generally performed by Computer Aided Molecular Design (CAMD) with software packages such as ProCAMD®,²⁹⁻³² a tool within the ICAS® framework.³³ These predictive methods are based on the selectivity at infinite dilution and activity coefficients. For more information, see Chapter 9. At the molecular scale of extractive distillation processes, generally there are no strong interactions and true complex formation such as the LLX-related acid-base interactions for which molecular modeling calculations are successfully applied. It is however still possible to study solvent interactions by using molecular modeling and for example optimize the geometry of interacting molecules, study binding between solvent and mixture (component), and also calculate the interaction energy between the solvent molecules and mixture component(s). Pre-selection based on the type of interaction, i.e. solvents that show no interaction, solvents that interact through hydrogen bonding or solvents that show very strong interaction (proton transfer) with the mixture component(s) is thereby possible, using the calculation method presented in section 3.2.5. It is also possible to include multiple molecules in these calculations, in order to for example calculate the interaction energy between a molecule or complex of molecules and (multiple) solvent molecules.

3.6 Conclusion

Molecular modeling is potentially a powerful tool to study interactions between molecules at a molecular scale. It has a strong potential of application as a tool for process engineers in the field of interactions related to liquid-liquid extraction, e.g. for acid-base interactions, as well as for interactions between solvent and the mixture related to extractive distillation. Simplifications such as decreasing carbon chain length are required to minimize computational time and allow for the application of molecular modeling on a standard personal computer. Nevertheless, the results are related to the results for molecules without these simplified geometries, as long as the geometrical shape is applied that can also be found in the complex. For geometry optimizations, the existence of local energy minima can result in multiple solutions for optimized geometries, based on the initial geometry. To take this into account it is of importance to apply a series of initial geometries for MM calculations. The diluent effect can be modeled with the HF model, which has a strong advantage

with respect to computational costs compared to the DFT model. The differences in the MM results with the solvation models CPCM and SM8 are only small and show similar profiles, although for the active diluent 1-octanol there is a difference in the absolute value of the interaction energy. Moreover, geometry optimizations with larger molecules and especially with an increased number of molecules are problematic for the SM8 model. The expected increased interaction strength and complex stabilization as a result of water molecules that are present around the acid-base complex could be modeled by including five water molecules in the model.

References

- (1) Wu, X.; Chang, Z.; Feng, J.; Dang, H.; Uslu, H.; Li, W. *J Ind Eng Chem* 2018, *66*, 168-175.
- (2) Singh, M. B.; Nayak, S. G.; Kanthe, A. D.; Patil, R. B.; Gaikar, V. G. *J Mol Liq* 2017, *232*, 1-8.
- (3) Benay, G.; Wipff, G. *J Phys Chem B* 2014, *118*, 3133-3149.
- (4) Singh, M. B.; Patil, S. R.; Lohi, A. A.; Gaikar, V. G. *Sep Sci Technol* 2018, *53*, 1361-1371.
- (5) Uslu, H.; Datta, D.; Bamufleh, H. S. *Ind Eng Chem Res* 2016, *55*, 3659-3667.
- (6) Bandlamudi, S. R. P.; Cooney, M. J.; Martin, G. L.; Benjamin, K. M. *Ind Eng Chem Res* 2017.
- (7) Seduraman, A.; Wu, P.; Klähn, M. *J Phys Chem B* 2012, *116*, 296-304.
- (8) Morales Medina, G.; Martínez Rey, R. *CT F-Cienc Tecn Fut* 2009, *3*, 205-224.
- (9) Núñez-Rojas, E.; Flores-Ruiz, H. M.; Alejandre, J. *J Mol Liq* 2018, *249*, 591-599.
- (10) Sahu, P.; Musharaf Ali, S.; Shenoy, K. T. *Chem Prod Process Model* 2017, *12*,
- (11) Uslu, H. *Sep Purif Technol* 2017, *173*, 151-155.
- (12) Aono, S.; Kato, S. *J Comput Chem* 2010, *31*, 2924-2931.
- (13) Chagnes, A.; Moncomble, A.; Cote, G. *Solvent Extr Ion Exch* 2013, *31*, 499-518.
- (14) Cuypers, R.; Burghoff, B.; Marcelis, A. T. M.; Sudhölter, E. J. R.; de Haan, A. B.; Zuilhof, H. *J Phys Chem A* 2008, *112*, 11714-11723.
- (15) Cuypers, R.; Murali, S.; Marcelis, A. T. M.; Sudhoelter, E. J. R.; Zuilhof, H. *ChemPhysChem* 2010, *11*, 3465-3473.
- (16) Krzyzaniak, A.; Schuur, B.; Sukumaran, M.; Zuilhof, H.; De Haan, A. B. *Chem Engineer Trans* 2011, *24*, 709-714.
- (17) Ramachandran, K. I.; Deepa, G.; Namboori, K. *Computational chemistry and molecular modeling: principles and applications*, Springer: Berlin, 2008.
- (18) Hehre, W. J. *A Guide to Molecular Mechanics and Quantum Chemical Calculations*; Wavefunction, Inc. 18401 Von Karman Ave., Suite 370, Irvine, CA92612, 2003.
- (19) Sherrill, C. D. *An Introduction to Hartree-Fock Molecular Orbital Theory*, School of Chemistry and Biochemistry, Georgia Institute of Technology, 2000.
- (20) Hartree, D. R. *Math Proc Cambridge* 2008, *24*, 111-132.
- (21) Fues, E. *Z Phys* 1922, *11*, 364-378.
- (22) Chai, J.-D.; Head-Gordon, M. *PCCP* 2008, *10*, 6615-6620.
- (23) Lutsker, V. *Range-separated hybrid functionals in the density*

- functional-based tight-binding method*. University of Regensburg, 2015.
- (24) Wavefunction, I. In *Spartan'16 Help*; Wavefunction, Inc.: Irvine, Ca., 2016.
- (25) Wavefunction, I. Spartan '16 Tutorial and User's Guide: <http://www.wavefun.com/>, 2016.
- (26) GhéLis, C.; Yon, J. *Protein Folding*; GhÉLis, C.; Yon, J., Eds.; Academic Press, 1982, pp 177-220.
- (27) Tamada, J.; King, C. *Ind Eng Chem Res* 1990, *29*, 1333-1338.
- (28) Sprakel, L. M. J.; Schuur, B. *Sep Purif Technol* 2019, *211*, 935-957.
- (29) Lei, Z.; Li, C.; Chen, B. *Sep Purif Rev* 2003, *32*, 121-213.
- (30) Brignole, E. A.; Bottini, S.; Gani, R. *Fluid Phase Equilib* 1986, *29*, 125-132.
- (31) Pretel, E. J.; López, P. A.; Bottini, S. B.; Brignole, E. A. *AlChE J* 1994, *40*, 1349-1360.
- (32) Lek-utaiwan, P.; Suphanit, B.; Douglas, P. L.; Mongkolsiri, N. *Comput Chem Eng* 2011, *35*, 1088-1100.
- (33) Harper, P. M.; Gani, R. *Comput Chem Eng* 2000, *24*, 677-683.

4

Solvent developments for
liquid-liquid extraction of carboxylic
acids in perspective

Abstract

The growing desire to produce organic acids through fermentation routes, as a starting point for bio-based plastics, has revived the scientific attention on carboxylic acid removal from aqueous streams. One of the main technologies to recover carboxylic acids from diluted aqueous streams is liquid-liquid extraction (LLX). In this review, solvent developments for LLX of carboxylic acids are reviewed. In the past decades, a significant number of research papers have appeared, describing completely new solvents such as ionic liquids, as well as improvements of the traditional state-of-the-art solvent systems comprising of amines and organophosphorous extractants in diluents. The state-of-the-art technology for acid extractions has long been using trioctylamine (TOA) — or Alamine 336, a commercial mixture of trialkyl amines — as the complexing agent. However, with dropping acid concentrations, the economic feasibility of the TOA based processes is compromised. This review discusses three main categories of solvents, i.e. composite solvents containing nitrogen based extractants, phosphorous based extractants and ionic liquids, and includes a discussion on solvent property models that may aid solvent selection. Furthermore, regeneration strategies are discussed, aiming to provide direction towards regenerations that do not further dilute streams that are already diluted before the LLX process. The main conclusion with respect to solvent regeneration when back-extraction is applied, is that solvent-swing strategies should be applied that maximize the ratio between the acid distribution coefficient in the forward extraction and in the back-extraction at minimal energy cost. This appears to be through evaporation of a part of the diluent after the primary extraction.

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4.1 Introduction

Organic acids are important building blocks for a range of other chemicals in industry, and are produced in considerable volumes. For example, the production of acetic acid by petrochemical processes was 10.6 million ton in 2008.¹ The acetic acid is, among others, applied in the production of acetic anhydride, the feedstock to produce salicylic acid and acetaminophen,² monochloro acetic acid³ and used as solvent for terephthalic acid production.² Lactic acid is used as a building block for the synthesis of polylactic acid (PLA),⁴ and as a precursor for acrylic polymers and polyesters.⁵ Another example of organic acid used as a building block is succinic acid, used for the production of polysuccinate esters and polyamides.⁶ Butyric acid is used as food additive and wildlife repellent.⁷ Citric acid is also used in the food industry, and one-third of the total production is used to substitute phosphorous in detergents.⁸ Levulinic acid (4-oxopentanoic acid) is used as a chiral reagent in the production of polymers and to produce methyl tetrahydrofuran.⁹

The current industrial production routes vary from acid to acid, where acetic acid is mainly produced from fossil feedstock through carbonylation of methanol,¹⁰ and lactic acid is currently mainly produced through fermentation.¹¹⁻¹³ Also for the acids that are currently mainly fossil based, there is incentive to produce them from renewable sources by green routes through fermentation. Bio-based plastics, e.g. based on succinic acid or adipic acid¹ are important products for which recovery strategies of the acid monomers are essential, because of the low concentrations after fermentative production. Also for lignocellulosic biomass derived acid production, e.g. levulinic acid¹⁴⁻¹⁶ and 2,5-furandicarboxylic acid,¹⁷ recovery from complex streams is challenging.

Separation by distillation requires evaporation of a large water fraction. Furthermore, several of the acids produced will decompose when exposed to elevated temperatures for longer time. Suitable separation techniques are based on the affinity of the solutes towards an affinity agent. Both liquid-liquid extraction (LLX) and adsorption are examples of affinity separations used for acid recovery,^{18,19} and LLX of organic acids from aqueous solutions can be applied to recover the acids or to concentrate them from waste streams, fermentation broths or leachates.²⁰

LLX of carboxylic acids has been practiced for many decades, and over the years various types of solvents have been applied, including physical solvents such as ethyl acetate and methyl *tert*-butyl ether (MTBE),²¹ and reactive solvents that form complexes with the acids.²² Often reactive solvents are

composite solvents, containing an extractant that forms complexes with the acids, and a diluent facilitating the complexation.²³⁻²⁶ In the past decade a third solvent class has appeared in the field of acid extractions, i.e. ionic liquids (ILs). With the seminal paper by Marták and Schlosser²⁷ it was shown that phosphonium ionic liquids show extremely high distribution ratios (the ratio of the acid concentration in the extract phase over the raffinate phase, see eq (1)) at very low acid concentrations, which is beneficial for the recovery from dilute streams. ILs may be applied in their pure form, but also diluted with a co-solvent or diluent. Considering the (strong) intermolecular interactions between the ions of the ILs and the carboxylic acids, ILs should be considered as a new class of reactive solvents for carboxylic acids. In the same time frame, also new reactive solvents have appeared,²⁸⁻³⁰ and other acids have been extracted with more traditional solvents.^{20,31-36} An overview of the recently reported solvents, i.e. extractants and diluents is presented in Figure 1. All the carboxylic acids that are referred to in this review are shown in Figure 2.

With all these parallel solvent developments, and the growing interest in bio-based acids, a comprehensive review can provide a perspective on the field of carboxylic acid extraction and future research directions. In the last decade, several reviews have appeared on recovery of metabolites from fermentation broths,^{19,37} and in 2005 a review on acid recovery through membrane based solvent extraction and pertraction appeared,³⁸ but in the recent years, no comprehensive review focusing on solvents for acid extraction has appeared. With this review, we intend to provide a comprehensive overview of the strategies that can be followed for carboxylic acid extraction, and the review of the literature on this topic includes a few important older papers such as that of Barrow and Yerger³⁹ published on the mechanism in acid extraction in 1954, and some of the work by King from the late 1970s and early 1990s,^{23-26,40-44} but mostly spans the last few decades.

After a LLX unit operation, the acid is dissolved in the solvent, and in recognition of the need to couple the LLX step to a solvent regeneration step, understanding extraction mechanisms and approaches to facilitate solvent regeneration are emphasized. In the following subsections, first the theoretical framework is discussed. Then effects of solvent composition and extraction conditions are discussed. In the last subsection, solvent regeneration strategies are discussed, their energy requirements are compared, and a perspective for future research is formulated.

Figure 1 Chemical structure of **a)** extractants used in reactive extraction, **b)** ionic liquids and **c)** physical solvents and diluents.

Figure 2 Structures of carboxylic acids reported in liquid-liquid extraction literature.

4.2 Theoretical framework

Key LLX processes for carboxylic acids that have been reported in the literature, include those for acetic acid,^{23,28,45-49} succinic acid,^{25,26,50,51} lactic acid,^{52,53} propionic acid⁵⁴ and citric acid.^{55,56} Most extraction systems contain an amine based extractant because of the high distribution ratios that can be obtained with tertiary amines. They exhibit a high extraction efficiency and high selectivity at room temperature, allowing them to concentrate the product at room temperature, after which the solutes can be back-extracted, e.g. at elevated temperatures.⁵⁷ The state-of-the-art LLX solvent technology is based on complexation with TOA, or the commercially available equivalent Alamine 336 (a mixture with C₈-C₁₀ alkyl chains), as the complexing agent.^{5,20,23,24,26,33,41,43,45,47,48,53,58,59} However, other types of extractants are also used for the extraction of carboxylic acids. Examples include trioctylphosphine oxide (TOPO),¹⁸ tributylphosphate (TBP) or mixtures with TOA and TBP,⁶⁰ quaternary ammonium salts^{61,62} and ionic liquids (ILs).^{27,62,63} Most processes, especially for very diluted acids, face a

challenging regeneration, e.g. TOA based^{25,41,45,64} but also TBP based.³⁵ The complexes between these extractants and acids are based on very strong bonds, resulting in regeneration difficulty.^{45,65}

Next to the extractant, the diluent is important for LLX of acids, and a proper diluent choice can improve the physical properties of the solvent such as the density and viscosity, and in addition promote extraction by improving solvation of the acid-extractant complex.^{26,61} Although scientifically of interest, some reported diluents are less suitable for operation at a commercial scale. For example, chlorinated hydrocarbons such as chloroform and dichloromethane (DCM) are (highly) toxic and can have severe environmental impacts. Several ethers are either too volatile, toxic and/or flammable, and MIBK (methyl isobutyl ketone) is a non-biodegradable compound.⁵ Next to toxicity, the affinity for water may complicate extraction processes, e.g. for solvents like MIBK and ethyl acetate.⁴⁷ Despite the fact that many of the reported systems are eventually not desirable in industrial practice for above mentioned safety, health, environmental and economic reasons, an overview of the vast number of studies on extraction mechanisms and extraction performances using these solvents certainly can assist in directing towards new solvents. Therefore, in this section, key extraction and process parameters are described, as well as the reported mechanisms in literature, also for less environmentally benign diluents.

4.2.1 Key extraction process parameters

Although mass transfer rates can play a key role in LLX processes, these are not only solvent dependent, but also largely dependent on equipment and operational parameters. Because this review focuses on solvent developments, the theoretical framework is limited to equilibrium extraction parameters. A key parameter is the distribution coefficient, defined in eq (1) as the ratio of the concentrations in the extract phase and the raffinate phase, where $[HA]$ is the concentration of HA in the extract phase and $[\overline{HA}]$ the concentration in the raffinate phase (summed concentration of all forms, e.g. dissociated and non-dissociated in the aqueous phase, and complexed and free acid in the organic phase).

$$K_{D,a} = \frac{[HA]}{[\overline{HA}]} \quad (1)$$

Commonly used units are mol/L and mass fraction. The extraction efficiency is defined in eq (2) as the ratio of the concentration of a compound HA in the extract phase over the initial concentration of HA in the aqueous feed phase, $[HA]_0$, multiplied by the solvent-to-feed flow ratio S/F.

$$E(\%) = \frac{\left[\overline{\text{HA}} \right]}{\left[\text{HA} \right]_0} \cdot \frac{S}{F} \cdot 100\% \quad (2)$$

The extraction selectivity towards compound a over b is expressed as the ratio of their distribution coefficients, in eq (3).

$$S_a = \frac{K_{D,a}}{K_{D,b}} \quad (3)$$

For extraction - back-extraction cycles, the ratio of the acid concentration in the overall extraction process, including the extraction and regeneration of the solvent, is defined as the concentration factor CF in eq (4).

$$CF = \frac{\left[\text{HA} \right]_{\text{product}}}{\left[\text{HA} \right]_{\text{feed}}} \quad (4)$$

Next to the equilibria that are involved in the extraction of acids, also equilibria for the co-extraction of other species present should be accounted for, as well as leaching of solvent into the aqueous stream. The mutual solubility of the extractant and diluent in the solvent and water are key parameters to describe these process features, but also the properties of the acid may affect water co-extraction.

4.2.2 Reactive extraction mechanisms

LLX of acids by reactive composite organic solvents can be represented as in Figure 3,^{28,48} including aqueous phase acid dissociation (eq (5)), physical partitioning (eq (6) and (7)), and organic phase complexation (eq (8) and (9)), where HA is the acid, B is the extractant and HA_nB_m represents complexes with stoichiometry n,m.

$$K_m = \frac{\left[\overline{\text{HA}} \right]}{\left[\text{HA} \right]} \quad (7)$$

$$K_c = \frac{\left[\overline{\text{HA}_n\text{B}_m} \right]}{\left[\overline{\text{HA}} \right]^n \left[\overline{\text{B}} \right]^m} \quad (9)$$

Depending on the extraction conditions, a variety of complexes may be found for some extractants with varying stoichiometry n and m. To describe

the equilibrium partitioning, sometimes a single equilibrium equation is defined that represents an average of multiple equilibria taking place simultaneously.⁶⁶ Alternatively, the multiple equilibria may be described separately.^{48,67} The extent of complex formation is governed by the solubility of the extractant in the diluent and the strength of the interaction between the extractant and the solute. Two types of binding are mainly observed, i.e. through proton transfer and hydrogen bonding.^{24,39,68} A combination of these two interactions is also possible,²⁴ and in the upcoming subsections, for the individual solvent classes (amines, phosphorous based extractants, and ILs), the mechanisms are discussed in more detail.

Figure 3 Schematic overview of the phase equilibrium and complexation reactions involved in the extraction of an acid HA from an aqueous solution into an organic phase containing an extractant B .

The temperature dependency of the extraction equilibrium is governed by the enthalpy change of the complexation reaction,⁴³ and can be determined using the Van 't Hoff equation. Through eq (10) and eq (11), eq (12) can be derived, showing the influence of the reaction enthalpy on the temperature dependency of the equilibrium constant, assuming constant enthalpy.

$$\Delta G = \Delta H - T\Delta S \quad (10)$$

$$\Delta G = -RT \ln K \quad (11)$$

$$\ln K = \frac{-\Delta H}{RT} + \frac{\Delta S}{R} \quad (12)$$

Then for two different temperatures, T_1 and T_2 , the ratio of K_2/K_1 is defined in eq (13).

$$\ln \frac{K_2}{K_1} = \frac{-\Delta H}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right) \quad (13)$$

Therefore, in the case of a small enthalpic effect, the change of the equilibrium acid distribution with changing temperature is also limited.⁵

4.2.2.1 Mechanisms for complexation with phosphorous based extractants

Examples of phosphorous based extractants are TOPO and TBP, see Figure 1. These solvents can strongly solvate the acid in the organic phase, thereby increasing the solubility and the distribution coefficient of the acid.¹⁸ Hydrogen bonded organic phase complexes (confirmed by ³¹P-NMR and FTIR spectroscopy^{69,70}) can be formed with varying stoichiometry, for which the generic equilibrium relations in eq (8) and (9) are valid.

For aliphatic monocarboxylic acids the formed complexes have (1,1)-stoichiometry,⁷¹ so $n = m = 1$, and Hano et al.¹⁸ assume the same stoichiometry for carboxylic acids with additional side groups. For complexation of aliphatic monocarboxylic acids with TBP diluted in dodecane, Morales et al.⁷² report an apparent (1,1)-stoichiometry, but a higher stoichiometry was observed for lactic acid due to additional interaction of the hydroxyl group with the extractant.⁷²

Hano et al.¹⁸ reported that for the extraction of carboxylic acids by TOPO in hexane, the extraction equilibrium is determined primarily by the hydrophobicity of the acids and not by the pK_a value (as is the case for systems with tri-*n*-octylamine (TOA), *vide infra*). This supports the finding of Scheler et al.⁶⁹ that the complexation is through hydrogen bonding. Hano et al. also report that the complexation constant for the complexation of lactic acid with TOPO decreases with decreasing polarity.

Also for TBP in hexane, no carboxylate signals were observed in FTIR⁶⁰ spectra of various carboxylic acid extractions, indicating a hydrogen bonding mechanism. Ingale et al.⁷⁰ suggested Lewis base TBP complexes with acetic acid and propionic acid based on FTIR spectral data. Kyuchoukov et al.⁷³ fitted complexation of dicarboxylic acids (itaconic, maleic, malic, oxalic, tartaric and succinic acid) with TBP in dodecane on LLX experimental data and found a varying stoichiometry ((1,1) and (1,2)-complexes) depending on the concentrations of both extractant and acid.

4.2.2.2 Mechanisms for complexation with amines

The nature of the diluent is one of the key factors that influence the mechanism of amine-carboxylic acid complexation. Diluents can be classified as dissociating and non-dissociating, and as active and inactive. Dissociating solvents reduce the interactions between the oppositely charged ions through their high relative permittivity, and facilitate acid dissociation upon complexation (see Figure 4 mechanism a), while solvents with a low relative permittivity suppress dissociation,⁷⁴ resulting in complexation between the amine and non-dissociated carboxylic acids.³⁹ Active diluents can participate in complex formation, e.g. through hydrogen bonding, and inactive diluents not. However, complexes in inactive diluents are seldom 1:1 in stoichiometry, and when the diluent is not stabilizing the extractant-acid complex, typically a second acid is involved that stabilizes the complex through hydrogen bonding (or even more acid molecules), see mechanism b in Figure 4.²⁴ Stabilization through active hydrogen bonding by the diluent has been reported for chloroform and octanol,^{24,75} and is displayed in mechanism d in Figure 4.³⁹ IR spectra support the proton transfer in this mechanism,⁶⁸ and indicate simultaneous and competitive occurrence of mechanisms c and d, e.g. for chloroform.³⁹

Figure 4 Mechanisms for the interaction between acetic acid and triethylamine, **a)** in dissociating solvents, **b)** in a completely inactive diluent, **c)** in a non-dissociating solvent and **d)** in chloroform.^{24,39}

The nature of the binding between the amine and the first acid can thus be ion pairing or hydrogen bonding, and the equilibrium constant strongly increases with decreasing pK_{a} .^{24,39} For higher order (2:1 and more) complexes, the second and further acids are complexed mainly through hydrogen bonding, and the equilibrium constant for formation of the (2,1)-complex from a second acid with the (1,1)-complex is barely dependent on the pK_{a} of the acid. Due to the increasing level of organization in active diluents upon complex stabilization by the diluent, the entropy decreases. Association of another acid molecule to this complex requires breaking of the stabilizing diluent-complex interaction, and therefore (1,1)-complexation is mostly found in active diluents.^{24,43} For example, propionic acid-TOA complexes are (1,1) ion pairs in 1-octanol,⁷⁵ and for acetic acid-TOA next to (1,1) only (1,2)-stoichiometry is reported in the proton-donating diluent propanol,⁵⁹ while in the inactive diluents hexane, cyclohexane, toluene and MIBK also larger (2,3)-complexes have been reported.⁵⁹ Using only inactive diluents may, next to lower acid distribution ratios, result in the formation of a third phase.⁷⁶ When aromatic compounds are involved, π -interactions can occur that result in $K_{1,1}$ values that are slightly higher than for systems with aliphatic diluents.²⁴

At very high acid concentrations, multiple acids may form a complex with a single amine. Overloading of acids is especially likely in aprotic diluents. In overloaded complexes, e.g. a (3,1)-complex, the third acid is cyclically bound to the (2,1)-complex, see Figure 5. In this cyclic formation the protonated amine can interact with the first and the third acid alternatingly, thereby stabilizing this complex.²⁴

Figure 5 Acetic acid overloading mechanism on triethylamine, in the (3,1)-complex the third acid is cyclically bound to a (2,1)-complex. TEA is triethylamine and HA is acetic acid.²⁴

When, instead of using eq (8) and eq (9) with the average (n,m)-stoichiometry, all complexation steps are considered individually, a more sophisticated model is realized, as exemplified in eq (14)-(16).

The corresponding complexation constants are defined in eq (17)-(19), respectively.

$$K_{1,1} = \frac{[\text{HA} \cdot \text{R}_3\text{N}]}{[\text{HA}][\text{R}_3\text{N}]} \quad (17)$$

$$K_{2,1} = \frac{[(\text{HA})_2 \cdot \text{R}_3\text{N}]}{[\text{HA}][\text{HA} \cdot \text{R}_3\text{N}]} \quad (18)$$

$$K_{3,1} = \frac{[(\text{HA})_3 \cdot \text{R}_3\text{N}]}{[\text{HA}][(\text{HA})_2 \cdot \text{R}_3\text{N}]} \quad (19)$$

For dicarboxylic acids, self-stabilization by interaction of both acid groups may occur, but depends on the molecular structure. For self-stabilizing dicarboxylic acids, such as maleic and succinic acid, (1,1)-complexes are common,²⁴ whereas fumaric acid cannot self-stabilize because of the double C = C bond in the molecule and forms (2,2)-complexes with amines instead.

For citric acid, a tricarboxylic acid, (structure in Figure 2), overloading of amines on the acid has been reported,⁵⁵ and in active diluents (1,1)-complexes and (1,2)-complexes are formed, whereas in inactive diluents also the agglomerated (2,3)-complexes are observed.⁵⁵

In literature, the equilibria are sometimes defined in a way that they span two phases,^{18,34,48,73} for example the apparent equilibrium constant of Qin et al.,⁴⁸ which is defined in eq (20), where TOA and the complexes in the organic phase are in equilibrium with the aqueous acid.

$$K_{p,1} = \frac{[\text{TOA} \cdot \text{HA}_p]}{[\text{TOA} \cdot \text{HA}_{p-1}][\text{HA}]} \quad (20)$$

4.2.2.3 Mechanisms for extraction with ILs

The interactions and physical properties of ILs with acids and water have been studied extensively, either by molecular simulations,^{77,78} experimentally⁷⁹ or combined.⁸⁰ Structuring and nano-structuring in ILs, and clustering effects are well known phenomena in ILs.⁸¹ The presence of reverse micelles was shown using dynamic light scattering in both phosphonium ionic liquids^{27,82,83} and ammonium ionic liquid.⁸⁴ Chen et al.⁷⁹ also report on clusters that are formed in many imidazolium ILs and studied the effects of these clusters on the properties and geometry of ILs. The formation of clusters is a result of the combination of electrostatic and intermolecular forces, such as hydrogen bonding, π -bonding, polarization, but also non-electrostatic interactions.⁷⁹

Two mechanisms play a role in the extraction of acids by ILs, i.e. the formation of complexes between IL and the organic acid, and the formation of reverse micelles that include the acid.⁶³ The formation of reverse micelles also increases the solubility of water, and also for water co-extraction, two possible mechanisms exist, i.e. molecules of water can be part of a complex between acid and IL, and water can be present in the reverse micelles. When the acid is extracted, complexes between the IL and acid are formed, breaking the reverse micelles. Complexes containing up to three lactic acid molecules, 2 water molecules and the IL were suggested.^{27,85}

A more detailed mechanism for the extraction of butyric acid with the trihexyl tetradecyl phosphonium di-2,4,4-trimethylpentyl phosphinate ($[P_{666,14}][Phos]$) IL was proposed by Marták and Schlosser.⁸⁶ They considered also IL diluted in dodecane next to pure IL. In their mechanism, they included also complexes between acid and IL with up to 11 acid molecules, next to physical extraction of butyric acid by the diluent and the apolar domains of the IL. These complexes aggregate through hydrogen bonding with water molecules. For water (co-)extraction they also suggest two mechanisms: competition with acid molecules and co-extraction with butyric acid. When dodecane was applied as a diluent, the dodecane molecules are located near the alkyl chains of the IL and extracted water molecules are localized in polar areas of the IL. This means that the solvent forms a non-homogeneous, pseudo-binary phase.^{78,82}

Reyhanitash et al.⁸⁷ studied on acetic acid solutions in $[P_{666,14}][Phos]$ and, using isothermal titration calorimetry, they measured thermal activity up to an overall stoichiometry of 5:1 (acid:ion pair). With thermal activity measured up to this stoichiometry, it is well possible that higher order complexes are possible for both acetic acid and butyric acid. In contrary to the suggestion by Marták and Schlosser,⁸⁶ they found that not all acid molecules are bound to the complexes through hydrogen bonding, but NMR studies revealed that the first acid is also (partly) exchanging its proton with the phosphinate anion, resulting in a complex ensemble of interactions in which both proton exchange and hydrogen bonding interactions play important roles.⁸⁷

4.2.3 Solvent properties and implications thereof on LLX processes

In the previous subsections, mechanisms for extractions have been discussed, including different mechanisms for the same solute, depending on the nature of the diluent. In this subsection characterization of solvent properties and implications thereof on LLX processes are discussed.

4.2.3.1 Solvent property models

In a solvent for LLX both the extractant and the diluent are of importance. There are different types of extractants, and the type of extractant also determines the mechanism of extraction. Since this review focuses on extraction of acids, the basicity of the extractants is the key parameter in the LLX process. Brønsted bases interact through proton transfer from the acid, whereas Lewis bases interact with carboxylic acids through electron pair donation to form an adduct. For the selection of affinity scales, Laurence et al.⁸⁸ suggest to classify acids on hardness and strength. The hardness of acids distinguishes between the size, polarizability and type of outer electrons. Carboxylic acids are hard acids with a small size, high positive charge on the acceptor atoms and low polarizability, these acids do not have outer electrons that are easily excited.⁸⁹ Two affinity scales are suggested for the scaling of bases for LLX of hard acids, the BF_3 -affinity scale for strong acids or strong interactions and the pK_{BHX} scale, which is the hydrogen bond basicity scale for hydrogen bonding of weak acids.⁸⁸ The BF_3 -affinity is defined as the negative enthalpy of complexation with BF_3 diluted in dichloromethane at 298 K (thus the value reported is positive for an exothermic complexation). The pK_{BHX} hydrogen bond basicity is based on the Gibbs energy of hydrogen bond formation of the Lewis base with 4-fluorophenol in CCl_4 at 298 K. The scaling of the extractants TOA, TOPO and TBP according to these scales is shown in Table 1.⁸⁹

Table 1 BF_3 -affinity (kJ/mol) and pK_{BHX} for trioctylamine (TOA), trioctylphosphine oxide (TOPO) and tributylphosphate (TBP).⁸⁹

	BF_3 -affinity (kJ/mol)	pK_{BHX}
TOA	135.87*	1.57
TOPO	119.28**	3.59
TBP	84.75***	2.66

*based on triethylamine, **based on triethylphosphine oxide, ***based on trimethylphosphate

Next to the extractant, the diluent affects the equilibrium in LLX to an important extent, i.e. being an active or inactive diluent has a significant impact on the mechanism of complexation. In order to predict diluent activity, the molecular properties should be understood. Several properties can be used to describe the nature of the diluents used in LLX of carboxylic acids, for example properties like polarity,^{29,45,61} the dielectric constant,⁷⁴ proton affinities,⁹⁰ hydrogen bond accepting and donating ability,^{91,92} and parameters like the octanol-water partitioning coefficient $\log P_{\text{o/w}}$ Hilde brand's solubility parameter,⁹³ Hansen parameters,⁹⁴ Schmidt's parameters DP and DP*,^{95,96} Kamlet-Taft parameters,⁹¹ acceptor and

donor number (AN and DN),⁹² Kosower's Z parameter⁹⁷ and the Dimroth-Reichardt E_T parameter⁹⁸ are in use. Table 2 lists the most commonly used parameters for characterization of diluents.

The linear solvation energy relationship (LSER)^{34,91,99} is used to correlate the solvation of the solute to a linear function of several solvent parameters. Use of LSER requires solubility parameters as input, e.g. the diluent parameters by Schmidt, to quantify the influence of the diluent on the solvation of an acid-amine complex and the solvation of the anion,^{95,96} or the solubility of water in the solvent.⁹⁵ The LSER can also be used in combination with Hildebrand-Hansen solubility parameters for alcohol diluents to predict the distribution coefficients for these systems.¹⁰⁰ Bizek et al.⁹⁵ modified the LSER to include the fraction of amine in the organic phase and also correlated the co-extraction of water with the composition of the organic phase.

To compare the effect of various diluents, the equation used by Bizek et al.⁵⁵ for the LSER, can be written as eq (21).

$$\ln K = \ln K^0 + \alpha DP^* \quad (21)$$

In this equation K is the equilibrium constant of the complexation in the organic phase. The equilibrium constant K^0 of a reference diluent is adjusted by the value α for a given solute and extractant, and DP^* is an empirical parameter that depends on the solvation of the acid-amine complex. The resulting equilibrium constant K is diluent specific. This model has been expanded by including more empirical values for anion solvating abilities of proton donating solvents.⁵⁵

LSER was also used in combination with the Kamlet-Taft parameters, α the hydrogen bond donor parameter, β the hydrogen bond acceptor parameter and π^* the polarizability parameter,⁹¹ as in eq (22), where Y is a property such as $\ln K_D$ of a specific compound in the solvent, proportional to the Gibbs energy. Y^0 describes this property in a hypothetical solvent with zero values for α , β and π^* , i.e. an apolar solvent without hydrogen bonding capability.

$$Y = Y^0 + a\alpha + b\beta + s\pi^* \quad (22)$$

The coefficients a , b and s are resulting from a fit to experimental data on interactions of the described property.⁹¹

Starting with the LSER equation as given in equation (22), Abraham and co-workers¹⁰¹⁻¹⁰⁵ have further expanded the LSER with molecular volume and the molar refractivity, and have shown that by linearly combining the five solute descriptors and the corresponding five solvent parameters (eq (23)), it is possible to roughly predict the partitioning of a solute into a solvent.

$$\log P = c + eE + sS + aA + bB + vV \quad (23)$$

In eq (23) $\log P$ is the partition coefficient between the solvent and water. Under several assumptions; i.e. no formation of hydrate or solvate, the solvent is not extremely water soluble, there is no dissociation or association, the same model can be used to determine the molar solubility of the solutes in organic solvents S_s , by using eq (24).¹⁰⁶

$$\log S_s = \log S_w + c + eE + sS + aA + bB + vV \quad (24)$$

In this equation S_w is the molar concentration of solute in water, the solvent coefficients are c , e , s , a , b and v , and the parameters E , S , A , B and V describe the solute properties excess molar refractivity, polarizability, overall hydrogen bond acidity, overall hydrogen bond basicity and the McGowan characteristic volume, respectively.¹⁰¹ Solvent parameters are to be obtained by fitting partitioning data of a series of solutes with known descriptors. This procedure is still reasonably labor intensive, and for composite solvents, it is questionable how well the extractability can be linearized. Generally, tools like the Abraham model can give good guidance in solvent selection and design, but not more, since quantification of distribution ratios is still reasonably inaccurate.

Another tool that has been developed in the past decades is the CONductor like Screening MOdel for Real Solvents (COSMO-RS),¹⁰⁷ which reduces the labor intensity for the researcher, and predicts distributions based on quantum chemical calculations and statistical thermodynamics. Predictions are however only qualitative in nature and to be used with caution when it comes to accurately quantifying extraction results.^{108,109} Comparison of various solvents with COSMO-RS though, especially when from the same family, often works satisfactory.¹¹⁰

4.2.3.2 Solvent dependent extraction phenomena

Next to acid - extractant complexes, also acid dimerization and water co-extraction are factors affecting extraction. These are diluent-dependent and discussed in this subsection.

Dimerization

With IR spectroscopy Fujii et al.¹¹¹ found that dimerization constants of acetic acid in organic solvents increase with decreasing solvent activity, taking into account both dipole interactions and hydrogen bonding. In more active solvents, dimerization is less pronounced due to competition with diluent interactions, such as dipole-hydrogen bonding interactions.⁵⁴ In the inert diluent n-hexane, strong dimer complexes form by double hydrogen bonds. Acid dimerization generally decreases with increasing temperature,

especially in solvents with low dielectric constants, which is due to the increasing entropy with increasing temperature. In solvents with higher dielectric constants, also the effect of temperature on the dielectric constant should be taken into account.¹¹²

Water co-extraction

The diluent also influences the water co-extraction that occurs in the process of LLX. For the extraction of citric acid with TOA it was found that water co-extraction increases in the order *chloroform* < *aromatics* < *dichloromethane* < *MIBK* < *1-octanol*.⁵⁵ This order is described by the hydration coefficients and the physical solubility of water in the solvents. For succinic acid extraction with Alamine 336, a similar water co-extraction trend was obtained, *heptane* < *chloroform* < *dichloromethane* < *nitrobenzene* < *MIBK* < *1-octanol*, following the diluent water solubility trend.¹¹³ At low acid concentrations, monocarboxylic acids show less water co-extraction than dicarboxylic acids, which is probably a result of the association between the water molecules and the carboxylate groups.⁴³

Active diluents increase acid distribution, which also results in increased water co-extraction.¹¹³ Opposing trends have been reported for the temperature-effect on water co-extraction. At low (<0.5 wt%) water concentrations in chloroform, the co-extraction increased up to 50 °C for succinic acid extraction with a tertiary amine while for the same system in MIBK there was no effect of temperature on the water co-extraction.¹¹³ At much higher concentrations (5-10 wt%) in hexanol no significant temperature-effect on water co-extraction was found for gallic acid extraction using TOA, TBP and Aliquat 336,⁶² while increasing extractant concentrations significantly increased water co-extraction.⁶²

There is no single general parameter that can describe the effect of the diluent on the water co-extraction. In most cases, a combination of parameters or specific interactions plays a role, including structuring of solvents, which has also been reported for ILs.¹¹⁴ Therefore, it is important to obtain more insight into the different effects that the diluent has on the extraction mechanism. For example, some very hydrophobic phosphonium ILs only dissolve in water on a ppm level, but relatively large amounts of water are co-extracted.^{46,115} The co-extraction of water is due to the ionic charges, that allow creation of local hydrophilic spots and depending on composition, micelle formation,^{82,84,86} occurrence of giant vesicles,¹¹⁶ or even formation of bicontinuous phases with continuous hydrophilic and hydrophobic domains.¹¹⁷ Ananikov and co-workers¹¹⁸ showed that even with an IL that is miscible in all ranges with water, on a microscopic level the system organizes itself in hydrophilic and hydrophobic domains.

Table 2 Diluent parameters for diluents commonly applied in liquid-liquid extraction.

	T_b (°C)	Water solubility	Dielectric constant	$\log P_{O/W}$	Dipole moment μ (D)	Kamlet-Taft parameters α (-), β (-)	Kamlet-Taft parameter π^* (-)	δ_D (MPa ^{1/2} Hansen)	δ (MPa ^{1/2} Hildebrand)	Z (kJ/mol)	E_t (kJ/mol)	AN (-)	DN (kJ/mol)	DP (-)	DP* (-)	bond
1-octanol	195 ⁵⁴	0.30 mg/L ⁵⁴	10.3 ⁵⁴	3.00 ⁵⁴	1.71 ⁵⁴	$\alpha = 0.70$ $\beta = 0.80$ ¹¹⁹	0.4, 0.57 ¹¹⁹	10.3 ¹²⁰	43.1 ⁵⁵	303	202 ¹¹⁹	33.1 ¹²¹	32 ¹²²			1 HBA 1 HBD
MIBK	114-117 ⁵⁴	19.1 g/L ⁵⁴	12.4 ⁵⁴ 13.1 ¹²³	1.31 ¹²⁴	2.81 ¹²³	$\alpha = 0$ $\beta = 0.12$ ¹²⁵	0.51 ¹²⁵	13.1 ¹²⁰ 12.6 ⁹⁴	41.8 ⁵⁵		165 ⁵⁴				2.50 ⁵⁵	1 HBA
Toluene	110.6 ⁵⁴	0.53 g/L ⁵⁴	2.379 ⁵⁴	2.69 ⁵⁴	0.36 ⁵⁴	$\alpha = 0$ $\beta = 0.11$ ¹²⁶	0.54 ¹²⁶	2.9 ⁹⁴	37.2 ⁵⁵	235	142 ²⁶	3.2 ²¹	0.1 ¹²² 3.6 ¹²¹	0.03 ⁵⁵	1.80	π -bond
Chloroform	334.3	8 g/L	4.7 ²⁷	1.97	1.01 ⁵⁵	$\alpha = 0.20$ $\beta = 0.10$ ¹²⁶	0.58 ¹²⁶	6.3 ⁹⁴	38.9 ⁵⁵	264 ¹²⁷	164 ¹²⁷	23.1 ¹²⁷	4 ¹²⁶ 0 ¹²²	-1.52 ⁵⁵	4.5 ⁵⁵	Cl-bond
Hexane	68.7 ⁵⁴		2.0 ⁵⁴	3.70 ⁵⁴	0.08 ⁵⁴	$\alpha = 0$ $\beta = 0.126$	-0.04 ¹²⁶	0 ⁹⁴	30.34 ¹²⁸		129 ¹²⁷ 130 ⁷⁴	0 ¹²⁷ 3.2 ²¹				
Kerosene	147 ⁵⁴		1.8 ⁵⁴		0.31 ⁶¹											
Chlorobenzene	131	0.5 g/L	5.65	2.84	1.54	$\alpha = 0$ $\beta = 0.07$ ¹²⁶	0.68 ⁷⁴	8.8 ⁹⁴		243 ⁷⁴	154 ²⁶	7.9 ²¹	3.3 ¹²² 2.2 ¹²¹			Cl-bond
Heptane	98 ⁵⁴		1.9 ⁵⁴	4.66 ⁵⁴	0 ⁵⁴	$\alpha = 0$ $\beta = 0.119$	-0.08 ¹¹⁹				130 ¹¹⁹		0 ¹²²			

4.3 Effects of solvent composition on solute distribution

An important factor governing acid distributions in composite solvents in both the primary LLX step and the back-extraction, is the composition of the solvent. In this section, solvent composition effects on acid distributions are reviewed for the three solvent classes, i.e. solvents based on phosphorous based extractants, solvents based on nitrogen based extractants and ILs.

4.3.1 Composite solvents using a phosphorous based extractant

Among the most used phosphorous based extractants are tributylphosphate (TBP), tributylphosphine oxide (TBPO), trioctylphosphine oxide (TOPO) and commercially available mixtures of alkyl phosphine oxides.^{18,35,60,129-131} TOPO and TBPO are solids at room temperature and require a diluent for application in LLX, whereas TBP can be applied pure. Phosphine oxides are stronger hydrogen bond acceptors than phosphate extractants.¹³²

Figure 6 Effect of extractant composition on the distribution ratio of acetic acid (HAc), for **a)** several phosphine oxides in several diluents at room temperature. (tributylphosphine oxide (TBPO) in Chevron 25 ■ ($[HAc]_0 = 0.1$ M), Chevron is a commercially available solvent based on a naphtha distillate, a mixture of approximately C_8 -alkyl aromatics),⁴⁴ TOPO in a (2/1) mixture of heptane and hexanol ● ($[HAc]_0 = 0.1$ M),⁴⁴ TOPO in undecane ▲ ($[HAc]_0 = 0.17$ M),¹³³ and TRPO (C_6 - C_8 chains) in kerosene ◆ (plotted against volume fraction extractant, ($[HAc]_0 \approx 2.7$ M),¹³⁴ and **b)** TBP in several diluents at room temperature in kerosene ▲ ($[HAc]_0 \approx 0.7$ M),¹³⁴ toluene × ($[HAc]_0 = 0.04$ M),¹³⁵ MIBK ◆ ($[HAc]_0 = 0.04$ M),¹³⁵ dodecane ● ($[HAc]_0 = 0.16$ M),⁷² and Chevron Solvent 25 ■ (plotted against weight fraction, $[HAc]_0 = 0.1$ M).⁴⁴ The lines are added to guide the eye.

The acetic acid distribution ratio as a function of the phosphine oxide extractant concentration is displayed in Figure 6a for several phosphine oxides in different diluents.^{44,133,134}

Both TOPO and TBPO show an optimal extractant concentration around a weight fraction of 0.2-0.4 in an active diluent. The optimum in the curve for TOPO and TBPO with increasing extractant concentration is due to the active role of the diluent in the complex formation. At a very high extractant loading, thus low diluent concentration, less stabilizing influence of the diluent results in less complexation, and hence, in a lower distribution. Furthermore, because the phosphine oxides are solids, this causes solubility problems at higher concentrations.⁴⁴ In the case of TBPO, the diluent is Chevron solvent 25, which according to the MSDS is based on a naphtha distillate, containing C₈-alkyl aromatics,⁴⁴ and an unknown (trade secret) compound. This most likely is a surfactant, as the solvent is used as a cleaning agent for engine injection systems, and this is thus an active diluent. The mixture of heptane and hexanol used for TOPO also contains an active ingredient, whereas kerosene and undecane are inactive diluents.

For the inactive diluents, i.e. the mixture of C₆-C₈ chained phosphine oxides (TRPO), and for TOPO in undecane, there is no optimum visible in Figure 6a, and especially for TRPO, the trend looks continuously increasing with increasing extractant loading, which may be explained by the absence of stabilizing interactions of the diluent, which cause the optimum with active diluents. The distribution coefficients in kerosene and in undecane though, are lower than in active diluents.

For TBP the distribution ratio of acetic acid as a function of the extractant concentration is shown in Figure 6b.^{44,72,134,135} TBP was only studied in inactive diluents and MIBK with very low and continuously increasing distribution ratios with increasing extractant concentration of 0.02 up to 2.1. Also compared to the phosphine oxides with $0.09 < K_D < 4.5$, the acid distribution with TBP is low.

4.3.1.1 Effect of temperature

Figure 7 shows the effect of temperature on the acetic acid distribution in TBP, TRPO and Alamine 336 with several inactive diluents for the extraction of acetic acid. Although K_D is low for all extractants because of the use of inactive diluents, the sensitivity for a temperature increase can be compared. Both phosphorous based extractants show a similar temperature sensitivity; the temperature sensitivity of the tertiary amine Alamine 336 is increased, especially around a temperature of 40 °C. Brouwer et al.¹³⁶ found

that for the complexation of levulinic acid and formic acid with 30 wt% TOPO the effect of temperature on the complexation is larger in the active diluent MIBK than in the inactive toluene.

Figure 7 Temperature-dependency of the distribution ratio of acetic acid in ■ 50 vol% TBP in kerosene¹³⁴ ($[HAc] = 3\text{ M}$ at equilibrium), ● 50 vol% TRPO in kerosene ($[HAc] = 3\text{ M}$ at equilibrium),¹³⁴ ◆ Cyanex 923 (TRPO, unknown concentration) in toluene¹²⁹ ($[HAc]_0 = 0.1\text{ M}$) and ▲ 25 vol% Alamine 336 in xylene.⁴⁵ The lines are added to guide the eye.

4.3.2 Composite solvents using a nitrogen based extractant

Trialkyl amines are nitrogen based extractants most used for acid extractions, usually TOA and Alamine 336 (a mixture of trialkylamines with C_8 - C_{10} chains),^{5,20,23,24,26,33,41,43,45,47,48,53,58,59} but also trihexyl amine⁵ and tridodecyl amine (TDDA)^{34,100} have been reported. Recently, a tertiary amine containing also a pyridine functionality, i.e. didodecylaminopyridine (DDAP) was reported.^{29,66} The most reported active diluents are 1-octanol, chloroform and MIBK, and the inactive diluents toluene, carbon tetrachloride (CCl_4) and hexane. In general, the distribution coefficients are lower for the inactive diluents. Similar to the trends observed for phosphorous based extractants, also for nitrogen based extractants the use of active or inactive diluents results in a distinct solvent composition dependency, see Figure 8a and b. With active diluents (Figure 8a) the distribution of acids is typically higher

than with inactive diluents, because of increased solubility of the acid-amine complexes due to the interactions with the diluent. In addition, the typical maximum in distribution at intermediate extractant concentration is observed for active diluents, whereas for inactive diluents the maximum in acid distribution with increasing extractant concentration is much less pronounced, if present at all.

Figure 8 Effect of volume fraction of extractant in the solvent on the distribution ratio of acetic acid, for TOA in **a)** several active diluents at room temperature (■ Alamine 336 in 1-octanol ($[HAc]_0 = 0.5$ M),⁴⁵ TOA in ▲ MIBK ($[HAc]_0 = 0.2$ M),⁴⁹ ▼ in chloroform ($[HAc]_0 = 0.1$ M),⁴⁴ ◆ in decanol/dodecane ($[HAc]_0 = 0.2$ M),⁷² and ◀ in 2-ethyl-hexanol ($[HAc]_0 = 0.55$ M)),⁴⁷ and **b)** several inactive diluents at room temperature (tri-iso-octylamine (T-i-OA) in ► toluene ($[HAc]_0 = 0.2$ M) and ○ hexane ($[HAc]_0 = 0.2$ M),¹³⁷ and ● TOA in toluene ($[HAc]_0 = 0.17$ M)).⁴⁹ The lines are added to guide the eye.

In Figure 8b the effect of volume fraction of extractant in a solvent with inactive diluent is shown. The continuously increasing trend with increasing tri-iso-octylamine (T-i-OA) concentration is comparable to the trend using TOA, although the acid distribution seems higher.^{49,137}

For dicarboxylic acids in inactive diluents, the extractant concentration has a more pronounced effect on the acid distribution than for monocarboxylic acids, and at a high amine concentration the distribution decreases pronouncedly,^{23,43} and presents an advantage for diluent-swing regeneration. Also for aromatic acids, the diluent effects can be different than for aliphatic acids. Athankar et al.³¹ showed that the extraction of benzeneacetic acid with TOA exhibits comparable distributions for the three inactive diluents benzene, toluene, xylene and for the active diluent hexanol, whereas

without TOA, hexanol extracts much better. Complex stabilization by π - π interactions is suggested. In all cases the typical maximum in distribution for active diluents is observed, although at a lower extractant concentration than for acetic acid, which may be due to the lower solubility of the aromatic acid.

Acid solubility limitations can also result in third phase formation, as is observed for TOA in toluene.^{138,139} The optimum observed for active diluents is a trade-off between increasing complexation by increasing the amount of amines and decreasing the complex stabilization by the diluent,^{44,140} and the composition of the optimum shifts to lower amine concentration with increasing diluent polarity.¹⁴¹

The observed optimum can also be explained through changing activity coefficients with varying solvent composition and by changing stoichiometry of the complexes,⁹⁵ resulting in a complex interplay of effects. For example, in propionic acid extraction with TOA in 1-octanol, amine-concentration dependent proton transfer affects the (1,1)-complexation constant $K_{1,1}$ (concentration-based equilibrium constant), and for an acid per amine loading of $Z < 1$, both the $K_{1,1}$ and the loading decrease with increasing TOA concentration, since at $Z < 1$ the (1,1)-complex is the dominating complex.^{23,75} The decreasing $K_{1,1}$ is accompanied by increasing values for $K_{2,1}$ and $K_{3,1}$,⁷⁵ which at $Z > 1$ results in an opposite loading tendency. Furthermore, there is a decrease in loading with increasing amine concentration for systems that include a diluent in the complex, and a loading increase for systems that exhibit aggregation and formation of complexes with a large number of acid and amine molecules.⁵⁹ For inactive diluents, increasing the amine concentrations above 1 mol/L will increase the loading of acid on the amine due to the increasing polarity (the amine is more polar than the diluent).⁴⁸

4.3.2.1 Correlation of distribution with molecular property parameters

Comparing acid distributions for various diluents, the distribution increases in the order *alkane* < *alkyl-substituted aromatics* < *aromatic*, *benzene* < *halogenated aromatic* < *ketones* < *proton-donating halogenated hydrocarbon* < *nitrobenzene* < *alcohols*.²³ This order corresponds with increasing Hildebrand solubility parameter and increasing acid-extractant solvation strength. Aromatic diluents show higher distribution ratios than alkanes due to complex stabilization by aromatic π -electrons.^{23,24} A comparison of distribution coefficients in both inactive and active diluents was reported by

Rasrendra et al.⁴⁷ for acetic acid, see Figure 9. Other distribution coefficients have been reported,^{45,48,49} which might be caused by changes in temperature, the presence of other compounds or variations in the volume ratio of the aqueous and organic phases.

Figure 9 Distribution coefficients for acetic acid ($[HAc]_0 = 0.6$ M) for extraction with 0.5 M TOA in several diluents.⁴⁷

In Figure 9, the diluents are ordered from left to right with decreasing polarity according to their $E_T(30)$. It is clear that active diluents show higher distribution coefficients than inactive diluents, but polarity alone does not perfectly correlate with the distribution coefficients, and in Figure 10 it can be seen that this is next to the $E_T(30)$ also the case for the Hildebrand solubility parameter δ and the Kamlet-Taft polarizability parameter π^* (for diluents with known π^*) for data of Qin et al.⁴⁸

Figure 10 Distribution coefficient for acetic acid ($[HAc]_0 = 0.6\text{ M}$) for extraction with 0.5 M TOA in several diluents with respect to **a)** the Hildebrand solubility parameter δ of the diluents, **b)** the $E_T(30)$ parameter of the diluents and **c)** the Kamlet-Taft polarizability parameter π^* .⁴⁸

Although direct parity with molecular property parameters is clearly not always possible, Figure 11 shows that there are huge differences in distribution coefficients with different diluents, and polarity does appear as a major factor.^{29,45} In Figure 11a it is shown that decreasing the polarity by addition of xylene clearly decreases the distribution coefficient. For other diluents, the same trend is shown in Figure 11b and Figure 11c. For the difference in polarity between chloroform and MIBK, not all parameters show the same trend, as can be seen in Table 2. In this case the higher distribution ratio using chloroform will be caused by the hydrogen-bond donor abilities of this diluent.

In the extraction of lactic acid from an aqueous stream, Krzyzaniak et al.²⁹ found that the distribution of lactic acid decreases with decreasing polarity of the diluent (Figure 11d).

Figure 11 Distribution coefficient of **a)** acetic acid ($[HAc]_0 = 0.6$ M) in liquid-liquid equilibrium with 0.5 M TOA in several diluents. (Data from Marti et al..⁴⁵) **b)** acetic acid ($[HAc]_0 = 0.6$ M in the case of chloroform and toluene, $[HAc]_0 = 0.42$ M in the case of MIBK) in liquid-liquid equilibrium with 0.5 M TOA in several diluents at room temperature. (Data from Ziegenfuss et al..⁴⁹) **c)** acetic acid ($[HAc]_0 = 0.6$ M) in liquid-liquid equilibrium with 0.5 M TOA in several diluents at 25 °C. (Data from Qin et al..⁴⁸) and **d)** lactic acid (HLA) ($[HLA]_0 = 13$ mM) in liquid-liquid equilibrium with 0.5 M TOA in several diluents. (Data from Krzyzaniak et al..²⁹)

The results by Qin et al.,⁴⁸ are similar to those by Ziegenfuss et al.⁴⁹ for chloroform, but for MIBK Qin et al. report a significantly lower value, explained by the lower acid concentration used by Ziegenfuss et al. for MIBK.

In nitrogen extractant systems other than using a tertiary amine, also trends for the effect of polarity are found. For the extraction of itaconic acid (methylene succinic acid) using the quaternary ammonium salt Aliquat 336, Wasewar et al.⁶¹ found a higher extraction when a solvent with a higher dipole moment was applied, caused by differences in self-association and partitioning of the acids in these solvents.

4.3.2.2 Effect of temperature

Temperature affects several factors in liquid-liquid equilibria of acids with amines, i.e. a small effect on the acid pK_a ,^{66,142} increasing acid solubility in organic solvents, and even more in water with increasing temperature.¹⁴² Water co-extraction also increases with increasing temperature.¹¹³ The most important temperature dependency is the decreasing acid-base complexation strength with increasing temperature,^{43,66} and as a result, reactive extraction with tertiary amines is much stronger temperature dependent than physical extractions.⁵

Figure 12 shows the effect of temperature on the distribution ratio for several solvents based on Alamine 336 and DDAP. It can be seen that with active diluents, the distribution ratios are much higher compared to the inactive diluents in Figure 7, and also that the temperature has more effect on the distribution. This may be explained by the larger enthalpy of complexation and larger $K_{1,1}$. Krzyzaniak et al.⁶⁶ studied the effect of temperature on various variables in the extraction of lactic acid by DDAP in 1-octanol. With increasing temperature the solubility of the acid in the organic phase increases, the acid dissociation constant in the aqueous phase decreases, and the decreasing complexation of acid and DDAP dominates. There is a strong dependency of the distribution ratio on temperature for DDAP. However, the distribution ratio is very high compared to the results for Alamine 336 because of the low acid concentration applied ($[HL_a] = 0.4$ mM at equilibrium).

Figure 12 Temperature-dependency of the distribution ratio of acetic acid ($[HAc]_0 = 0.5$ M) in 25 vol% Alamine 336 in ■ 1-octanol and ● xylene;⁴⁵ lactic acid ($[HLA] = 0.4$ mM at equilibrium) in × 20 wt% DDAP in 1-octanol⁶⁶ and succinic acid ($[HA]_0 \approx 0.3$ M) in 0.29 M Alamine 336 in □ MIBK and in ○ chloroform.⁴³ The lines are added to guide the eye.

4.3.2.3 Effect of the nature of the acid

It was found that the acidity and hydrophobicity of the acid increased the loading of acid on TOA,⁴⁸ these trends are both straightforward correlations, i.e. the more hydrophobic the larger the preference for an organic phase, and the stronger the acid, the stronger the interaction with the base. In Figure 13, results of Qin et al.⁴⁸ on the relation between the apparent complexation constant $K_{1,1}$, i.e. the biphasic equilibrium constant from eq (20) and the hydrophobicity $\log P_{O/W}$ of acids with similar pK_a are shown. There is a clear relation between the hydrophobicity and the apparent complexation constant, which off course is due to the increasing partitioning to the organic phase with increasing hydrophobicity.

Figure 13 $\log K_{1,1}$ vs. $\log P_{O/W}$ for complexation of 0.5 M TOA with acetic, propionic, butyric and valeric acid in several diluents: ■ in 1-octanol, ● in MIBK and ▲ in CCl_4 .⁴⁸ The lines are added to guide the eye.

4.3.3 Composite solvents based on ILs

4.3.3.1 Effect of composition

ILs can be diluted for practical applications to reduce the viscosity, modify the solubility of solutes, or enable certain reactions to take place,¹⁴³ reduce cost, and decrease loss of solvent from the extract phase.¹⁴⁴ Moreover, dilution of the IL phase might prevent third phase formation that is observed in some acid extractions by IL.⁶³ Examples include the extraction of tocopherols with imidazolium ILs using methanol as a co-solvent,¹⁴⁵ and extraction of tocopherol by amino acid imidazolium ILs from a reaction product mixture with methyl linoleate.¹⁴⁶ The co-solvent dimethylformamide decreased the viscosity and increased the distribution coefficients and selectivity.¹⁴⁶

Dilution can be done with either polar or apolar diluents, and the molecular property models described in section 4.2.3 have also been applied to describe the effect of co-solvents on the physical properties of the IL. E.g. for 1-butyl-3-methylimidazolium acetate,¹⁴³ using the LSER with Kamlet-Taft parameters as well as the Dimroth-Reichardt's energy, it was shown that even adding up to 80 mol% of the co-solvents water, methanol and dimethylsulfoxide only had a small effect on the parameters. This was explained by the cluster formation in the ILs that contain the co-solvent.

Modeling and experiments for extraction of oils and high-value components from biomasses using ILs with co-solvent methanol showed that above 80 vol% of methanol the co-solvent completely surrounds the aggregates of the imidazolium IL which removes the effect of the IL on the lipids, thereby reducing the extraction efficiency.^{80,143}

Clustering is an important aspect of IL mixtures, which may be affected by dilution. E.g. for methanol as a co-solvent in phosphonium ILs, experiments and simulations showed that at mass fractions of the IL below 0.1 the mixture is very similar to methanol, then for $0.1 < x_{\text{IL}} < 0.7$, a transition regime occurred with more IL properties and interactions. Above 0.7 the solvent behaves like an IL. The mechanism is dominated by anions solvating the cations and methanol, followed by solvation of the cations by methanol.⁷⁸ The effects of different polar co-solvents were studied with molecular dynamics simulations as well. All co-solvents that were used, increased the aggregation of the IL. Chloroform and acetone have a stronger effect on aggregation than methanol, whereas acetic acid induces less aggregation. Similar differences were found for the clusters that were formed in the IL-co-solvent mixture. With acetic acid, methanol and propanol mainly cation-anion pairs are present, whereas larger clusters are observed in acetone, chloroform and DMSO.⁸⁰ Differences in types of polar co-solvents were also studied by Gao et al.¹⁴⁷ using an imidazolium IL for the recovery of solvents in the processing of biomass, where aqueous biphasic systems are required for separation. A two phase system with the IL was more likely to be formed with a lower hydrogen bond basicity and lower polarizability of the co-solvents. With solvatochromic dyes, Mellein et al.¹⁴⁸ showed that in mixtures of ILs with organic co-solvents, the polarity is mostly dependent on the IL and not on the organic co-solvent, except for very low concentrations of IL. The competition between the interactions between cation and anion of the IL, and the interactions with the organic co-solvent was illustrated with the Kamlet-Taft hydrogen bond donor parameter, α , of the mixture, being dominated by the stronger hydrogen bonding co-solvent.¹⁴⁸

With apolar diluents, reverse micelles may occur, in which a part of the IL ions are located.¹⁴⁹ Upon diluting with dodecane to effectively decrease the viscosity, also a reduced distribution was observed for lactic acid²⁷ and butyric acid, see Figure 14.^{84,150}

Figure 14 Effect of volume fraction of IL in dodecane on the distribution ratio of acid in equilibrium for ■ lactic acid (aqueous equilibrium concentration of ≈ 0.2 M) with Cyphos IL-104,²⁷ ● butyric acid (aqueous equilibrium concentration of ≈ 0.12 M) with $[C_n C_n C_n C_1 N][BTMPP]$ (Aliquat 336 cation with Cyanex 272 anion),⁸⁴ and ▲ butyric acid (aqueous equilibrium concentration of ≈ 0.11 M) with $[C_{12} C_6 C_6 C_6 P][BTMPP]$.¹⁵⁰ The lines are added to guide the eye.

Upon extraction, butyric acid was shown to reduce the viscosity of IL-104 in systems with less than 50 wt% of IL-104 in dodecane, which is caused by the formation of micelles of dodecane in the water saturated solvent, which was determined by dynamic light scattering. The aggregates had a size below 100 nm and decreased in size with increasing concentration of the acid.¹⁵¹

In CO₂-pressurized extraction of acetic acid, it was found that the CO₂ behaves as a modifier of the phosphonium IL phase, increasing the distribution coefficient up to seven times at CO₂ pressures of up to 40 bar.⁴⁶ For a phosphonium IL based extraction of carboxylic acids, the presence of salts in the feed results in the extraction of acidic forms of anions originating from the salts, thereby reducing the acid distribution. The acid distribution also decreases because some of the salts increase the pH of the aqueous phase.¹¹⁵

Hydrophilic ILs diluted in water can help dissolve hydrophobic species better by forming hydrotropes,^{152,153} whereas they may also form aqueous two phase systems (ATPS) with aqueous salt solutions. These ATPSs have a

faster phase separation, a lower viscosity, no use of volatile organic solvents and more options for varying the polarity compared to ATPSs based on organic solvents and polymers.^{154,155} Other possibilities to form ATPSs are with carbohydrates and water, amino acids and water, and polymers and water.¹⁵⁴ Pratiwi et al.¹⁵⁵ compared IL based ATPSs with traditional salt-alcohol systems to extract succinic acid. Acid distribution ratios in the IL based systems were generally better than in the salt - alcohol systems with values ranging from close to zero for many salt - alcohol systems and $0.11 < K_D < 3.5$ for the IL based systems. Especially phosphate based aqueous phases showed good acid distributions into imidazolium rich phases, which is of interest because many fermentation broths contain significant amounts of phosphate, and might be directly suitable for application in ATPSs with an IL.

4.3.3.2 Effect of temperature

With increasing the temperature there is either no or only a small effect on the distribution ratio of lactic acid upon extraction with a phosphonium IL (Cyphos IL-104).²⁷ The increased temperature did however decrease the viscosity and the water solubility in the IL solvent, which may be a result from less stability of the reverse micelles at elevated temperatures.²⁷ For 25 - 40 °C, the temperature effect on imidazolium-IL extraction of ferulic acid and caffeic acid could be described with a linear relation between the natural logarithm of the distribution ratio and the inverse of the temperature, with the slope determined by the (endothermic) enthalpy of complexation ranging from 3 to 10 kJ/mol.¹⁵⁶ For all types of imidazolium-ILs studied, an increase of temperature had only a small but positive effect on the distribution ratio.¹⁵⁶ A small increase of distribution ratio with increasing temperature was also found for the imidazolium-IL based extraction of phenols.¹⁵⁷

4.4 Solvent regeneration

There are several regeneration methods for the recovery of solvents and acids after acid extraction. In the case of volatile acids, or volatile solvents or both, the simplest option appears to be evaporation or distillation of the acid directly from the solvent, or *vice versa*.^{22,158-160} When neither the acid nor the solvent is volatile, other regeneration strategies are to be followed,¹⁶¹ such as reactive back-extraction or back-extraction using a diluent-swing or a temperature-swing. Sometimes simple solutions appear, such as precipitation upon removal of co-extracted water, e.g. for succinic acid, fumaric acid, and adipic acid.⁴² In many processes, also raffinate treatment is necessary to recover leached solvent, and sometimes raffinate properties are tailored on purpose, e.g. to salt-out the carboxylic acid.¹⁶² Salting-out with MgCl_2 allowed for thermal decomposition to form MgO , which could re-enter the process to basify the broth during fermentation.¹⁶²

4.4.1 Regeneration by evaporation and stripping

Regeneration in the case of acids that are reasonably volatile might be performed through direct evaporation of the acids from high boiling solvents. Recent developments include molecular distillation applied for IL regeneration.¹⁶³ In the case recovery can be done simply by evaporation, the theoretical heat duty corresponds with evaporation of the acid and the co-extracted water, and subsequent distillation of the aqueous acid stream. Direct evaporation may impose huge heat duties, such as the 31.5 GJ per ton levulinic acid as calculated by Brouwer et al.,¹³⁶ or even regeneration difficulties when the affinity between solvent and acid is too high. Reyhanitash et al.⁸⁷ found that at low acid loading in the IL $[\text{P}_{666,14}][\text{Phos}]$, it is impossible to distill off the acids from the IL due to partial proton exchange from the carboxylic acids to the phosphinate anion of the IL, and strong hydrogen bonding leading to (1,1)-complexes of the phosphinate anions with carboxylic acid/carboxylate. At higher acid loadings, direct thermal recovery may be applied, but at loadings of one acid molecule per ion pair and below, an alternative regeneration has to be considered such as washing with an aqueous solution of a volatile base,⁸⁷ preferably assisted by dilution of the IL with an inactive diluent, based on the dilution-effect on the distribution shown in Figure 14.

Han et al.¹⁶⁴ used inactive diluents to recover lactic acid from extract phases with methylene chloride in a simple distillation process where lactic acid is removed via the reboiler and methylene chloride was obtained from the condenser. The efficiency of the process at a temperature of 50 °C was approximately 70% for all inactive alkane diluents, except for the active chlorobenzene (16.7%). The effect of the volume percentage of active diluent

is significantly larger than that of the temperature difference. Especially at low concentrations of active diluent (<40%) the effect of concentration on the efficiency is high for the inactive diluents. The effect of temperature is smaller for active diluents and those with a higher polarity and follows the order *chloroform* < *pentane* < *MIBK* < *chlorobenzene*.¹⁶⁴

4.4.2 Regeneration by reactive back-extraction

To maximize solvent regeneration, back-extraction with a strong acid may be applied, e.g. HCl has been reported, that can be distilled off later in the process.^{5,64,141} Because of the back-extraction with HCl, the solute concentration in the back-extract is higher than in the feed. However, still further processing is required to recycle the HCl and regenerate the solvent. In addition, when using HCl-solutions for back-extraction, too low yields for viable processes are obtained. Alternatively, bases may be used for back-extraction to obtain higher yields, e.g. using sodium hydroxide producing sodium carboxylate, and recovery using aqueous amines in distillation where amides are produced,⁵ and with concentrated ammonia where ammonium lactate was produced.¹⁶⁵ For all non-volatile bases, additional treatment is necessary to recover the carboxylic acid in pure acidic form, resulting in by-product formation. Especially for the production of bio-based plastics on a bulk scale, huge volumes of by-products (salts) are not desirable. The use of a volatile amine for the back-extraction allows for subsequent decomposition of the formed salt,^{5,61,87,141} which appears to be a sustainable solution. However, additional recovery challenges might occur when the amine is leached into the solvent phase. Back-extraction with trimethylamine (TMA) followed by thermal cracking or esterification of the trimethyl ammonium carboxylate, was shown to allow for full regeneration of lactic acid and succinic acid from Amberlite LA-2 and Alamine 336 in different diluents.²⁵

4.4.3 Regeneration by physical back-extraction

With physical back-extraction typically less difficulties are faced in the regeneration stage after the back-extraction, but concentrations might be limited. Some elegant solutions, e.g. using supercritical CO₂, shown by Kroon et al.¹⁶⁶ to selectively recover a phenylalanine ester from an imidazolium IL after extraction, may be applicable for acids as well, yielding the final product after releasing the pressure from the CO₂-rich phase. When the extraction and back-extraction are done with the same solvent, impurities may be removed from the system, but it is hard to increase the concentration of the solutes, and when maintaining the same temperature as in the extraction, the concentration of the solutes typically even reduces, requiring a heavy heat duty to distill off the water from the back-extract.⁶⁶ Methods to concentrate the back-extract are desirable.

Making use of the short-cut calculations for the minimum solvent-to-feed-ratio $(S/F)_{\min}$ (eq (25) in combination with (26)),¹⁶⁷ and the minimum wash-to-extract-ratio $(W/E)_{\min}$ (eq (27)),⁶⁶ the concentration factor as defined in eq (4) can be calculated. Where X_{in} is the concentration in the feed stream, X_{out} the concentration in the raffinate and Y_{in} the ingoing concentration of the extract stream. The $(W/E)_{\min}$ is calculated by dividing the fraction of lactic acid that is removed from the extract stream, $y_{\text{in}} - y_{\text{out}}$, by the initial concentration of lactic acid in the extract y_{in} multiplied by the inverse of the distribution obtained in the forward extraction $1/K_D$. In this case an ingoing concentration of the wash stream of zero was assumed.

$$\frac{S'}{F'_{\min}} = \frac{X_{\text{in}} - X_{\text{out}}}{Y_{\text{out,max}} - Y_{\text{in}}} \quad (25)$$

$$Y_{\text{out,max}} = K_D \cdot X_{\text{in}} \quad (26)$$

$$\left(\frac{W}{E}\right)_{\min} = \frac{y_{\text{in}} - y_{\text{out}}}{\frac{1}{K_D} y_{\text{in}}} \quad (27)$$

Two approaches to concentrate through back-extraction are temperature-swing and diluent-swing.⁴³ For temperature-swing, the temperature in the back-extraction column is increased to lower the complexation constants. In a diluent-swing method, the composition of the extract-phase is changed by removing an active diluent or adding an inactive diluent as an anti-solvent. Especially when strong effects in acid distribution are observed with extractant concentration, this approach is interesting, at the drawback of needing extra operations to add and remove diluent.

4.4.3.1 Temperature-swing regeneration

The opportunity of temperature-swing regeneration is dependent on the mechanism and strength of interaction. Various (hypothetical) isotherms are drawn in Figure 15 (based on eq (6), (14) and (15)), for (1,1)-complexation in Figure 15a, and for (1,1) and (2,1)-complexation in Figure 15b. Strong (1,1)-complexation results in a stronger curvature, displayed for physical partitioning with $K_m = 0.1$. Decreasing $K_{1,1}$ with temperature results in less curved lines at higher temperatures.⁴³ For higher K_m values, higher organic phase concentrations are observed, as well as less curved equilibrium lines more close to each other. This effect is stronger with a higher enthalpy of complexation.

Figure 15 *a)* Effect of increasing $K_{1,1}$ value on the equilibrium curve for a system with an extractant concentration of 0.24 M, $K_{1,1}$ ranges from 5 - 90, $K_{2,1}$ is 0. The physical extraction $K_m = 0.1$. The organic phase and aqueous phase have an equal volume, and *b)* effect of increasing $K_{2,1}$ value on the equilibrium curve for the same system, $K_{2,1}$ ranges from 0 - 40, $K_{1,1}$ is 5.

Figure 15b shows typical equilibrium curves for increasing $K_{2,1}$, and the shape of these equilibrium curves can be compared with gas adsorption isotherms where there is a difference between either Langmuir monolayer adsorption or BET theory multilayer adsorption.^{136,168} The graph associated with monolayer adsorption (Type 1) is more curved than the one associated with the multilayer adsorption (Type II).^{113,136,168} In the case of complex formation of different stoichiometry, type I applies to (1,1)-complex formation and type II might indicate the formation of larger complexes. In type II there is an increase in acid concentration in the organic phase for higher aqueous concentrations of acid, which can be correlated with the critical acid concentration as reported by Tamada.²³ However, this is only based on the complexation in the solvent phase, excluding diluent effects on the physical extraction and solubility of acids and complexes.

Solvents with phosphorous based extractants

Figure 7 shows that for the phosphorous based extractants, the distribution coefficient of acids decreases with increasing temperature. This can be applied in a temperature-swing regeneration process. The effectiveness of temperature-swing may be indicated by the curvature of the equilibrium line between the aqueous and organic phase in the McCabe-Thiele diagram. Substantially curved lines may result in a tangent pinch that complicates back-extraction.⁴³ Brouwer et al.¹³⁶ showed that the effect of temperature on the acid distribution ratio is even stronger when active diluents are applied instead of inactive diluents. The combination of TOPO in MIBK

resulted in a high distribution ratio of levulinic acid and a high selectivity of levulinic acid and formic acid over sulphuric acid. Brouwer et al.¹³⁶ applied a double extraction-temperature-swing back-extraction to concentrate levulinic acid and formic acid from aqueous streams using 30 wt% TOPO in MIBK as solvent. Because of the more curved isotherm of formic acid at lower concentrations (comparable to isotherms shown in Figure 15a for high $K_{1,1}$ -values), in the first extraction step the concentration factor of formic acid is lower than that of levulinic acid. After the second step, at higher concentrations, the overall concentration factors of both acids become equal.

Solvents with nitrogen based extractants

For the complexation of TOA, the decrease in entropy and the exothermic complexation enthalpy are larger for succinic acid than for lactic acid. Therefore, according to Tamada and King⁴³ temperature-swing regeneration is more applicable for the extraction of succinic acid by Alamine 336 in MIBK. This is because as a result of the larger enthalpy of complexation the temperature effect on the distribution ratio is also larger, as can be explained by eq (13). These differences in enthalpy and entropy may be caused by differences between these acids in the partial molar heat of mixing of either the complex in the solvent or the acid in the aqueous phase, or a difference in the enthalpy of complexation.⁴³ For extraction of lactic acid by Alamine 336, San-Martin et al.⁵² reveal a larger enthalpy of complexation for the (1,2) and (1,3)-complexes with toluene as the diluent, compared to MIBK or chloroform. Therefore the temperature effect for the extraction with toluene applied as the diluent is also larger. However, the distribution ratios in this system are around 1, much smaller than typical values around 3 - 8 or even higher for the lactic acid distribution ratio in the case of active diluents,^{23,29,43} increasing the S/F ratio and energy required.

Ionic liquid based solvents

For acid extraction with ILs there is either no effect of temperature or only a very small (positive) effect of increasing temperature,^{27,156,157} which makes the IL based solvent not a good candidate for temperature-swing regeneration. However, a positive effect of increased temperature on the solvent is a decreased viscosity and water solubility, which may be advantageous in a process.²⁷ Another positive effect of increased temperature and decreased viscosity, reported for metal ion extraction, is the increased ion transfer rate that can reduce the processing time.¹⁶⁹ In the extraction of metals with imidazolium ILs there is also a positive relation between the distribution of metal ions and the temperature.¹⁷⁰ When the temperature was decreased to room temperature after equilibrating at elevated temperatures, the change of metal ion distribution was slow and did not decrease to the expected

value at room temperature. These phenomena are considered a result of non-reversible temperature induced differences in the non-homogeneous structure of the IL and its effect on parameters such as viscosity, water solubility and therefore also on metal ion partitioning.¹⁷⁰

4.4.3.2 Diluent-swing regeneration

Tangent pinches in temperature swing operations might be solved with a diluent swing,¹¹³ yielding a combination of the two swings.⁴³ The diluent swing at isothermal operation may as well offer an opportunity to increase the concentration, as follows from the solvent composition-dependent distribution, which is observed in all three classes of composite solvents (Figure 6, Figure 8 and Figure 14).

Especially at lower concentrations of solute, diluent-swing might be advantageous because of a larger equilibrium shift for low concentrations of solute.¹¹³ Literature examples of back-extractions using diluent-swing mostly involve amine extractants. For example, Krzyzaniak et al.²⁹ used heptane as an anti-solvent to lower the distribution in the back-extraction of lactic acid with DDAP in 1-octanol. The high volatility of heptane allows for distilling off the anti-solvent after the back-extraction. In a single stage back-extraction process, a three times dilution in heptane increased the recovery from approximately 10-20 % to 60-70 %, ²⁹ and a maximum concentration factor of 3.15-6.06 for 373 K in the back-extraction step was calculated. The outlet concentration was only 0.041-0.078 M due to very diluted starting conditions.⁶⁶ Heptane was also applied to strongly decrease the distribution of succinic acid, by promoting intramolecular hydrogen bonding of succinic acid, and reducing acid-extractant interactions,¹⁷¹ making this a good strategy for back-extraction.

Another option is to use a gaseous anti-solvent, for example propane, which reduces the need of distillation of the anti-solvent.¹⁷² In such processes the anti-solvent is simply removed by releasing the pressure.

4.4.4 Energy considerations in the regeneration process

In the previous sections, various options for regeneration have been reviewed, and in this section some calculations on energy duty should direct on which regeneration strategy is most interesting for future research. For temperature-swing regeneration processes, the heat requirement includes primarily heating of streams entering the regenerator, and for diluent-swing regeneration processes, energy is needed to distill off the diluent. An advantage of temperature-swing regeneration is that diluent distillation can be avoided, resulting in less unit operations.

To further study the effect of the K_D in the extraction step and the regeneration step, three different types of regeneration processes are compared in this work, (1) temperature-swing, see Figure 16, (2) diluent-swing by evaporating part of the diluent, see Figure 17, and (3) diluent-swing by adding an anti-solvent, see Figure 18. For the comparison of the three configurations, the ratio of the distribution ratios in the forward and backward extraction is referred to as K_D/K'_D and is described in eq (28).

$$\frac{K_D}{K'_D} = \frac{K_{D, \text{ forward extraction step}}}{K'_{D, \text{ backward extraction step}}} \quad (28)$$

The goal of the comparison of the three regeneration processes is to obtain a general insight on the influences of the parameters K_D , K_D/K'_D and the initial concentration of the acid on the energy requirements of regeneration processes. In all of these processes there is an extraction column and an extra column to regenerate the solvent. In the diluent-swing processes there is an extra distillation column to evaporate a part of the solvent or the anti-solvent.

Figure 16 Flowsheet of extraction process with temperature-swing back-extraction followed by evaporation. If applicable, the evaporator can be replaced by a distillation column.

Figure 17 Flowsheet of extraction process with diluent-swing back-extraction by distilling of the solvent followed by evaporation. If applicable, the evaporator can be replaced by a distillation column.

Figure 18 Flowsheet of extraction process with diluent-swing back-extraction by adding anti-solvent followed by evaporation. If applicable, the evaporator can be replaced by a distillation column.

The following assumptions were made:

- The solvent-to-feed ratio (S/F) was set to $1.5 \times (S/F)_{\min}$, which was calculated by eq (25) in combination with eq (26) for $Y_{\text{out,max}}$.
- The weight fraction of the feed leaving the extractor x_{out} was set to 0.001, for both extraction and back-extraction.
- 90 % recovery of the acid in the feed stream is assumed.
- Leaching of solvent or water co-extraction are not taken into account.
- The model solvent phase is 30 vol% TOA in octanol, with the corresponding heat capacity and density.
- For ‘diluent-swing - evaporation’ the heat capacity and heat of evaporation of octanol are used, and after evaporation there is 70 vol% TOA in the solvent.
- For ‘diluent-swing - anti-solvent’ the heat capacity and heat of evaporation of heptane are used, and a volume ratio of 1:1 is used.
- The evaporation process uses only 25 % of the energy that would be required for evaporating the stream in a normal process by using a five effect evaporator.
- A temperature difference of 10 °C is used in the heat integration to heat ingoing streams of the back-extraction units and the evaporators.
- $E_{\text{product}}/E_{\text{evaporation}}$, or E/E is the energy required for the process expressed as a fraction of the energy that would be required for using evaporation of the feed stream to reach the same concentration factor.
- A constant value of K_D is assumed, but the shape or possible pinch points of the equilibrium curve is not taken into account.
- The boiling point of the acid is assumed to be higher than that of the solvents.

Figure 19 Effect of initial acid concentration, distribution coefficient and ratio of distribution coefficients in back-extraction and extraction on the concentration factor and energy requirements of three acid extraction processes, based on temperature-swing (squares), based on diluent-swing by evaporation (circles) and based on diluent-swing by adding an anti-solvent (diamonds). Blue symbols represent an initial acid concentration $[HA]_0$ of 5 wt% and black symbols represent 1 wt%.

For all three processes, the initial acid concentration was varied between 1 and 5 wt%. For the distribution value of acid between the aqueous and organic phase, either 2 or 8 was used. For K_D/K'_D , 2 and 2.5 were used. For diluent-swing with anti-solvent, an additional factor of 2 for K_D/K'_D was applied over the standard factor to account for the changing nature of the diluent (decreased solvent polarity). For all combinations of variables, the results for the obtained concentration factor, as defined in eq (4), and the energy required compared to the energy of evaporation are shown in Figure 19.

In general, the influence of the initial acid concentration is small; a higher concentration slightly decreases the obtained concentration factor and increases the energy demand compared to that for evaporation. Also, temperature-swing regeneration requires more energy than each of the diluent-swing processes. Unlike for temperature-swing regeneration, the relative energy demand decreases strongly with increasing K_D for both diluent-swing processes. For temperature-swing regeneration, the effect of increasing K_D/K'_D on the relative energy required is larger than for increasing K_D , as was also found by Tamada.¹¹³

The process of diluent-swing by evaporation yields the highest concentration factors and has the lowest energy requirements compared to other processes. For diluent-swing regeneration both by evaporation and by addition of anti-solvent, the effect of increasing K_D is stronger than increasing K_D/K'_D . This is remarkable taking into account that for the anti-solvent process an additional factor of 2 is added for K_D/K'_D . The effect of K_D/K'_D is similar for regeneration by both temperature-swing and diluent-swing by addition of anti-solvent.

Brouwer et al.¹³⁶ calculated the energy requirements for a temperature-swing based regeneration process. In a double extraction–back-extraction cycle for levulinic acid and formic acid the concentration factor for both acids was 2.45, using a heater duty of 4.5 MJ per kg of lactic acid that is produced.¹³⁶ However, still a final distillation column is required to obtain the pure products. After the pre-concentration by the double extraction–back-extraction cycles, the distillation heat duty reduced from 31.5 MJ/kg acid to 11.3 MJ/kg acid.¹³⁶

Tamada¹¹³ studied the performance of both diluent-swing and temperature-swing processes to achieve 95 % recovery of succinic acid. The process of temperature-swing is based on a binary solvent of Alamine 336 in MIBK over a temperature range of 25-80 °C, and the diluent-swing process is based on Alamine 336 in chloroform where half of the solvent was evaporated. The concentration factor at a feed concentration of 0.1 M is approximately 9 for diluent-swing and around 7 for temperature-swing, which is high because the complexation of a tertiary amine is more temperature dependent than the complexation of a phosphine oxide¹³⁶ or aminopyridine.⁶⁶ In the case of 1.2 times the minimum solvent-to-feed ratio for a feed concentration of 0.1 M the temperature-swing process used approximately 9 MJ/kg acid produced, which is only a third of the energy of the diluent-swing process (26 MJ/kg acid produced), although resulting in lower concentrations of the product (product concentration of 0.44 M instead of 0.64 M for diluent-swing).¹¹³ For the temperature-swing regeneration process, a large shift in equilibrium allows for the use of less water in the regenerator and therefore a higher product concentration. For the diluent-swing the costs are mainly determined by the required total diluent flow that dominates the costs of evaporation in the regeneration. Higher distribution ratios can reduce this solvent flow.¹¹³

Similar to the results presented in Figure 19, the results from Tamada¹¹³ also imply that not only the distribution ratio K_D influences the energy and amount of solvent required in a regeneration process, also the distribution

ratio that is achieved at the changed conditions in the back-extraction step K'_D has a strong effect. This distribution ratio in the back-extraction step was also incorporated by Krzyzaniak et al.⁶⁶ in eq (27) as $1/K_D$.

4.5 Conclusions

Solvent developments for liquid-liquid extraction (LLX) of carboxylic acids were described for three main categories of solvents: composite solvents containing nitrogen based extractants, phosphorous based extractants and ionic liquids. The mechanism of extraction is influenced by multiple variables. Next to the characteristics of the acid and the extractant, the diluent plays an important role in the mechanism. There are many parameters that aim to describe the effect of the diluent on the liquid-liquid equilibrium. However, there is no single parameter that can describe all effects. The mechanism of complexation describes the various types of complexes that are formed in the organic phase during LLX. The complexes that are formed are also dependent on the diluent, and they determine the loading of the organic phase. The diluent not only influences the extraction in terms of polarity, solvation capacity and the dimerization constant of the acid in a specific diluent, but active diluents also affect the extraction through specific interactions and stabilization of complexes. Furthermore, the diluent influences the enthalpy change of the complexation reaction which determines the temperature effect. Reverse micelles are often present in IL solvents. This specific formation of clusters is a result of the combination of electrostatic and intermolecular forces. Two mechanisms play a role in the extraction of acids by ionic liquids, formation of complexes between IL and organic acid, and formation of reverse micelles that include the acid. Water can also be extracted through these two mechanisms.

The effect on the loading differs for dicarboxylic and monocarboxylic acids. For dicarboxylic acids, there is a decrease in loading with increasing diluent concentration, while for monocarboxylic acids there is only a small effect of increasing diluent concentration. The effect for dicarboxylic acids is an advantage in the case of diluent-swing regeneration. The hydrophobicity of the acids and the presence of additional functional groups are also important factors in the mechanism of LLX. In general, more hydrophobic and stronger monocarboxylic acids have a higher distribution ratio in TOA and also show a higher loading of TOA. Systems other than amine based extractants are also affected by the polarity and specific interactions of the diluent.

Using active, polar and proton donating diluents for the extraction of carboxylic acids results in higher values of the distribution ratio compared to inactive diluents. However, with such solvents the back-extraction of the

acids is more complicated. Therefore, combining both active and inactive diluents is a promising approach. Ionic liquids can be diluted to improve practical applications by reducing the viscosity, thereby modifying the solubility of solutes. Adding a polar diluent to an ionic liquid mixture can also increase the distribution coefficients. An important advantage is that an IL mixture with up to 80 mol% of co-solvent can still have the main properties of the IL.

The most beneficial swing for regeneration is diluent-swing regeneration by evaporation of a part of the diluent. This regeneration process increases the concentration factor that is obtained and reduces the energy demand. This means that not only a high K_D is important, but so is the swing in K_D .

Based on this, future work should focus on systems where K_D/K'_D is high. This implies that, instead of improving the K_D a good approach is to start with K_D values that are moderate. Since the affinity is lower in these cases, a high K_D/K'_D might be obtained by using a binary diluent that consists of both an active and an inactive diluent. Furthermore, in temperature-swing regeneration processes, a higher K_D/K'_D is obtained for a higher enthalpy of complexation. Therefore, research should focus on which combinations of extractants and diluents result in the largest enthalpies of complexation.

References

- (1) Straathof, A. J. J. *Chem Rev* 2014, *114*, 1871-1908.
- (2) Jess, A.; Wasserscheid, P.; Wiley-VCH: Weinheim, Germany :, 2013.
- (3) Koenig, G.; Lohmar, E.; Rupprich, N. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA, 2000.
- (4) Castro-Aguirre, E.; Iñiguez-Franco, F.; Samsudin, H.; Fang, X.; Auras, R. *Adv Drug Deliver Rev* 2016, *107*, 333-366.
- (5) Wasewar, K. L.; Yawalkar, A. A.; Moulijn, J. A.; Pangarkar, V. G. *Ind Eng Chem Res* 2004, *43*, 5969-5982.
- (6) Song, H.; Lee, S. Y. *Enzyme Microb Technol* 2006, *39*, 352-361.
- (7) Kubitschke, J.; Lange, H.; Strutz, H. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA, 2000.
- (8) Connor, J. M. *Global Price Fixing*; Springer Berlin Heidelberg: Berlin, Heidelberg, 2007, pp 113-136.
- (9) Bozell, J. J.; Moens, L.; Elliott, D. C.; Wang, Y.; Neuenschwander, G. G.; Fitzpatrick, S. W.; Bilski, R. J.; Jarnefeld, J. L. *Resour Conserv Recy* 2000, *28*, 227-239.
- (10) Le Berre, C.; Serp, P.; Kalck, P.; Torrence, G. P. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA, 2000.
- (11) Gao, C.; Ma, C.; Xu, P. *Biotechnol Adv* 2011, *29*, 930-939.
- (12) John, R. P.; G.S, A.; Nampoothiri, K. M.; Pandey, A. *Biotechnol Adv* 2009, *27*, 145-152.
- (13) Ghaffar, T.; Irshad, M.; Anwar, Z.; Aqil, T.; Zulifqar, Z.; Tariq, A.; Kamran, M.; Ehsan, N.; Mehmood, S. *J Radiat Res Appl Sci* 2014, *7*, 222-229.
- (14) Girisuta, B. *Levulinic acid from lignocellulosic biomass*. Doctoral Thesis, University of Groningen 2007.
- (15) Jeong, G.-T.; Kim, S.-K.; Park, D.-H. *Biot Bioproc Eng* 2013, *18*, 88-93.
- (16) Nhien, L. C.; Long, N. V. D.; Kim, S.; Lee, M. *Ind Eng Chem Res* 2016, *55*, 5180-5189.
- (17) van Putten, R.-J.; van der Waal, J. C.; de Jong, E.; Rasrendra, C. B.; Heeres, H. J.; de Vries, J. G. *Chem Rev* 2013, *113*, 1499-1597.
- (18) Hano, T.; Matsumoto, M.; Ohtake, T.; Sasaki, K.; Hori, F.; Kawano, Y. *J Chem Eng Jpn* 1990, *23*, 734-738.
- (19) López-Garzón, C. S.; Straathof, A. J. J. *Biotechnol Adv* 2014, *32*, 873-904.
- (20) Shan, X.; Qin, W.; Dai, Y. *Chem Eng Sci* 2006, *61*, 2574-2581.
- (21) Lo, T. C.; Baird, M. H. I.; Hanson, C. *Handbook of solvent extraction*; Wiley: New York :, 1983.
- (22) Wasewar, K. L. *Int J Chem Eng Appl* 2012, *3*, 249-255.

- (23) Tamada, J. A.; Kertes, A. S.; King, C. J. *Ind Eng Chem Res* 1990, *29*, 1319-1326.
- (24) Tamada, J. A.; King, C. J. *Ind Eng Chem Res* 1990, *29*, 1327-1333.
- (25) Tung, L. A.; King, C. J. *Ind Eng Chem Res* 1994, *33*, 3224-3229.
- (26) Tung, L. A.; King, C. J. *Ind Eng Chem Res* 1994, *33*, 3217-3223.
- (27) Marták, J.; Schlosser, Š. *Sep Purif Technol* 2007, *57*, 483-494.
- (28) Ijmker, H. M.; Gramblička, M.; Kersten, S. R. A.; Van Der Ham, A. G. J.; Schuur, B. *Sep Purif Technol* 2014, *125*, 256-263.
- (29) Krzyzaniak, A.; Leeman, M.; Vossebeld, F.; Visser, T. J.; Schuur, B.; de Haan, A. B. *Sep Purif Technol* 2013, *111*, 82-89.
- (30) Rocha, M. A. A.; Raeissi, S.; Hage, P.; Weggemans, W. M. A.; van Spronsen, J.; Peters, C. J.; Kroon, M. C. *Chem Eng Sci*.
- (31) Athankar, K. K.; Wasewar, K. L.; Varma, M. N.; Shende, D. Z. *J Chem Eng Data* 2016, *61*, 2335-2345.
- (32) Burghoff, B.; Cuypers, R.; van Ettinger, M.; Sudhölter, E. J. R.; Zuilhof, H.; de Haan, A. B. *Sep Purif Technol* 2009, *67*, 117-120.
- (33) Uslu, H.; Datta, D.; Bamufleh, H. S. *J Mol Liq* 2015, *212*, 430-435.
- (34) Uslu, H.; Inci, I. *Chem Eng Technol* 2009, *32*, 1951-1957.
- (35) Malmay, G. H.; Monteil, F.; Molinier, J. R.; Hanine, H.; Conte, T.; Mourgues, J. *Bioresour Technol* 1995, *52*, 33-36.
- (36) Das, D.; Juvekar, V. A.; Roy, S. B.; Bhattacharya, R. *J Radioanal Nucl Chem* 2014, *300*, 333-343.
- (37) Dafoe, J. T.; Daugulis, A. J. *Biotechnol Lett* 2014, *36*, 443-460.
- (38) Schlosser, Š.; Kertész, R.; Marták, J. *Sep Purif Technol* 2005, *41*, 237-266.
- (39) Barrow, G. M.; Yerger, E. A. *J Am Chem Soc* 1954, *76*, 5211-5216.
- (40) King, C. J. *ChemTech* 1992, *22*, 285-291.
- (41) Poole, L. J.; King, C. J. *Ind Eng Chem Res* 1991, *30*, 923-929.
- (42) Starr, J. N.; King, C. J. Water-enhanced solubility of carboxylic acids in organic solvents and its applications to extraction processes; Lawrence Berkeley Lab. 1991.
- (43) Tamada, J.; King, C. *Ind Eng Chem Res* 1990, *29*, 1333-1338.
- (44) Wardell, J. M.; King, C. J. *J Chem Eng Data* 1978, *23*, 144-148.
- (45) Marti, M. E. *Sep Sci Technol* 2016, 1-11.
- (46) Reyhanitash, E.; Zaalberg, B.; Ijmker, H. M.; Kersten, S. R. A.; Schuur, B. *Green Chem* 2015, *17*, 4393-4400.
- (47) Rasrendra, C. B.; Girisuta, B.; van de Bovenkamp, H. H.; Winkelman, J. G. M.; Leijenhurst, E. J.; Venderbosch, R. H.; Windt, M.; Meier, D.; Heeres, H. J. *Chem Eng J* 2011, *176-177*, 244-252.
- (48) Qin, W.; Li, Z.; Dai, Y. *Ind Eng Chem Res* 2003, *42*, 6196-6204.
- (49) Ziegenfu, H.; Maurer, G. *Fluid Phase Equilib* 1994, *102*, 211-255.
- (50) Procházka, J.; Heyberger, A.; Volaufová, E. *Sep Sci Technol* 2005,

- 39, 1073-1091.
- (51) Gu, B. H.; Zheng, P.; Yan, Q.; Liu, W. *Sep Purif Technol* 2014, 138, 47-54.
- (52) San-Martín, M.; Pazos, C.; Coca, J. *J Chem Technol Biot* 1996, 65, 281-285.
- (53) Matsumoto, M.; Takahashi, T.; Fukushima, K. *Sep Purif Technol* 2003, 33, 89-93.
- (54) Wasewar, K. L.; Keshav, A.; Seema. *Int J Res Rev Appl Sci* 2010, 3, 290-302.
- (55) Bízek, V.; Horáček, J.; Koušová, M. *Chem Eng Sci* 1993, 48, 1447-1457.
- (56) Prochazka, J.; Heyberger, A.; Bizek, V.; Kousova, M.; Volaufova, E. *Ind Eng Chem Res* 1994, 33, 1565-1573.
- (57) Eyal, A. M.; Canari, R. *Ind Eng Chem Res* 1995, 34, 1789-1798.
- (58) Syzova, N.; Eyal, A. M.; Vitner, A.; Hazan, B. *Solvent Extr Ion Exch* 2004, 22, 31-49.
- (59) Inci, I. *J Sci Ind Res* 2002, 61, 817-822.
- (60) Matsumoto, M.; Otono, T.; Kondo, K. *Sep Purif Technol* 2001, 24, 337-342.
- (61) Wasewar, K. L.; Shende, D.; Keshav, A. *Ind Eng Chem Res* 2011, 50, 1003-1011.
- (62) Rewatkar, K.; Shende, D. Z.; Wasewar, K. L. *J Chem Eng Data* 2016, 61, 3217-3224.
- (63) Oliveira, F. S.; Araujo, J. M. M.; Ferreira, R.; Rebelo, L. P. N.; Marrucho, I. M. *Sep Purif Technol* 2012, 85, 137-146.
- (64) Siebold, M.; Frieling, P.v.; Joppien, R.; Rindfleisch, D.; Schügerl, K.; Röper, H. *Process Biochem* 1995, 30, 81-95.
- (65) Jongmans, M. T. G.; Londoño, A.; Mamilla, S. B.; Praght, H. J.; Aaldering, K. T. J.; Bargeman, G.; Nieuwhof, M. R.; Kate, A. t.; Verwer, P.; Kiss, A. A.; van Strien, C. J. G.; Schuur, B.; de Haan, A. B. *Sep Purif Technol* 2012, 98, 206-215.
- (66) Krzyzaniak, A.; Schuur, B.; de Haan, A. B. *Chem Eng Sci* 2014, 109, 236-243.
- (67) Li, Z.; Qin, W.; Dai, Y. *J Chem Eng Data* 2002, 47, 843-848.
- (68) Lei, Z.; Li, C.; Li, Y.; Chen, B. *Sep Purif Technol* 2004, 36, 131-138.
- (69) Scheler, C.; Popovic, M.; Iannotti, E.; Mueller, R.; Bajpai, R. *Seventeenth Symposium on Biotechnology for Fuels and Chemicals: Presented as Volumes 57 and 58 of Appl Biochem Biot*; Wyman, C. E.; Davison, B. H., Eds.; Humana Press: Totowa, NJ, 1996, pp 29-38.
- (70) Ingale, M. N.; Mahajani, V. V. *Sep Technol* 1994, 4, 123-126.
- (71) Masaru, N.; Tatsuya, S. *Bull Chem Soc Jpn* 1978, 51, 705-709.
- (72) Morales, A. F.; Albet, J.; Kyuchoukov, G.; Malmay, G.; Molinier, J.

- J Chem EngData* 2003, *48*, 874-886.
- (73) Kyuchoukov, G.; Morales, A. F.; Albet, J.; Malmay, G.; Molinier, J. *J Chem Eng Data* 2008, *53*, 639-647.
- (74) Reichardt, C. *Solvents and solvent effects in organic chemistry*; 3rd, updated and enl. ed. ed.; Wiley-VCH: Weinheim, 2003.
- (75) Li, Z.; Qin, W.; Dai, Y. *Tsinghua Sci Technol* 2002, *7*, 41-45.
- (76) Keshav, A.; Wasewar, K. L.; Chand, S.; Uslu, H. *Fluid Phase Equilib* 2009, *275*, 21-26.
- (77) Wang, Y.; Jiang, W.; Yan, T.; Voth, G. A. *Acc Chem Res* 2007, *40*, 1193-1199.
- (78) Gupta, A.; Sharma, S.; Kashyap, H. K. *J Chem Phys* 2015, *142*, 134503.
- (79) Chen, S.; Zhang, S.; Liu, X.; Wang, J.; Wang, J.; Dong, K.; Sun, J.; Xu, B. *PCCP* 2014, *16*, 5893-5906.
- (80) Bandlamudi, S. R. P.; Cooney, M. J.; Martin, G. L.; Benjamin, K. M. *Ind Eng Chem Res* 2017.
- (81) Hayes, R.; Warr, G. G.; Atkin, R. *Chem Rev* 2015, *115*, 6357-6426.
- (82) Blahusiak, M.; Schlosser, S. *J Chem Thermodyn* 2014, *72*, 54-64.
- (83) Marták, J.; Schlosser, Š. *Desalination* 2006, *199*, 518-520.
- (84) Blahusiak, M.; Schlosser, S.; Martak, J. *Sep Purif Technol* 2013, *119*, 102-111.
- (85) Marták, J.; Schlosser, Š. *Chem Pap* 2006, *60*, 395-398.
- (86) Marták, J.; Schlosser, Š. *J Chem Eng Data* 2016, *61*, 2979-2996.
- (87) Reyhanitash, E.; Egor Fufachev; Kaspar D. van Munster; Michael B.M. van Beek; Lisette M.J. Sprakel; Carmen N. Edelijn; Bert M. Weckhuysen; Sascha R.A. Kersten; Pieter Bruijninx; Schuur, B. Carboxylic acid recovery from phosphonium phosphinate ionic liquid. *submitted* 2017.
- (88) Laurence, C.; Graton, J.; Gal, J.-F. *J Chem Educ* 2011, *88*, 1651-1657.
- (89) Laurence, C.; Gal, J.-F. *Lewis Basicity and Affinity Scales*; John Wiley & Sons, Ltd, 2009, p i-xv.
- (90) Maksić, Z. B.; Kovačević, B.; Vianello, R. *Chem Rev* 2012, *112*, 5240-5270.
- (91) Kamlet, M. J.; Abboud, J. L. M.; Abraham, M. H.; Taft, R. W. *J Org Chem* 1983, *48*, 2877-2887.
- (92) Gutmann, V. *Coord Chem Rev* 1976, *18*, 225-255.
- (93) Hildebrand, J. H.; Scott, R. L. *The solubility of nonelectrolytes*; Reinhold Pub. Corp., 1950.
- (94) Hansen, C. M. *The Three Dimension Solubility Parameter and Solvent Diffusion Coefficient; Their Importance in Surface Coating Formulation*; Danish Tech. Press, 1967, p 106 pp.

- (95) Bizek, V.; Horacek, J.; Rericha, R.; Kousova, M. *Ind Eng Chem Res* 1992, *31*, 1554-1562.
- (96) Schmidt, V.; Rybakov, K.; Rubisov, V. *Russ J Inorg Chem* 1980, *25*, 1062-1064.
- (97) Kosower, E. M. *J Am Chem Soc* 1958, *80*, 3253-3260.
- (98) Reichardt, C. *Chem Rev* 1994, *94*, 2319-2358.
- (99) Abraham, M. H. *Chem Soc Rev* 1993, *22*, 73-83.
- (100) Gemici, A.; Uslu, H.; Gök, A.; Kirbaşlar, Ş. İ. *J Chem Eng Data* 2015, *60*, 919-924.
- (101) Bradley, J.-C.; Abraham, M. H.; Acree, W. E.; Lang, A. S. *Chem Cent J* 2015, *9*, 12.
- (102) Acree, J. W. E.; Abraham, M. H. *J Chem Technol Biot* 2006, *81*, 1441-1446.
- (103) Abraham, M. H.; Acree, W. E. *J Phys Org Chem* 2008, *21*, 823-832.
- (104) Abraham, M. H.; Acree, W. E.; Leo, A. J.; Hoekman, D. *New J Chem* 2009, *33*, 568-573.
- (105) Jean-Claude, B.; William, A.; Andrew, L. *Compounds with known Abraham descriptors*. Online database at <https://ndownloader.figshare.com/files/1684722>, 2014.
- (106) Abraham, M. H.; Smith, R. E.; Luchtefeld, R.; Boorem, A. J.; Luo, R.; Acree, W. E. *J Pharm Sci* 2010, *99*, 1500-1515.
- (107) Eckert, F.; Klamt, A. *AIChE J* 2002, *48*, 369-385.
- (108) Garcia-Chavez, L. Y.; Hermans, A. J.; Schuur, B.; de Haan, A. B. *Sep Purif Technol* 2012, *97*, 2-10.
- (109) Li, X.; Kersten, S. R. A.; Schuur, B. *Ind Eng Chem Res* 2016, *55*, 4703-4710.
- (110) Bokhove, J.; Schuur, B.; de Haan, A. B. *Chem Eng Sci* 2012, *82*, 215-222.
- (111) Fujii, Y.; Yamada, H.; Mizuta, M. *J Phys Chem* 1988, *92*, 6768-6772.
- (112) Pham, H. H.; Taylor, C. D.; Henson, N. J. *J Phys Chem B* 2013, *117*, 868-876.
- (113) Tamada, J.; King, C. J. *Extraction of Carboxylic Acids by Amine Extractants*. Berkeley, CA, 1989.
- (114) Canongia Lopes, J. N. A.; Pádua, A. A. H. *J Phys Chem B* 2006, *110*, 3330-3335.
- (115) Reyhanitash, E.; Zaalberg, B.; Kersten, S. R. A.; Schuur, B. *Sep Purif Technol* 2016, *161*, 61-68.
- (116) López-Barrón, C. R.; Li, D.; DeRita, L.; Basavaraj, M. G.; Wagner, N. J. *J Am Chem Soc* 2012, *134*, 20728-20732.
- (117) Shimizu, K.; Costa Gomes, M. F.; Pádua, A. A. H.; Rebelo, L. P. N.; Canongia Lopes, J. N. *J Mol Struct: TheoChem* 2010, *946*, 70-76.

- (118) Kashin, A. S.; Galkin, K. I.; Khokhlova, E. A.; Ananikov, V. P. *Angew Chem Int Ed* 2016, *55*, 2161-2166.
- (119) Jessop, P. G.; Jessop, D. A.; Fu, D.; Phan, L. *Green Chem* 2012, *14*, 1245-1259.
- (120) Gemici, A.; Uslu, H.; Kirbaşlar, Ş. İ. *J Chem Eng Data* 2015.
- (121) Michelsen, P. J. *Relationship between chromatographic retention and donor and acceptor numbers*. Rochester Institute of Technology, 1990.
- (122) Cataldo, F. *Eur Chem Bull* 2015, *4*, 92-97.
- (123) Kumar, S.; Babu, B. V. *J Chem Eng Data* 2009, *54*, 2669-2677.
- (124) IARC. IARC Monograph MIBK. <https://monographs.iarc.fr/ENG/Monographs/vol101/mono101-008.pdf>
- (125) Mishra, P. K.; Mondal, M. K.; Srivastava, P. *Separation Processes: Emerging Technologies for Sustainable Development*; Centre of Advanced Study, Department of Chemical Engineering & Technology, Institute of Technology, Banaras Hindu University, 2009.
- (126) Stenutz, R.; A collection of tables for chemistry, <http://www.stenutz.eu/>
- (127) Mayer, U.; Gutmann, V.; Gerger, W. *Monatsh Chem* 1975, *106*, 1235-1257.
- (128) Hansen, C. M. *J Paint Technol* 1967, *39*, 104-117.
- (129) Wisniewski, M.; Pierzchalska, M. *J Chem Technol Biot* 2005, *80*, 1425-1430.
- (130) Qin, W.; Zhang, Y.; Li, Z.; Dai, Y. *J Chem Eng Data* 2003, *48*, 430-434.
- (131) Matsumoto, M.; Uenoyama, S.; Hano, T.; Hirata, M.; Miura, S. *J Chem Technol Biot* 1996, *67*, 260-264.
- (132) Cuypers, R.; Burghoff, B.; Marcelis, A. T. M.; Sudhölter, E. J. R.; de Haan, A. B.; Zuilhof, H. *J Phys Chem A* 2008, *112*, 11714-11723.
- (133) Abdulrahman, A. *Acetic acid removal from pre-pulping wood extract*. Master's Thesis, University of Maine, 2010.
- (134) Cai, W.; Zhu, S.; Piao, X. *J Chem Eng Data* 2001, *46*, 1472-1475.
- (135) Yang, Y.-Z.; Yang, Y.-H.; Sun, G.-X.; Meng, X.-J.; Wang, Z.-Q.; Sun, S.-X. *Chem J Chinese U* 1996, *17*, 515-518.
- (136) Brouwer, T.; Blahusiak, M.; Babic, K.; Schuur, B. *Sep Purif Technol* 2017, *185*, 186-195.
- (137) Verma, T. *Reactive Extraction of acetic acid*. Rourkela, Odisha, 2014.
- (138) Keshav, A.; Wasewar, K. L.; Chand, S. *J Chem Technol Biot* 2009, *84*, 484-489.
- (139) Demesa, A. G.; Laari, A.; Tirronen, E.; Turunen, I. *Chem Eng Res Des* 2015, *93*, 531-540.
- (140) Kyuchoukov, G.; Yankov, D. *Ind Eng Chem Res* 2012, *51*, 9117-

- (141) Malmarmy, G.; Albet, J.; Putranto, A.; Hanine, H.; Molinier, J. *J Chem Eng Data* 1998, *43*, 849-851.
- (142) Canari, R.; Eyal, A. M. *Ind Eng Chem Res* 2004, *43*, 7608-7617.
- (143) Ladesov, A. V.; Kosyakov, D. S.; Bogolitsyn, K. G.; Gorbova, N. S. *Russ J Phys Chem A* 2015, *89*, 1814-1820.
- (144) Manohar, C. V.; Banerjee, T.; Mohanty, K. *J Mol Liq* 2013, *180*, 145-153.
- (145) Yang, Q.; Xing, H.; Cao, Y.; Su, B.; Yang, Y.; Ren, Q. *Ind Eng Chem Res* 2009, *48*, 6417-6422.
- (146) Ni, X.; Xing, H.; Yang, Q.; Wang, J.; Su, B.; Bao, Z.; Yang, Y.; Ren, Q. *Ind Eng Chem Res* 2012, *51*, 6480-6488.
- (147) Gao, J.; Chen, L.; Xin, Y.; Yan, Z. *J Chem Eng Data* 2014, *59*, 2150-2158.
- (148) Mellein, B. R.; Aki, S. N. V. K.; Ladewski, R. L.; Brennecke, J. F. *J Phys Chem B* 2007, *111*, 131-138.
- (149) Dong, Y.; Sun, X.; Wang, Y.; Chai, Y. *AIChE J* 2016, *62*, 2163-2169.
- (150) Schlosser, Š.; Marták, J.; Blahušiak, M. *Chem Pap* 2018, *72*, 567-584.
- (151) Marták, J.; Schlosser, Š. *J Chem Eng Data* 2017, *62*, 3025-3035.
- (152) Claudio, A. F. M.; Neves, M. C.; Shimizu, K.; Canongia Lopes, J. N.; Freire, M. G.; Coutinho, J. A. P. *Green Chem* 2015, *17*, 3948-3963.
- (153) Cláudio, A. F. M.; Cognigni, A.; de Faria, E. L. P.; Silvestre, A. J. D.; Zirbs, R.; Freire, M. G.; Bica, K. *Sep Purif Technol* 2018, *204*, 30-37.
- (154) Freire, M. G.; Claudio, A. F. M.; Araujo, J. M. M.; Coutinho, J. A. P.; Marrucho, I. M.; Lopes, J. N. C.; Rebelo, L. P. N. *Chem Soc Rev* 2012, *41*, 4966-4995.
- (155) Pratiwi, A. I.; Yokouchi, T.; Matsumoto, M.; Kondo, K. *Sep Purif Technol* 2015, *155*, 127-132.
- (156) Yan-Ying, Y.; Wei, Z.; Shu-Wen, C. *Chinese J Anal Chem* 2007, *35*, 1726-1730.
- (157) Fu, X.; Dai, S.; Zhang, Y. *Chinese J Anal Chem* 2006, *34*, 598-602.
- (158) Hong, Y.; Hong, W.; Han, D. *Biot Bioproc Eng* 2001, *6*, 386-394.
- (159) Ricker, N. L.; Pittman, E. F.; King, C. J. *J Sep Process Technol* 1980, *1*, 23-30.
- (160) Shah, V. H.; Pham, V.; Larsen, P.; Biswas, S.; Frank, T. *Ind Eng Chem Res* 2016, *55*, 1731-1739.
- (161) Blahušiak, M.; Kiss, A. A.; Babic, K.; Kersten, S. R. A.; Bargeman, G.; Schuur, B. *Sep Purif Technol* 2018, *194*, 301-318.
- (162) De Haan, A.B.; Van Krieken, J.; Dekic Zivkovic, T.; Lactic Acid extraction, Patent number: WO2013093028A1, 2013.
- (163) Blahušiak, M.; Schlosser, S.; Cvengros, J.; Martak, J. *Chem Pap*

- 2011, *65*, 603-607.
- (164) Han, D.; Hong, Y.; Hong, W. *Korean J Chem Eng* 2000, *17*, 528-533.
- (165) Jung, M.; Schierbaum, B.; Vogel, H. *Chem Eng Technol* 2000, *23*, 70-74.
- (166) Kroon, M. C.; van Spronsen, J.; Peters, C. J.; Sheldon, R. A.; Witkamp, G.-J. *Green Chem* 2006, *8*, 246-249.
- (167) Haan, A. B. d.; Bosch, H. *Industrial separation processes: fundamentals*; Walter de Gruyter, GmbH, & Co., KG: Berlin; 2013.
- (168) Brunauer, S.; Deming, L. S.; Deming, W. E.; Teller, E. *J Am Chem Soc* 1940, *62*, 1723-1732.
- (169) Germani, R.; Mancini, M. V.; Savelli, G.; Spreti, N. *Tetrahedron Lett* 2007, *48*, 1767-1769.
- (170) Germani, R.; Mancini, M. V.; Spreti, N.; Profio, P. D.; Savelli, G. *Green Sust Chem* 2011, *01 (04)*, 10.
- (171) Hong, Y.; Hong, W.; Chang, H. *Biotechnol Lett* 2000, *22*, 871-874.
- (172) McMorris, J.; Husson, S. M. *Sep Sci Technol* 2001, *36*, 1129-1148.

The background is a complex, low-poly geometric pattern in various shades of red, from dark maroon to bright, almost white highlights. The pattern consists of numerous triangles and polygons of different sizes, creating a faceted, crystalline appearance. In the center of the image, a large, white, stylized number '5' is prominently displayed. The number has a modern, slightly rounded font style. Below the number, there is a line of text in a white, sans-serif font.

5

Improving understanding of solvent
effects on intermolecular interactions
in reactive liquid-liquid extraction

Abstract

Isothermal titration calorimetry (ITC) and molecular modeling (MM) were combined with liquid-liquid equilibrium data to obtain a better understanding of solvent effects on the complexation in reactive liquid-liquid extraction. Two examples with ample extraction literature available were studied, acetic acid extraction and phenol extraction. Interactions with binary solvents were studied. Based on the insight and quantification of complexation with MM and ITC, models describing the liquid-liquid equilibrium (LLE) were formulated and validated with experiments, showing that ITC can predict LLE. ITC together with MM can indeed yield additional insight in the complexation behavior in reactive liquid-liquid extraction and may guide solvent selection procedures.

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5.1 Introduction

Liquid-liquid extraction (LLX) is a commonly used technique with applications in the petrochemical industry,¹ pharmaceutical industry,²⁻⁴ nylon industry,⁵ wastewater treatment⁶ and fermentation processes.⁷⁻⁹ For feed streams where one of the components is present in very low concentration, distillation is intrinsically inefficient.¹⁰ Affinity based separation processes such as liquid-liquid extraction that address the dilute solute are promising alternatives for such dilute solute streams. With the changing orientation of the chemical industry towards more renewable feedstock, affinity separations become much more important.¹¹ The selection or design of the most appropriate solvent is not straight forward, as the solvent should preferentially have a high capacity and selectivity in the extraction step to reduce the solvent-to-feed ratio, but regeneration should also be possible to recycle the solvent and obtain the solute preferentially in concentrated streams. Good understanding of the intermolecular interactions in solvents that are typically reactive is required to find the best combination of a good distribution in the primary separation, while allowing for proper regeneration of the solvent.

For physical solvents a number of solvent screening approaches is available, e.g. based on the linear solvation energy relationship (LSER) or the more expanded Abrahams model.¹² The drawback of these models is that new solvents first need to be parametrized based on distributions of solutes with known parameters, which is labor intensive. Alternatively, COSMO-RS may be applied,¹³ a software package deriving its parameters from quantum chemical calculations. This might still be time-consuming if the solvent is not in the database. For reactive solvents, affinity scales describing the interaction between extractants and solutes may be more applicable for solvent screening.¹⁴ Examples of these scales are the BF_3 -affinity scale for strong interactions and the pK_{BHX} hydrogen-bond basicity scale for weak interactions.¹⁵

All of these approaches may yield initial screening results, after which in-depth studies are required, because typically conditions change between the extraction and regeneration and the effect of the conditions on the solvent is highly important information in the selection of a solvent and design of an LLX process.¹⁶ Since this effect cannot be based on the affinity scales or empirical linear relationships, a good insight in and understanding of the mechanism and interactions of the complexation is required. We aim to obtain this insight by combining theoretical and practical methods, including direct homogeneous measurement of interaction energy through isothermal titration calorimetry (ITC), and molecular modeling (MM).

The studies are complemented and validated using liquid-liquid-equilibria (LLE). With this approach, direct results are obtained on the complexation behavior between solvent and solute, and interpretation thereof is aided by MM. The extractions of acetic acid (HAc) and the less acidic phenol (PhOH) serve as case studies that were selected because of industrial relevance, resulting in ample literature being available, e.g. on the extraction of acids from fermentation processes^{7,8} and other biobased streams¹⁷ and removal of phenol from wastewater,^{18,19} that can be used for comparison.

A key factor in extraction processes is the ratio of the distribution coefficient (eq (1)) in the forward extraction over the back-extraction.¹⁶ The effect of operational parameters such as the choice of diluent and the temperature on the intermolecular interactions between solute and extractant (and thus indirectly the distribution ratio) was studied with ITC and MM for extraction systems using tri-*n*-octylamine (TOA),¹⁹⁻²¹ trioctylphosphine oxide (TOPO) and tributylphosphate (TBP).²²⁻²⁷ Extractant structures are given in Figure 1. Based on the insights in the intermolecular interaction behavior with temperature and diluent composition, future research can be directed, not only with regard to solvent composition but also for extractant design. With the upcoming biorefinery separations, development of new LLX systems is highly important and may be aided using the combination of ITC and MM reported here.

Figure 1 Structure of extractants trioctylamine (TOA), trioctylphosphine oxide (TOPO) and tributylphosphate (TBP) applied in this work.

5.2 Theory

The distribution ratio of an acid HA as defined in eq (1) results from a set of simultaneous equilibria displayed in Figure 2. The overbar indicates organic phase compounds, and B is the extractant.

$$K_{D,a} = \frac{\overline{c_a}}{c_a} \quad (1)$$

Figure 2 Schematic overview of reactions in a liquid-liquid equilibrium.

Next to aqueous phase acid dissociation (K_a) and physical acid partitioning (K_m), complexes with B in various stoichiometries can be observed depending on the system and the conditions.²⁸ E.g. for tertiary amines, next to direct binding of the first acid to the amine, additional acid molecules can bind sequentially to the acid amine complex through hydrogen bonding.^{28,29} It is assumed that the interactions of all sequentially hydrogen bonding acids are identical, but may be different from the interaction of the first acid with the amine. The example in Figure 3a²⁸ shows proton transfer from the first acid to the extractant, whereas also extraction mechanisms in which hydrogen bonding is the dominating interaction for the first acid have been reported.^{22,28,30}

Figure 3 Complex of trioctylamine with **a**) three acetic acid molecules and **b**) acetic acid and the active diluent 1-octanol.

To account for the difference in interaction of the first acid and following acids with the extractant, a consecutive reactions model can be applied in the case of overloading of the amine.³¹ The first reaction is described in eq (2).

In this reaction the (1,1)-complex is formed with reaction enthalpy $\Delta H_{1,1}$. The equilibrium constant of this reaction $K_{1,1}$ can be defined as:

$$K_{1,1} = \frac{[\text{HAB}]}{[\text{HA}][\text{B}]} \quad (3)$$

And the consecutive reactions are described in eq (4) as a lumped equation, which may be done assuming all hydrogen bond based affinities are similar.

In this reaction the (1,1)-complex reacts with n acid molecules to form the new complex, the reaction enthalpy of this reaction is $\Delta H_{n+1,1}$. The equilibrium constant of this reaction $\Delta H_{n+1,1}$ is defined as:

$$K_{n+1,1} = \frac{[(\text{HA})_{n+1} \text{B}]}{[\text{HAB}][\text{HA}]^n} \quad (5)$$

5.2.1 Model extension for active diluent complexation

Active diluents such as 1-octanol may actively participate in complex formation.^{28,29,32,33} For the active diluent 1-octanol (O), the reaction is described by eq (6), where HAB is the acid-extractant complex and HABO is the complex with 1-octanol. Other active diluents such as chloroform interact similarly. Figure 3b shows the complex formation between the extractant TOA, the acetic acid and the diluent.

The equilibrium constant of this reaction $K_{1,1,O}$ is defined as:

$$K_{1,1,O} = \frac{[HABO]}{[HAB][O]} \quad (7)$$

5.2.2 Isothermal titration calorimetry (ITC)

With ITC any type of thermal interaction effects between molecules can be analyzed, and in a previous publication its applicability and accuracy for studying LLX was described.³¹ From the titration curve the enthalpy of the reaction ΔH , the stoichiometry of complexation n and the binding association constant K , can be fitted to model equations. From these parameters ΔG and ΔS can be calculated, using eq (8) and (9).³⁴ By determining all thermodynamic parameters, ITC can provide insight in the extraction mechanism.

$$\Delta G = -RT \ln K \quad (8)$$

$$\Delta G = \Delta H - T\Delta S \quad (9)$$

Assuming a constant $\Delta H_{1,1}$, the dependence of the equilibrium constant on the temperature T is given in eq (10), which is derived from eq (8) and eq (9).

$$\ln \frac{K_{T_2}}{K_{T_1}} = \frac{-\Delta H}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right) \quad (10)$$

The temperature dependent shift in equilibrium constant has a major effect on the shift in distribution ratio of the acid with a change of temperature.

The fitting parameters of the sequential binding model of eq (2)-(5) are $K_{1,1}$, $\Delta H_{1,1}$, $K_{n+1,1}$, $\Delta H_{n+1,1}$ and n , and are fitted to the total energy released Q_{tot} in eq (11). For the model where the molecule of 1-octanol is incorporated in the complex, the total energy released is fitted to eq (12), including the additional fitting parameters $K_{1,1,O}$ and ΔH_3 .

$$Q_{\text{tot}} = V_{\text{tot}} \left([\text{HAB}] \Delta H_{1,1} + \left[(\text{HA})_{n+1} \text{B} \right] (\Delta H_{1,1} + n \Delta H_{n+1,1}) \right) \quad (11)$$

$$Q_{\text{tot}} = V_{\text{tot}} \left([\text{HAB}] \Delta H_{1,1} + \left[(\text{HA})_{n+1} \text{B} \right] (\Delta H_{1,1} + n \Delta H_{n+1,1}) + [\text{HABO}] (\Delta H_{1,1} + \Delta H_3) \right) \quad (12)$$

5.3 Experimental

5.3.1 Chemicals

Chemicals were used without further purification and commercially obtained from Sigma Aldrich (acetic acid (HAc, > 99.7 %), phenol (PhOH, > 99 %), trioctylamine (TOA, 98 %), trioctylphosphine oxide (TOPO, 99 %), 1-octanol (> 99 %), heptane (99 %), methylisobutylketon (MIBK, ≥ 99 %), chloroform (≥ 99 %), ethyl acetate (99.8 %)), from Acros Organics (tributylphosphate (TBP, 99 %)) and from VWR International (toluene (> 99.5 %)).

5.3.2 Isothermal titration calorimetry (ITC)

Isothermal titration calorimetry was performed on a TA Instruments TAM III Microcalorimeter, operated with the procedure previously published.³¹ For experiments with TBP a 1 mL sample vial was used that contained about 0.65 mL of organic solvent. Unless mentioned otherwise, the extractant concentration was 0.24 M. The injection volume was set between 5 - 20 µL and the injection interval was 75 minutes to ensure that the signal was back at the baseline level. In the case of acetic acid, blank titration measurements were performed to correct for dilution of the titrant. For the experiment with 2.4 M TBP in heptane (> 50 vol%) the data were corrected with the heat released from the last injection because the sample mixture is much more polar than the pure heptane in the blank measurement. For the experiments with phenol and TOA the data were corrected with the energy released by the last injection because of the low K-value and heat release, whereas for TOPO and TBP the data were corrected based on the results of blank measurements. Previous work on a similar system of acetic acid and 0.24 M TOA with a parameter fit based on the sequential model of eq (2)-(5) showed standard deviations of 11 % in $K_{1,1}$, 4.2 % in $\Delta H_{1,1}$, 26 % in $K_{n+1,1}$, 12 % in $\Delta H_{n+1,1}$ and 1.4 % in n .³¹

5.3.3 Liquid-liquid equilibria (LLE)

LLE experiments were performed by mixing 3 ml of an aqueous acid solution with 3 ml of an organic solution in 10 mL glass vials. The initial acetic acid concentration was 2.0 wt% and the initial phenol concentration was 1.0 wt%. Vials were extensively shaken by hand and vortex mixer, and then placed into a shaking water bath with a shaking speed of 200 rpm for 4 hours. Thereafter the phases were allowed to settle for 1 hour, after which samples were taken from the aqueous phase for analysis. The concentrations in the organic phase were determined by a mass balance. The temperature in the shaking bath was set to either 20 °C or 60 °C.

5.3.4 HPLC

The aqueous phase of the LLE experiments was analyzed with an Agilent HPLC 1200 series equipped with a Refractive Index (RI) Detector (error ≤ 1 %). The columns used are an Agilent Hi-plex H+ Column (300*7.7 mm) or a GROM Resin H+ IEX (250*8 mm) column, with a 5 mM H₂SO₄ solution mobile phase and a flow rate of 0.6 mL/min.

5.3.5 Molecular modeling

Molecular Modeling of the intermolecular interactions was performed with Wavefunction Spartan'16 Parallel software. The interaction between two molecules can be described using the energy of the system of molecules as a function of the intermolecular distance. To obtain these profiles for the acids and extractants applied in this study, calculations were performed with a constrained distance between the acid and extractant modeled. For each distance, the optimized geometries and energy profiles were calculated for the molecules with the Hartree-Fock 6-31G* level of calculation, since higher order calculations showed no significant differences. The calculated energies were normalized by referencing them to systems with a very large intermolecular distance whose interaction energy was set at zero. For solvation the SM8 model was used in combination with the Hartree-Fock method, which is a parametrization for all atoms that treats the solvent as a continuous field. The carbon chain length of extractants with long hydrocarbon tails was shortened to reduce the computation time. A comparison between complexes of trioctylamine (TOA) and tripropylamine (TPA) with up to five acid molecules showed that the structures and relative interaction energies of the complexes are not significantly dependent on the carbon chain length of the amine. There is only an increase in the absolute interaction energy for the complex of the first acid with TOA, a direct result of the increased carbon chain length. This will however have a similar effect for all applied diluents and extractants.

5.4 Results and discussion

5.4.1 Typical ITC experiment

In Figure 4 the results of a typical ITC experiment are displayed, in which acetic acid is titrated into the solvent comprising of 0.24 M TOA in toluene at 20 °C. In Figure 4a the heat released by the reaction of the components is shown. The ‘S-curve’ in Figure 4b is obtained by integrating the heat release from Figure 4a. The first data point (at the lowest value of molar ratio) is very high. A deviant first data point is seen more often in the experiments and is probably caused by either air that is present in the injection line, diffusive loss of titrant³⁵ or an extra drop of titrant at the tip of the injection line. This integrated curve is used to fit the thermodynamic parameters of the system.

Figure 4 ITC results for a typical experiment, with **a)** heat flow of periodical titration of acetic acid to trioctylamine (0.24 M) in toluene at $T = 20\text{ }^{\circ}\text{C}$, injection volume = 10 μL , and **b)** integrated ITC curve.

Figure 5 shows the integrated ITC-results and sequential reaction model

fit for an experiment in which the accuracy of the first part of the curve is improved by decreasing the injection volume of the first six injections. The larger negative $\Delta H_{1,1}$ (-23.2 kJ/mol) than $\Delta H_{n+1,1}$ (-20.0 kJ/mol) results from the double S-shape of the isotherm, and indicates that the first acid is bound stronger than the subsequent acids.

Figure 5 ITC results for titrating acetic acid to trioctylamine (0.24 M) in toluene at $T = 20\text{ }^{\circ}\text{C}$, injection volume = 3 μL for the first injection, 5 μL for injections 2-6, 10 μL for injection 7-21 and 15 μL for further injections. ■ experimental data, dashed line represents the sequential reaction model fit based on eq (2)-(5).

5.4.2 Solvent composition effects on complex formation

For each of the three extractants studied for acetic acid complexation, several diluents were applied. The results are displayed in Figure 6, with 0.24 M TOA in Figure 6a, with 0.24 M TOPO in Figure 6b, and with 0.24 M TBP in Figure 6c. In Figure 6a, different types of curves can be distinguished. For TOA in chloroform, the heat effect is larger than for the other diluents and the first measurement point is very low compared to the rest, a typical problem with the first point that was also shown for the typical experiment in Figure 4. TOA in 1-octanol results in the second largest heat effect, also reducing strongly around a molar ratio of 1. The other diluents all show the steep part at higher molar ratio. Where toluene and heptane exhibit a flat region in the beginning of the curve, MIBK and ethyl acetate show an increasing heat release.

The active and protic diluents chloroform and 1-octanol thus promote complexation, indicated by the large heat release. Due to competitive hydrogen bonding of these diluents, a 1:1 stoichiometry is observed. The inactive diluents toluene and heptane exhibit a lower energy release, but due to the absence of hydrogen bonding with the diluent, multiple acids add to the complexes through hydrogen bonding. MIBK and ethyl acetate are active hydrogen bond accepting diluents, and the loss of hydrogen bonds between extractant and diluent results in a reduced net heat release at low stoichiometry. Their hydrogen bonds are less strong than the double hydrogen bonds between two acids, also resulting in overloading.

Figure 6 Effect of diluent on ITC ‘S - curve’ for the net heat of complexation of the reaction of acetic acid and extractant in the active protic solvents ● 1-octanol, ▲ chloroform, in the hydrogen bond accepting solvents ◆ ethyl acetate and ▼ MIBK and in the inactive solvents Δ toluene and □ heptane, with **a)** 0.24 M TOA, **b)** 0.24 M TOPO and **c)** TBP (2.3 M in ethyl acetate, 1.1 M in MIBK, 1.8 M in toluene and 2.4 M in heptane).

The effect of the diluent on the heat of complexation of acetic acid with TOPO (Figure 6b), is different than for TOA (Figure 6a). For the active and protic 1-octanol as a diluent the heat of complexation is almost negligible. The other diluents all show a steep decrease in the heat of complexation around a stoichiometry of 1 acid per TOPO molecule, indicating 1:1 stoichiometry. Apparently the nature of the complexes does not favor additional interactions with acids. For the inactive diluents toluene and heptane a larger heat of complexation is shown than for the hydrogen bond accepting diluents MIBK and ethyl acetate. From this we can conclude that the interaction between TOPO and 1-octanol is of similar intensity as the interaction between TOPO and acetic acid. This effect might also be the reason why the heat of complexation is lower for MIBK and ethyl acetate.

Similar trends were obtained for the heat of complexation of acetic acid with TBP (Figure 6c) although with a much higher TBP concentration because at 0.24 M it was not possible to obtain a proper ‘S-curve’. It should be mentioned that from increasing the TBP concentration also a change in the K-value is expected, as K depends on extractant concentration.^{24,31,36} For TBP no protic diluents were applied, since all other diluents already showed a low heat of complexation and low complexation constants, visible through shallow slopes in the ITC-curves.

5.4.3 Fitting of the data

The isotherms in Figure 6a were fit with the sequential binding model that allows the formation of two types of complexes, described by eq (2) and eq (4). The fitted parameters are shown in Table 1 for complexation at a temperature of 20 °C.

Table 1 Fit parameters of ITC data on complexation of acetic acid with 0.24 M TOA in several diluents at $T = 20$ °C. Parameter fits are based on the sequential model in eq (2) and eq (4).

Diluent	$\Delta H_{1,1}$ (kJ/mol)	$K_{1,1}$	$\Delta H_{n+1,1}$ (kJ/mol)	$K_{n+1,1}$	n
Toluene	-23.2	22.3	-20	68.5	1.6
Heptane	-17.9	22.5	-20.9	45.4	1.9
MIBK	-22.2	5.6	-20.4	47.5	1.5
Ethyl acetate	-24.6	5.9	-21.3	43.3	1.6
Chloroform	-50	15	-25.1	5	0.4
Water saturated 1-octanol	-38	97.1	-19.6	0.6	0.8

From Table 1 it clearly reads that in the protic diluents 1-octanol and chloroform stronger 1:1 complexes are observed at higher $\Delta H_{1,1}$, whereas n and $K_{n+1,1}$ are lower than for non-protic diluents. When 1-octanol was saturated with water, the presence of water increased $\Delta H_{1,1}$ and $K_{1,1}$. For the hydrogen bond accepting diluents the typical signal showing initial increasing heat of complexation with increasing stoichiometry is indeed fitted with a higher $K_{n+1,1}$ than $K_{1,1}$.

The fit results for TOPO and TBP are given in Table 2 and Table 3, respectively. The parameters were fit using only the first reaction of the model, eq (2), since clearly no overloading occurs and applying extra equations decreases the accuracy of the parameter fit.³¹ Fitting of the data for the diluents 1-octanol and chloroform appeared to be more difficult than for the other diluents, because there is no flat part in the beginning of the curve for the lower stoichiometry systems. Although the extractant concentration was taken into account for the fitting, comparing the results directly is difficult because of the influence of the concentration on $K_{1,1}$. No fit was possible at all for the energy of complexation with TOPO when 1-octanol was used, because the measured energy is too low.

Table 2 Fit parameters of ITC data on complexation of acetic acid with 0.24 M TOPO in several diluents at $T = 20$ °C. Parameters fits are based on the (1,1)-complexation in eq (2).

Diluent	$\Delta H_{1,1}$ (kJ/ mol acid)	$K_{1,1}$
Toluene	-18	57
Heptane	-28	13
MIBK	-16	11
ethyl acetate	-18	19
1-octanol		

Table 3 Fit parameters of ITC data on complexation of acetic acid with TBP in several diluents at $T = 20$ °C. The concentration of TBP was 1.8 M in toluene, 2.4 M in heptane, 1.1 M in MIBK and 2.3 M in ethyl acetate. Parameter fits are based on the (1,1)-complexation in eq (2).

Diluent	$\Delta H_{1,1}$ (kJ/mol acid)	$K_{1,1}$
Toluene	-7.9	2.9
Heptane	-22	0.3
MIBK	-6.2	3.7
ethyl acetate	-9.1	1.2

5.4.4 Binary diluents

Mixtures of 1-octanol and toluene were applied in varying composition as binary diluents with the extractant TOA to study the diluent composition effect on the complexation of TOA with acetic acid. The results are displayed in Figure 7. For these experiments a high TOA concentration of 1 M was used to decrease the 1-octanol to TOA concentration ratio and to improve the slopes of the curves for easier comparison. In Figure 7, it can be observed that with increasing 1-octanol fraction in the solvent the stoichiometry shifts down to favor more the (1,1)-complex being stabilized by 1-octanol.

Figure 7 Effect of 1-octanol concentration in the binary diluent of 1-octanol and toluene on the ITC ‘S - curve’ for the heat of complexation of the reaction of acetic acid with 1 M TOA (≈ 45 vol%) at 20 °C in: $\bigcirc$ 0 vol% 1-octanol, $\square$ 50 vol% 1-octanol, ∇ 75 vol% 1-octanol and $\triangle$ 100 vol% octanol. Lines are based on the data fit with the model parameters of Table 4.

Using eq (2), eq (4) and eq (6), the ITC results of Figure 7 were also fit to determine the thermodynamic parameters. The results are shown in Table 4. Two trends are observed with increasing the volume fraction of 1-octanol, 1) a decrease of $\Delta H_{n+1,1}$ that is most likely a result of the competition between acetic acid and 1-octanol, and 2) a decrease of $K_{1,1}$, except for the 100 % 1-octanol diluent, where also a decrease in all ΔH and K -values is observed. In the solvent where the diluent only consists of 1-octanol, there is a 1-octanol to TOA ratio of 4. An explanation for the decrease in all parameters at this composition may be that this ratio of 1-octanol to TOA is too high for optimal complex solvation.

Table 4 Model parameters for complexation of acetic acid with 1 M TOA (≈ 40 vol%) in binary diluent of 1-octanol and toluene at 20 °C. Parameter fits are based on the three complex model combining eq (2), eq (4) and eq (6).

Vol% 1-octanol	$\Delta H_{1,1}$ (kJ/mol)	$K_{1,1}$	$\Delta H_{1,1,0}$ (kJ/mol)	$K_{1,1,0}$	$\Delta H_{n+1,1}$ (kJ/mol)	$K_{n+1,1}$	n	[O]/[TOA]
0	-20.5	10.4			-18	19	1.7	0
50	-20.6	0.1	-11.2	48.5	-16.2	855	1.6	2
75	-24	0.03	-13.8	58.2	-15.3	622	1.4	3
100	-18.4	0.067	-10.4	30.6	-11.4	288	1.7	4

5.4.5 Effect of temperature

To study the effect of temperature on acetic acid complexation with TOA in various diluents, ITC measurements were done at 60 °C and the determined thermodynamic parameters were compared with those at 20 °C. These results are shown in Table 5. In general all K -values are lower at 60 °C than those at 20 °C (see Table 1). For the value of $K_{n+1,1}$ this effect is even stronger than for $K_{1,1}$. As a result, the average stoichiometry of the complexes is also lower at an elevated temperature, which may be explained by reduced formation of hydrogen-bonds at elevated temperatures. In contrary to the observations for the other diluents, for 1-octanol that is not saturated with water, the value of $\Delta H_{1,1}$ significantly increases with increasing temperature, whereas $\Delta H_{n+1,1}$ reduces. This implies that in absence of water the interaction with the first acid is stronger at 60 °C than at 20 °C and the interaction of the following acids is weaker. This may also be explained by less favored hydrogen-bonding at elevated temperatures. For the water-saturated 1-octanol there is no such effect since the presence of water can improve hydrogen bonding.

Table 5 Fit parameters of ITC data on complexation of acetic acid with 0.24 M TOA in several diluents at $T = 60\text{ }^{\circ}\text{C}$. Parameter fits are based on the sequential binding model in eq (2) and eq (4).

Diluent	$\Delta H_{1,1}$ (kJ/mol)	$K_{1,1}$	$\Delta H_{n+1,1}$ (kJ/mol)	$K_{n+1,1}$	n
Toluene	-25.4	11.8	-23.7	10.5	1.4
Heptane	-18.5	13.4	-25.4	6.2	1.5
MIBK	-23.3	2.2	-18.9	19.5	1.5
Ethyl acetate	-26.2	2.8	-23.4	6.8	1.5
Unsaturated 1-octanol (0.36 M)	-39.2	12.5	-12.8	2.2	1.4
Water saturated 1-octanol	-38.6	14	-14.5	2.7	0.7

5.4.6 Extraction of phenol

The isotherms for the interaction of phenol with the three extractants measured with ITC are shown in Figure 8, with the fit parameters in Table 6. For each of the extractants in the complexation with phenol there is approximately a 1:1 ratio between phenol and extractant, therefore the (1,1)-complexation reaction of eq (2) was used for fitting of the data. The release of energy from complexation with TOPO is larger than for the other two extractants. Compared with the data in Figure 6, the K-values are clearly lower for the complexation with phenol than for acetic acid in the case of TOA and TOPO. However, the K-values are difficult to compare since larger complexes ($n = 3$) are formed with TOA and the applied concentration of TBP is 0.36 M with phenol and 1.8 M with acetic acid.

The differences in affinity of acetic acid and phenol for the extractants are a result of the ability of TOA to accept a proton from acetic acid, which is not possible for phenol.³⁷ Because the molecules of phenol cannot get ionized, TOA is not a suitable extractant for phenol. The weak interaction that is measured between TOA and phenol further implies that also hydrogen bonding between TOA and phenol is not strong enough to compete with the π - π interactions between phenol and the diluent toluene.

Figure 8 Integrated ITC data for complexation with ■ TOA (0.25 M), ● TOPO (0.21 M) and ▲ TBP (0.36 M) in toluene for phenol at 20 °C.

Table 6 ITC results for complexation of phenol with TOA (0.25 M), TOPO (0.21 M) and TBP (0.36 M) in toluene at 20 °C, for ITC data of Figure 8. Parameter fits are based on the (1,1)-complexation in eq (2). Because of the low $K_{1,1}$ the error for the parameters for these results is up to a standard deviation of 20 % in ΔH and 8 % in $K_{1,1}$.

Extractant	$\Delta H_{1,1}$ (kJ/mol phenol)	$K_{1,1}$
TOA	-20	5.7
TOPO	-55	8.7
TBP	-30	11

5.4.7 Validation of ITC data with LLE

To predict the distribution in biphasic extraction systems on the basis of ITC data, the acid dissociation constant of acetic acid ($= 1.75 \cdot 10^{-5}$)³⁸ and the physical distribution of acetic acid are needed, as graphically illustrated in Figure 2. The physical distribution was measured for the applied diluents, and the results are given in Table 7.

Table 7 Physical extraction of acetic acid by several diluents: distribution coefficients K_D of acetic acid ($c_0 = 2.0$ wt%) in a liquid-liquid equilibrium with pure diluents at 20 °C and 60 °C.

Physical solvent	$K_{D,Hac}$ (M/M), $T = 20$ °C	$K_{D,Hac}$ (M/M), $T = 60$ °C
Heptane	0.00064 ± 0.020	0.0019 ± 0.020
Toluene	0.013 ± 0.020	0.015 ± 0.020
MIBK	0.48 ± 0.030	0.46 ± 0.030
1-octanol	0.46 ± 0.030	0.51 ± 0.031

The calculated distribution coefficients using the complexation constants determined by ITC for acetic acid extraction with TOA in several diluents at 20 °C and 60 °C, or $K_{D,model}$, are compared with experimentally determined liquid-liquid equilibria $K_{D,LLE}$ in Figure 9. It follows that overall, the model based on ITC data predicts the value of K_D for the diluents 1-octanol and MIBK reasonably well, although at lower values of $K_{D,LLE}$ there is underprediction, this might be an indication that dimerization in the organic phase should be taken into account to improve the model, since there is more dimerization in less polar diluents where also K_D is lower. However, incorporating dimerization as an extra equation in the fitting model for the ITC data also results in fitting of more variables, thereby reducing the accuracy of the fit.

Figure 9 Calculated distribution coefficients of acetic acid, or $K_{D,model}$, compared with experimentally determined values $K_{D,LLE}$ for liquid-liquid extraction of acetic acid ($c_0 = 2.0$ wt%) with 0.24 M TOA in several diluents: at $T = 20$ °C in ■ heptane, ▲ toluene, ▼ MIBK, and ● (water saturated) 1-octanol; and at $T = 60$ °C in □ heptane, △ toluene, ▽ MIBK, and ○ (water saturated) 1-octanol.

Compared to acetic acid, phenol is a much weaker acid and also for this weaker acid the LLE was studied, and interactions with the extractants were studied in 1-octanol and toluene with ITC. For the experimental results in Table 8, the concentration of TOPO in the diluents is lower than for the other extractants due to limited solubility. From these results it is clear that higher values of K_D are obtained in the active diluent 1-octanol for the pure diluent and the TOA based solvent. For TOPO and TBP based solvents toluene shows higher values of K_D . Next to that, higher values for K_D are also obtained for phenol compared to acetic acid, which is due to the more hydrophobic nature of this molecule. In the diluent toluene π - π interactions between phenol and toluene contribute to the very high values of the distribution coefficient.

In contradiction to the case of acetic acid extraction, for extraction of phenols the tertiary amine TOA does not show the highest distribution, see Table 8. Similar results are reported in literature.³⁹⁻⁴² LLE experiments with TOPO, TBP and even pure 1-octanol result in a higher distribution coefficient than that in the case of TOA, although because of limited solubility the concentration of TOPO is only 11 wt% (≈ 0.24 M), compared to those of TOA (0.92 M) and TBP (1.46 M).

Table 8 Distribution coefficient K_D for phenol ($c_0 = 1.0$ wt%) and acetic acid ($c_0 = 2.0$ wt%) with different extractants at a temperature of 20 °C.

Solvent	$K_{D,Hac}$ (M/M)	$K_{D,PhOH}$ (M/M)	Solvent	$K_{D,Hac}$ (M/M)	$K_{D,PhOH}$ (M/M)
Pure toluene	0.013 ± 0.020	1.89 ± 0.058	Pure 1-octanol	0.46 ± 0.030	32 ± 4.0
TOA (40 vol% in toluene)	0.73 ± 0.012	10.3 ± 0.23	TOA (40 vol% in 1-octanol)	7.2 ± 0.17	30 ± 3.8
TOPO (11 wt% in toluene)	0.86 ± 0.038	185 ± 23	TOPO (11 wt% in 1-octanol)	0.75 ± 0.035	45 ± 5.6
TBP (40 vol% in toluene)	0.89 ± 0.038	210 ± 26	TBP (40 vol% in 1-octanol)	0.79 ± 0.036	117 ± 14

Comparing the ITC and LLE results (Table 1-Table 3, Table 6 and Table 8) with the BF_3 -affinity and pK_{BHX} -scale,¹⁵ it can be concluded that for extraction of phenol the pK_{BHX} -scale is more applicable since it clearly predicts a high K_D for TOPO and TBP (taking into account the lower concentration of TOPO). For extraction of acetic acid with TOA in toluene the differences in K_D are too small to compare it with one of the scales, while for acetic acid in TOA in 1-octanol, where protonation of the extractant is expected, the BF_3 -affinity scale clearly predicts the high K_D for TOA.

5.4.8 Molecular modeling

Aiming to understand the differences in mechanisms in the various systems, molecular modeling was used. For the interaction of both acetic acid and phenol with the three extractants TOA, TOPO and TBP energy profiles were created using a solvation model with 1-octanol and with toluene, see Figure 10.

Figure 10 Energy profile for varying the distance between the acid and extractant in complexation with ■ TOA, ● TOPO and ▲ TBP; calculated with Hartree-Fock 6-31G* level of calculation with SM8 solvation in 1-octanol, using Wavefunction Spartan'16 Parallel, for **a)** acetic acid in 1-octanol, **b)** phenol in 1-octanol, **c)** acetic acid in toluene and **d)** phenol in toluene. The lines are added to guide the eye.

In the case of acetic acid interaction in 1-octanol (Figure 10a), for all three extractants there is a (local) minimum visible at an intermolecular distance of 2 Å, characteristic for hydrogen bonding.^{43,44} In addition, for TOA there is a minimum at a lower intermolecular distance around 1 Å, which is around the covalent bond distance for the N-H bond,³⁸ which indicates a dative bond implying proton transfer. A deeper energy valley could be expected for proton transfer with TOA than for hydrogen bonding with TOPO and TBP, as proton transfer is a stronger interaction. It might be that neglecting interactions with surrounding water molecules influences the energy profile significantly. To study the influence of water molecules in the near vicinity of the complex, a simulation was run with five water molecules for a similar system comprising of trimethylamine and acetic acid, indeed confirming that in the presence of water the characteristic proton transfer shows a deeper energy valley. In Figure 10c, the results are shown for interaction between acetic acid and the extractants using toluene as a diluent. Here there is no (local) minimum at the typical distance of the N-H bond that would occur due to proton transfer, only at the distance for hydrogen bonding for all three extractants, so no proton transfer takes place between acetic and TOA when toluene is the diluent. The effect of diluent on the complexation of a tertiary amine and acetic acid was also studied with MM for the diluents chloroform, ethyl acetate, MIBK and heptane. Just as was the case for TOA in 1-octanol and toluene (Figure 10a and c), for these diluents also two local minima are visible in the total energy. All diluents except 1-octanol show the lowest energy for hydrogen bonding, although for chloroform the local minimum around a proton transfer distance is relatively strong, followed by ethyl acetate and MIBK. Similar to toluene, for heptane the proton transfer state is even less favorable than the reference state in which there is no interaction.

With ITC (Table 1) it was also shown that for 1-octanol mainly the (1,1)-complex is formed and has a large enthalpy of complexation, followed by chloroform with a lower $K_{1,1}$ value. The difference between chloroform and the diluents MIBK and ethyl acetate is less clear in MM than in the ITC-data. It may be concluded that with the exception of chloroform, the findings of MM directly support the results from ITC (Table 1), where only for 1-octanol and chloroform larger differences between ΔH of the first and following acids were found, and only smaller differences in ΔH for the non-proton donating diluents as well as lower values for ΔH . No proton transfer was calculated for interaction between acetic acid and TOA in toluene, this is in accordance with the ITC results (Figure 6a and Table 1) where TOA showed only a small difference in ΔH for the first and following acid interactions.

In 1-octanol, TOPO and TBP both only show an energy minimum at the typical distance of hydrogen bonding, with a larger energy value than TOA at that distance (Figure 10a). This could not be compared with ITC results, since no isotherms could be measured for interaction of TOPO and TBP as a result of a too strong interaction between extractant and 1-octanol. The strong hydrogen bonding ability that is expected based on this interaction with 1-octanol is indeed visible in the MM results, also compared to TOA. In toluene (Figure 10c), for TOPO and TBP also no proton transfer was calculated for interaction with acetic acid, which is in accordance with the ITC results (Figure 6b and c and Table 2 and Table 3).

The liquid-liquid equilibria in 1-octanol in Table 8 show a very high K_D of acetic acid for TOA and a lower K_D for TBP and TOPO, which is in accordance with the proton-transfer that was only found for TOA using MM (Figure 10a). The bond energy in molecular modeling is a bit higher for TOPO than for TBP in both 1-octanol and toluene (Figure 10a and c). This can be related to the liquid-liquid equilibria, since the values for K_D are almost equal but in the LLE experiments TOPO was applied at a much lower concentration because of solubility limitations.

Figure 10b shows the interaction between phenol and the three extractants TOA, TOPO and TBP in 1-octanol and Figure 10d shows the results in toluene. There is no energy minimum visible in the region of proton transfer in any of the graphs. For TOA there is also no energy minimum in the region of hydrogen bonding for both 1-octanol and toluene. Moreover, for both diluents the energy minimum is indicating a larger bond energy for TOPO than for TBP. Equal to the case of acetic acid, interactions of phenol with TOPO and TBP in 1-octanol could also not be analyzed with ITC, therefore only the modeling results for toluene can be compared with the ITC-results (Figure 8 and Table 6). In these ITC measurements very little interaction with TOA was shown and TOPO showed more interaction, followed by TBP. This exactly matches the molecular modeling results and is also confirmed in the LLE results for the phenol-extractant system (Table 8), in which a low K_D was found using TOA and high values of K_D were found for TBP and TOPO. Overall, it can be concluded that the use of MM strengthens the interpretation of the heat effects measured by ITC and together these two techniques can aid research on new solvents by allowing for much better understanding of the intermolecular interactions that occur in solvent systems.

5.5 Conclusion

Isothermal titration calorimetry (ITC) was applied to directly characterize the thermodynamics of complexation in the study of liquid-liquid extraction of organic acids, and molecular modeling (MM) was used to aid the interpretation of the ITC data. Complexations of acetic acid and phenol with extractants TOA, TOPO and TBP were studied in various diluents. It was found that the choice of diluent can affect the mechanism of complexation, and that the interaction between TOA and acetic acid has larger negative values of ΔH and larger complex stoichiometry than between TOA and phenol. When protic diluents were applied the stoichiometry of the complexes was reduced because of competition between the acid and diluent, whereas inactive diluents resulted in more overloading of the amine. At elevated temperatures, all K -values are lower, where especially $K_{n+1,1}$ decreases strongly as a result of less tendency towards overloading of the amine at elevated temperatures. In contradiction to the case of acetic acid, for phenol TOPO is a very suitable extractant, already at a concentration of only 11 wt% in 1-octanol TOPO outperforms the other extractants. The differences between the interaction with phenol and acetic acid could be described using the BF_3 -affinity scale for acetic acid and the hydrogen bond basicity $\text{p}K_{\text{BHX}}$ -scale for phenol, which was confirmed by ITC and MM.

The model based on ITC data can be used to predict LLE, and further interpretation by MM showed two local minima for the tertiary amine - acetic acid complex at typical distances for hydrogen bonding and proton transfer. For active diluents such as 1-octanol proton transfer is preferred and hydrogen bonding for the other diluents. This shows that the combination of ITC with MM is a strong approach to study the thermodynamics of intermolecular interactions in liquid-liquid extraction processes and can help to improve the understanding of the interaction mechanism. Improved understanding of the effect of molecular structure of the extractant and diluent on the extraction and regeneration can help in the design of new solvents to improve solvent based processes such as liquid-liquid extraction.

References

- (1) Meyers, R. A. *Handbook of petroleum refining processes*; 3rd ed.; McGraw-Hill: New York, 2004.
- (2) Verkuijl, B. J. V.; Schuur, B.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *Org Biomol Chem* 2010, *8*, 3045-3054.
- (3) Schuur, B.; Verkuijl, B. J. V.; Minnaard, A. J.; de Vries, J. G.; Heeres, H. J.; Feringa, B. L. *Org Biomol Chem* 2011, *9*, 36-51.
- (4) Rowley, D.; Steiner, H.; Zimmen, E. *J Soc Chem Ind-L* 1946, *65*, 237-240.
- (5) van Delden, M. L.; Kuipers, N. J. M.; de Haan, A. B. *Sep Purif Technol* 2006, *51*, 219-231.
- (6) Kiezyk, P. R.; Mackay, D. *Can J Chem Eng* 1971, *49*, 747-752.
- (7) Krzyzaniak, A.; Leeman, M.; Vossebeld, F.; Visser, T. J.; Schuur, B.; de Haan, A. B. *Sep Purif Technol* 2013, *111*, 82-89.
- (8) Li, Q.-Z.; Jiang, X.-L.; Feng, X.-J.; Wang, J.-M.; Sun, C.; Zhang, H.-B.; Xian, M.; Liu, H.-Z. *J Microbiol Biotechnol* 2016, *26*, 1-8.
- (9) Hartl, J.; Marr, R. *Sep Sci Technol* 1993, *28*, 805-819.
- (10) Blahušiak, M.; Kiss, A. A.; Kersten, S. R. A.; Schuur, B. *Energy* 2016, *116*, 20-31.
- (11) Kiss, A. A.; Lange, J.-P.; Schuur, B.; Brilman, D. W. F.; van der Ham, A. G. J.; Kersten, S. R. A. *Biomass Bioenerg* 2016, *95*, 296-309.
- (12) Bradley, J.-C.; Abraham, M. H.; Acree, W. E.; Lang, A. S. *Chem Cent J* 2015, *9*, 12.
- (13) Eckert, F.; Klamt, A. *AIChE J* 2002, *48*, 369-385.
- (14) Jongmans, M. T. G.; Londoño, A.; Mamilla, S. B.; Pragt, H. J.; Aaldering, K. T. J.; Bargeman, G.; Nieuwhof, M. R.; Kate, A. t.; Verwer, P.; Kiss, A. A.; van Strien, C. J. G.; Schuur, B.; de Haan, A. B. *Sep Purif Technol* 2012, *98*, 206-215.
- (15) Christian Laurence; Gal, J.-F. *Lewis Basicity and Affinity Scales*; John Wiley & Sons, Ltd, 2009.
- (16) Sprakel, L. M. J.; Schuur, B. *Sep Purif Technol* 2019, *211*, 935-957.
- (17) Girisuta, B.; Janssen, L. P. B. M.; Heeres, H. J. *Ind Eng Chem Res* 2007, *46*, 1696-1708.
- (18) Cuypers, R.; Burghoff, B.; Marcelis, A. T. M.; Sudhölter, E. J. R.; de Haan, A. B.; Zuilhof, H. *J Phys Chem A* 2008, *112*, 11714-11723.
- (19) Uslu, H.; Datta, D.; Bamufleh, H. S. *J Mol Liq* 2015, *212*, 430-435.
- (20) Marti, M. E. *Sep Sci Technol* 2016, 1-11.
- (21) Rasrendra, C. B.; Girisuta, B.; van de Bovenkamp, H. H.; Winkelman, J. G. M.; Leijenhof, E. J.; Venderbosch, R. H.; Windt, M.; Meier, D.; Heeres, H. J. *Chem Eng J* 2011, *176-177*, 244-252.
- (22) Hano, T.; Matsumoto, M.; Ohtake, T.; Sasaki, K.; Hori, F.; Kawano, Y. *J Chem Eng Jpn* 1990, *23*, 734-738.

- (23) Cai, W.; Zhu, S.; Piao, X. *J Chem Eng Data* 2001, *46*, 1472-1475.
- (24) Wasewar, K. L.; Shende, D. Z. *J Chem Eng Data* 2011, *56*, 288-297.
- (25) Brouwer, T.; Blahusiak, M.; Babic, K.; Schuur, B. *Sep Purif Technol* 2017, *185*, 186-195.
- (26) Wisniewski, M.; Pierzchalska, M. *J Chem Technol Biot* 2005, *80*, 1425-1430.
- (27) Yang, Y.-Z.; Yang, Y.-H.; Sun, G.-X.; Meng, X.-J.; Wang, Z.Q.; Sun, S.-X. *Chem J Chinese U* 1996, *17*, 515-518.
- (28) Tamada, J. A.; King, C. J. *Ind Eng Chem Res* 1990, *29*, 1327-1333.
- (29) Barrow, G. M.; Yerger, E. A. *J Am Chem Soc* 1954, *76*, 5211-5216.
- (30) Masaru, N.; Tatsuya, S. *Bull Chem Soc Jpn* 1978, *51*, 705-709.
- (31) Sprakel, L. M. J.; Schuur, B. *Ind Eng Chem Res* 2018, *57*, 12574-12582.
- (32) Wang, K.; Chang, Z.; Ma, Y.; Lei, C.; Jin, S.; Wu, Y.; Mahmood, I.; Hua, C.; Liu, H. *Fluid Phase Equilib* 2009, *278*, 103-108.
- (33) Hong, Y. K.; Hong, W. H. *Bioprocess Eng* 2000, *22*, 281-284.
- (34) Falconer, R. J.; Penkova, A.; Jelesarov, I.; Collins, B. M. *J Mol Recognit* 2010, *23*, 395-413.
- (35) Boyce, S. E.; Tellinghuisen, J.; Chodera, J. D. *bioRxiv, Biochem.* 2015, 23796/23791-23796/23797.
- (36) Qin, W.; Li, Z.; Dai, Y. *Ind Eng Chem Res* 2003, *42*, 6196-6204.
- (37) Aono, S.; Kato, S. *J Comput Chem* 2010, *31*, 2924-2931.
- (38) Lide, D. R. *CRC handbook of chemistry and physics*; 74th ed.; CRC Press: Boca Raton, 1993.
- (39) Zidi, C.; Tayeb, R.; Dhahbi, M. *J Hazard Mater* 2011, *194*, 62-68.
- (40) Zidi, C.; Tayeb, R.; Ali, M. B. S.; Dhahbi, M. *J Membrane Sci* 2010, *360*, 334-340.
- (41) Cichy, W.; Schlosser, Š.; Szymanowski, J. *J Chem Technol Biot* 2005, *80*, 189-197.
- (42) Gutierrez, R.; Urtiaga, A.; Ortiz, I. *J Chem Technol Biotechnol* 2010, *85*, 1215-1222.
- (43) Gilli, P.; Pretto, L.; Bertolasi, V.; Gilli, G. *Acc Chem Res* 2009, *42*, 33-44.
- (44) Krishtalik, L. I. *BBA-Bioenergetics* 2000, *1458*, 6-27.

6

Molecular design and engineering for
affinity separation processes

Abstract

A molecular design approach based on isothermal titration calorimetry (ITC) and molecular modeling (MM) was investigated for the development of new extractants in liquid-liquid extraction (LLX) systems. The molecular designs were validated in LLX experiments. Key in the regeneration of a solvent by a temperature-swing back-extraction is the temperature dependency of the complexation equilibrium, which is related to the enthalpy of complexation ΔH . The relation between the molecular structure of extractants and the thermodynamics of complexation in LLX was studied for extraction of acetic acid by basic extractants and 4-cyanopyridine by phenols. For the basic extractants, longer alkyl chains and additions of rings decreased ΔH , whereas for the phenols the acidity of the phenolic proton, and hence the complexation enthalpy, could be increased by electron withdrawing substituents.

Using ΔH as determined with ITC, the temperature dependency of the liquid-liquid equilibrium could indeed be described. Also enthalpy-entropy compensation (EEC) could be observed in the data obtained by ITC, i.e. for extractants of the same family with a larger enthalpy of complexation, an opposite effect on the entropy of complexation was observed.

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6.1 Introduction

Liquid-liquid extraction (LLX) is an important separation technique in industry, especially when solutes are present at low concentrations and distillation is intrinsically highly energy inefficient.^{1,2} LLX is applied in various fields in industry, e.g. for recovery of acids from fermentation broths,³ and in the pharmaceutical industry,⁴ metallurgical industry⁵ and the petrochemical industry.⁶ LLX always requires a solvent regeneration step, with changing conditions between the forward extraction step and the regeneration step.

Solvent and process improvements with the aim to increase the acid distribution are widely reported in literature.^{7,8} Solvents consisting of a complexing agent (extractant) and a diluent are mostly used. The use of extractants improves the acid distribution by forming a complex with the acid.⁹⁻¹⁴ Understanding of the mechanism of extraction is key to be able to design processes with optimized extraction performance, while it also allows for effective solvent regeneration.

An important factor in the mechanism is the molecular structure of the extractant and its effect on the mechanism and extraction performance. For some specific LLX cases, the effect of the extractant structure on the extraction efficiency is reported, e.g. the effect of chain length of a tertiary amine on the extraction of succinic acid¹⁵ and itaconic acid.¹⁶ In another study polar diluents were reported to be the most suitable for several amine extractants.¹⁷ For the extraction of lactic acid, Krzyzaniak et al.¹⁸ showed that amongst a guanidine, proton sponge, tertiary amine, toluamide and a bis-N-oxide, the highest acid distribution was obtained with the tertiary aminopyridine N,N-didodecyl-4-amine-pyridine (DDAP).¹⁹ Bokhove et al.²⁰ report that for removal of 4-cyanopyridine from aqueous streams the substituted phenol 3-bromophenol performs best in liquid-liquid equilibrium (LLE) studies.

Ideally, an extractant would extract highly effective under extraction conditions and release the target molecule again under regeneration conditions, e.g. in a back-extraction. To optimize the back-extraction yield, diluent-swing, temperature-swing or a combination thereof may be applied.²¹⁻²³ The simplest and least invasive approach to manipulate affinity is by changing the temperature, thus performing extractions at low temperature and then increasing the temperature for the solvent regeneration. This requires a (preferentially strong) temperature

dependency of the intermolecular interactions between solvent and solute. This study focuses on the effects of molecular structure on the thermodynamic parameters of the complexation between extractant and solutes. Based on this understanding, extractant structures may be designed and optimized, aiming at a strong temperature-dependency of their interactions with solutes. The effect of extractant structure on the temperature dependency of extractions was studied for two industrially relevant cases, i.e. acetic acid extracted by basic extractants and the base 4-cyanopyridine extracted by (substituted) phenols (see Figure 1 for the structures of the applied extractants). Carboxylic acids such as acetic acid are often dilutely present in product streams from fermentation and industrial wastewater streams. These acids are valuable and can be used as building blocks for other chemical products such as polymers.^{24,25} Removal of pyridines from industrial wastewater streams of low concentration is required because of their toxicity.^{26,27}

Tertiary amines			
Triethylamine (TEA)	Trioctylamine (TOA)	Triiododecylamine (TDDA)	
Aminopyridines			
Dioctylamine pyridine (DOAP)	Octylamine pyridine (MOAP)	Didodecylamine pyridine (DDAP)	2-methyl-didodecylamine pyridine (2MDDAP)
Diphenyl amine pyridine (DPPA)		Diphenyl dodecylamine pyridine (DPMDAP)	
Phenol and substituted phenols			4-Cyanopyridine
Phenol ($pK_a = 9.99$)	Nonylphenol ($pK_a = 10.7$)	2-Bromophenol ($pK_a = 8.45$)	4-Cyanopyridine

Figure 1 Molecular structures of tertiary amines and aminopyridines for extraction of acetic acid and molecular structures of phenol and substituted phenols for extraction of 4-cyanopyridine.

For the design of a successful separation process by LLX, an efficient regeneration of the solvent is key.²⁸ The regeneration is often neglected in the process of finding the optimal extractant,^{11,14,29-34} and only the highest acid distribution is pursued which may even compromise regeneration feasibility. Especially for high-boiling acids, back-extraction is essential to recover the

acid from the solvent, but also in other instances where boiling off the solute is not an option, back-extraction is often the preferred approach.

Ideally, using a relatively quick method, the influence of the molecular properties on the temperature dependency of the extractant-solute interactions can be understood, in order to identify the feasibility of a temperature-swing back-extraction. With the typical solvent screening techniques such as the linear solvation energy relationship (LSER),³⁵ COSMO-RS software,^{20,36} and several affinity scales³⁷ this is not possible. We aim at quantification and understanding of the interactions responsible for the extractability of the solutes by applying isothermal titration calorimetry (ITC) combined with molecular modeling (MM), because this additional insight in the interactions allows for understanding of the behavior with varying conditions such as temperature.

MM can be applied to determine and validate the mechanisms of interactions in complex formation^{38,39} and was also applied in solvent screenings for LLX processes, e.g. the extraction of phenol^{40,41} and lactic acid.¹⁸ ITC is a method that is widely applied to study thermal effects of intermolecular interactions in the field of biomolecular research,⁴²⁻⁴⁵ but it is also a suitable technique to study interactions for LLX.^{40,41,46} Recently, the accuracy of the technique for quantification of complexation constants in LLX systems was reported.⁴⁷ When ITC is combined with MM the important mechanisms of the extraction process can be determined.⁴⁸ With this work the combination of ITC and MM was studied as a suitable approach for investigating the effect of the extractant structure on the LLX performance.

6.2 Theory

6.2.1 Equilibria in complexation

Reactive LLX includes complexation in the organic phase (see Figure 2), distribution of acid over the phases as a result of physical extraction, and dissociation in the aqueous phase, resulting in the overall distribution as defined in eq (1), where $[A]$ and $[\bar{A}]$ are the concentrations of acid A in the aqueous and organic phase, respectively. A_{tot} includes all forms of A present in the specific phase, including dissociated acid and acid present in complexes.

$$K_{D,a} = \frac{[\bar{A}_{\text{tot}}]}{[A_{\text{tot}}]} \quad (1)$$

For complex formation between acids and extractants, the interaction between the extractant and the first acid is different from the next acids binding to the complex in terms of energy and bond type.^{10,49,50}

Therefore, complex formation between acid A and extractant B can be best described with a model based on two sequential reactions,⁴⁷ see eq (2) and the sequential reaction of the $\overline{AB}$ complex with n molecules of A in eq (4).^{40,51} The equilibrium constants for these reactions are defined in eq (3) and (5), respectively.

$$K_{1,1} = \frac{[\overline{AB}]}{[\overline{A}][\overline{B}]} \quad (3)$$

$$K_{n+1,1} = \frac{[\overline{A_{n+1}B}]}{[\overline{AB}][A]} \quad (5)$$

Figure 2 a) Schematic overview of liquid-liquid extraction (LLX) process of a mixture of acid A and water with a solvent containing complexing agent B and an additional column for back-extraction of the acid and regeneration of the solvent, and **b)** a schematic zoom in on the interface between the aqueous phase and the solvent phase with equilibrium reactions in the biphasic system. For simplicity, aqueous phase dissociation of the acid is not displayed, but does take place.

6.2.2 Effect of temperature on the equilibrium

Given the relations for the Gibbs energy of complexation in eq (6) and (7), and assuming that ΔH and ΔS are not dependent on temperature, the ratio of the complexation constant at temperature T_2 and T_1 can be equated as eq (8). The ratio of the forward and backward-extraction distribution ratios K_D/K'_D is directly coupled to this effect of temperature, from which the correlation with the enthalpy of complexation follows directly.

$$\Delta G = -RT \ln K \quad (6)$$

$$\Delta G = \Delta H - T\Delta S \quad (7)$$

$$\ln \frac{K_{T_2}}{K_{T_1}} = \frac{-\Delta H}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right) \quad (8)$$

6.3 Materials and methods

6.3.1 Chemicals

All aminopyridines (dioctylamine pyridine (DOAP, 99.2 %), octylamine pyridine (MOAP, 99.7 %), didodecylamine pyridine (DDAP, 99.5 %), 2-methyl-didodecylamine pyridine (2MDAP, > 99.4 %), diphenyl amine pyridine (DPPA, 83.4 %) and diphenyl dodecyl amine pyridine (DPMDAP, 88.8 %) were obtained from Syncom BV and used without further purification. All other chemicals were also used without further purification and purchased from Sigma Aldrich unless indicated otherwise (acetic acid (HAc, > 99.7 %), phenol (PhOH, > 99 %), triethylamine (TEA, >= 99.5 %), tributylamine (TBA, 99 %), trihexylamine (THA, 96 %), trioctylamine (TOA, 98 %), trioctylphosphine oxide (TOPO, 99 %), 1-octanol (> 99 %), heptane (99 %), methylisobutylketon (MIBK, $\geq$ 99 %), 2-bromophenol (2-BrPhOH, 98 %), 3-bromophenol (3-BrPhOH, 98 %), 4-nonylphenol (nonyl-PhOH, > 90 %)), Merck (tridodecylamine (TDDA, $\geq$ 95 %)), Acros Organics (tributylphosphate (TBP, 99 %)) and VWR International (toluene (> 99.5 %)).

6.3.2 Isothermal titration calorimetry (ITC)

The TA Instruments TAM III Microcalorimeter was used for isothermal titration calorimetry (ITC). The apparatus and operation procedure were previously published.⁴⁷ With ITC the thermodynamic parameters ΔH , n and K can be determined assuming ideal solubility, from which ΔS and ΔG can be calculated using eq (6)-(7). For the ITC experiments a set of sample and reference cells with equal volumes is used. For the experiments with tertiary amines and aminopyridines the volume is 4 mL, a concentration

of 0.24 M extractant in water saturated 1-octanol was applied (unless mentioned otherwise) and pure acetic acid was titrated. For the experiments with phenols the cell volume is 1 mL, the concentrations of the phenolics were 3.0 M 4-nonylphenol, 5.0 M phenol, 3.1 M 2-bromophenol and 3.2 M 3-bromophenol dissolved in toluene, and a solution of 0.75 M 4-cyanopyridine in toluene was titrated. For a higher density of data points in the lower range of molar ratio the first injected amounts of titrant were smaller than the subsequent injections. The interval between the injections was 90 minutes and the temperature was either 20 °C or 60 °C. For the experiments with tertiary amines, phosphates and phosphine oxides the heat released by the sample was corrected with the heat released in a blank titration. For the blank titration the same titrant is used in combination with a solvent without the reactive extractant that only contains the diluent. For the experiments with the aminopyridines the heat released was only corrected by the heat of the last injection, thereby taking into account the energy of dilution of the titrant. For the experiments with bromophenols, with a very low heat of interaction and equilibrium constant, the data were not corrected by the heat released by the last injection, but by a fitted constant value to also account for drifting of the baseline. In experiments with bromophenols, this was much more important than with amines, based on the significance of the heat effect relative to the heat of injection in these experiments. In all cases the correction value was small compared to the total energy but strongly improved the model fit, because it reduces the error in the heat of injection at a high molar ratio that strongly influences the fitting of K , whereas this region does not contain true information on the complexation. A stoichiometry of $n = 1$ was imposed based on experimental data. A first injection of 3 μL was performed to correct for diffusive loss of titrant and this injection was not included in the data fitting.⁵² In general, for ITC measurements an error of 1-5 % for the equilibrium constant K and around 1 % for the enthalpy of complexation ΔH can be assumed under ideal conditions.⁵²⁻⁵⁴ However, more realistic values for the measurement error can be obtained from a series of identical experiments. To investigate on this, three sets of six identical experiments were performed for a similar reaction model based on (1,1)-complexation followed by a sequential reaction.⁴⁷ In that study, we calculated a standard deviation of 11 % in $K_{1,1}$, 4.2 % in $\Delta H_{1,1}$, 26 % in $K_{n+1,1}$, 12 % in $\Delta H_{n+1,1}$ and 1.4 % in n for the sequential reaction model of eq (2)-(5), and 12 % in $K_{n,1}$, 1.6 % in n and 2.5 % in $\Delta H_{n,1}$ for a $n:1$ reaction model based on a single set of identical sites.⁴⁷ These errors would induce an error of 6.5 % in $\Delta S_{1,1}$, 20 % in $\Delta S_{n+1,1}$, 3 % in $\Delta G_{1,1}$ and 7 % in $\Delta G_{n+1,1}$, for the sequential model and 6.4 % in $\Delta S_{n,1}$ and 3 % in $\Delta G_{n,1}$ for the $n:1$ reaction model. For accurate ITC results the product of the concentration of the sample and the equilibrium constant should be sufficiently high so that an S-shaped curve is obtained.

6.3.3 Molecular modeling with Wavefunction Spartan '16 Parallel

For MM calculations, Wavefunction Spartan'16 Parallel software was used, employing a Hartree-Fock 6-31G* level of calculation in combination with the SM8 model for solvation of the molecules. The SM8 model applies a parametrization based on a large set of experimental data and treats the solvent as a continuous field, without incorporating specific interactions.⁵⁵ At first, the geometries of the extractant and the solute molecule were optimized. If the molecules were present in Spartan's SSPD database (a collection of pre-calculated molecules with e.g. geometric structures and energy), those geometries were used as the initial geometry. To reduce the computational time the carbon chains of extractant molecules were shortened. The energy profiles were calculated based on the total energy at a series of constrained distances between the proton of the acid and the proton accepting atom of the extractant molecule. At each intermolecular distance the geometry of the set of molecules was optimized and the energy was calculated for the molecules. All energies were referenced to the situation where the molecules are far apart and zero interaction energy can be assumed.

6.3.4 Liquid-liquid equilibria

Liquid-liquid equilibria (LLE) were determined by mixing 3 mL of an aqueous phase with either 4-cyanopyridine (4.8 mM or 95 mM) with 3mL of the solvent consisting of 0.1 M (substituted) phenols in toluene, or acetic acid (2 wt% or 5 wt%) with 3 mL of the solvent consisting of 0.24 M amine extractant in the diluent water saturated 1-octanol. The applied 10 mL glass vials were first shaken thoroughly by a lab vortex shaker after which they were put in a shaking bath at a shaking speed of 3 Hz for at least four hours at either 20 °C or 60 °C (4 hours was found sufficient to reach equilibrium). After this, the shaking was stopped and the liquids were allowed to settle for 2 hours. The aqueous phase was then analyzed by HPLC. For the HPLC analysis an Agilent HPLC 1200 series was used with a RID-detector. The column used was a GROM Resin H+ IEX (250*8 mm) at a temperature of T = 50 °C or an Agilent Hipselex-H column at 65 °C. The mobile phase used was a 5 mM H₂SO₄ aqueous solution at a flowrate of 0.6 mL/min.

6.4 Results and discussion

Aiming to improve the understanding of the effect of molecular structure of the extractant on the complexation with the solute, for acetic acid and 4-cyanopyridine a series of ITC-experiments were performed with extractants having a variety of structure modifications. For the interaction of acetic acid with tertiary amines and aminopyridines in 1-octanol the results for each of the curves displayed in Figure 3a show an energy release upon interaction. This indicates exothermic complexation. The complexation is slightly more exothermic for the tertiary amines than the aminopyridines. The steep part of the isotherms is located at approximately $n = 1$, after which the interaction energy is strongly decreased. This indicates a 1:1 stoichiometry and the data were therefore fitted with the 1:1 reaction model in eq (2)-(3). The first data points in any experiment show some fluctuation, which is likely caused by pending droplets, that do not properly fall of the tip of the needle, but with a second drop do, and then a larger volume is injected at once. To eliminate errors in fitting, the first data points were omitted, for the overall results and conclusions, the effects are negligible. The values of ΔH and $K_{1,1}$ were calculated and listed in Table 1. Table 1 also shows the fitted parameters of other aminopyridines for which similar curves were measured as those in Figure 3a. Based on the shape of the curves, also these parameters were fitted with the 1:1 reaction model. For DPMDAP and DPPA, the value of $K_{1,1}$ is much lower than for the other extractants, which is most likely due to the presence of benzene rings in the structures of these extractants. The accuracy of these ITC results was determined from standard deviations in the parameter fit in this work and was related to the previously published values for a fit based on a $n:1$ reaction,⁴⁷ because in this work a 1:1 reaction is applied. Larger standard deviations were derived, i.e. 13 % in $K_{1,1}$, 6 % in n and 4 % in $\Delta H_{1,1}$, versus 12 % in $K_{n,1}$, 1.6 % in n and 2.5 % in $\Delta H_{n,1}$, for the $n:1$ reaction model.⁴⁷ The resulting standard deviations in $\Delta S_{1,1}$ and in $\Delta G_{1,1}$ were 13 % and 3 %, respectively.

Table 1 Fitted parameters based on eq (2)-(3) with $n = 1$ for ITC results at $T = 20\text{ }^{\circ}\text{C}$ of the complexation reaction between (top) complexation of acetic acid with 0.24 M tertiary amines and aminopyridines in water saturated 1-octanol, and (bottom) 0.75 M 4-cyanopyridine with 3.0 M 4-nonylphenol, 5.0 M phenol, 3.1 M 2-bromophenol and 3.2 M 3-bromophenol dissolved in toluene.

Amine	$\Delta H_{1,1}$ (kJ/mol)	$K_{1,1}$ (L/mol)	ΔG (kJ/mol)	ΔS (J/mol/K)	
DOAP	-34.5	41	-9.1	-87	
TOA	-37.3	78	-10.6	-91	
DDAP	-34.2	57	-9.9	-83	
TDDA	-37	84	-10.8	-89	
MOAP	-34.7	89	-10.9	-81	
DPMDAP	-19.9	2.9	-2.6	-59	
2MDDAP	-32.3	61	-10	-76	
DPPA	-20.9	6.5	-4.6	-56	
Phenol					d_0 (kJ/mol)
Phenol (5.0 M)	-24	1.3	-0.6	-81	0.487
2-bromophenol (3.1 M)	-26	1.4	-0.9	-86	-0.032
3-bromophenol (3.2 M)	-32	1.9	-1.5	-103	0.318
4-nonylphenol (3.0 M)	-7.8	5.1	-4.0	-12.9	-0.323

Figure 3 ITC results for the complexation at $T = 20\text{ }^{\circ}\text{C}$ of **a)** acetic acid with 0.24M ■ TOA, □ TDDA, ● DOAP and ○ DDAP in water saturated 1-octanol, **b)** 0.75 M 4-cyanopyridine with ■ 3.0 M 4-nonylphenol, ● 3.1 M phenol ▲ 3.1 M 2-bromophenol and ◆ 3.2 M 3-bromophenol dissolved in toluene.

6.4.1 Acetic acid interaction with amines and aminopyridines

Comparing the results for DOAP with those for TOA as given in Table 1, as well as comparing DDAF with TDDA, it can be observed that the replacement of an alkyl chain with a pyridine ring significantly reduces the (negative) ΔH and K of complexation, indicating that the ring structure reduces the hydrogen bonding ability. The clear (1,1)-stoichiometry for both the tertiary amines and the aminopyridines in 1-octanol indicates that 1-octanol stabilizes the (1,1)-complex.⁸ This means that there is competition between 1-octanol and additional acid molecules for hydrogen bonding with the (1,1)-complex. In each (1,1)-complex, only one of the two available nitrogen atoms of the aminopyridines interacts with an acid molecule. Based on the ITC results it is not clear whether the nitrogen atom of the pyridine or the amine is dominant, or a combination of both. This is because the change in the thermodynamic parameters cannot be associated with just one of the nitrogen atoms, since there is not only an additional (pyridine) nitrogen atom available for interaction in the aminopyridines, but also one of the carbon chains of the amine nitrogen is replaced compared to the tertiary amines (without a pyridine ring). To further investigate on the nature of the interactions between the aminopyridines and carboxylic acids, MM studies were performed. The interaction energies between acetic acid and either an aminopyridine or a tertiary amine, calculated with MM, are displayed in Figure 4 as a function of the distance between the acidic proton and the basic nitrogen atom in the extractant.

Figure 4 Molecular modeling of the interaction of acetic acid with $\square$ DEAP (interaction with nitrogen atom in pyridine ring) and $\bullet$ TPA in 1-octanol, using the Hartree-Fock 6-31G* level of calculation and SM8 model for solvation. The distance is the intermolecular distance between the proton of the acetic acid and the nitrogen atom of the aminopyridine. The lines are added to guide the eye.

For the aminopyridine, both the interaction with the nitrogen atom of the pyridine ring and the amine nitrogen were taken into account. Not shown in Figure 4, is the interaction between the nitrogen atom of the tertiary amine group of the aminopyridine, since no energy minimum was found in the computation. Thus, the main interaction of the acid is with the pyridine nitrogen. The weaker interaction of the amine nitrogen is a result of withdrawal of electrons from the amine nitrogen through the conjugated π -system of the pyridine.

For the interaction with the pyridine nitrogen, two minima are found. The energy minimum at 2 Å (Figure 4), which is a typical distance for hydrogen bonding,^{56,57} is deeper for the aminopyridine than for the tertiary amine (without the pyridine ring), indicating a more favored hydrogen bonding for the aminopyridines. The hydrogen bonding ability is strengthened by the electron donating behavior of the amine nitrogen to the aromatic pyridine ring. The energy minimum for interaction with HAc at 1 Å (Figure 4), which is a typical distance for proton transfer,⁵⁸ is similar for both compounds. For the tertiary amine without a pyridine ring this minimum is significantly deeper than the minimum for hydrogen bonding, indicating that the mechanism including proton transfer is accompanied by a stronger enthalpic effect. Overall, the stronger hydrogen bonding for DDAP will result statistically in more hydrogen bonds than for TOA, and since the hydrogen bonding energy is slightly less than the proton transfer energy, the net result that would be expected is a lower enthalpy of complexation for DDAP than for TOA. These findings support the ITC results in Table 1, and show that by combining ITC with MM insight was obtained in the mechanisms of these extractant systems. Furthermore, it also explains the trends in previously reported results, where a good extraction capacity was reported, but limited temperature-swing possibilities for DDAP.^{19,23}

Based on differences in the molecular structure it is expected that by decreasing the rotational freedom around the pyridine nitrogen, the thermodynamics (ΔH and ΔS) of interactions can be changed. Table 1 indeed shows that for DPMDAP and DPPA these values are strongly decreased, as well as the complexation constant which indicates a weaker affinity for interaction with the acid. Also for DOAP and DDAP compared to TOA and TDDA, respectively, smaller negative values for ΔH and ΔS are shown in Table 1. For a smaller negative value of ΔH , a weaker temperature dependency is expected based on eq (8) assuming that the parameters ΔH and ΔS themselves are independent of temperature, this will be further studied in section 6.4.3.

6.4.2 4-Cyanopyridine interactions with phenolic compounds

The results of the ITC study on the complexation of 4-cyanopyridine with several (substituted) phenols in toluene are displayed in Figure 3b. All data were fitted with the model of eq (2) and (3), with a forced stoichiometry of $n = 1$, because for none of the experiments with phenolic compounds an S-shaped curve was obtained. The fitted parameters are listed in Table 1. Because of the relatively low heat of interaction for the (substituted) phenols an additional fitting parameter d_0 was required to account for drifting of the baseline due to e.g. variations in sample viscosity or room temperature during the experiment. The accuracy of these ITC results was also determined and related to the previously published values.⁴⁷ Since no S-shaped curve was obtained, which is required for accurate ITC data analysis, the standard deviations for the fitted parameters are relatively large, i.e. 20 % in $K_{1,1}$, 5 % in n and 7 % in $\Delta H_{1,1}$, leading to 17 % in $\Delta S_{1,1}$ and 5 % in $\Delta G_{1,1}$.

From the results in Table 1 it follows that substitution of a phenol ($pK_a = 9.99$) with an electron withdrawing bromide group increases ΔH , which is due to the increased acidity of the phenol by the inductive effect of bromide substitution (for 2-bromophenol the $pK_a = 8.45$ and for 3-bromophenol the $pK_a = 9.03$). However, the differences in ΔH are smaller than the 8 % statistical error that is expected because of the shape of the isotherm. Substitution at the meta-position (3-bromophenol) results in an even stronger increase than substitution at the ortho-position (2-bromophenol). This cannot directly be explained by the difference in acidity, since 2-bromophenol exhibits a lower pK_a than 3-bromophenol. The distribution of 4-cyanopyridine is also lower when 2-bromophenol in toluene is used in a liquid-liquid equilibrium,²⁰ which supports the finding of a lower K -value and therefore ΔG in the case of 2-bromophenol. For 4-nonylphenol, the alkyl-substitution has a positive inductive effect and thereby decreases the acidity of the phenol. This results in the very low ΔH that was found for the complexation of 4-nonylphenol and 4-cyanopyridine. Also for these components the effect of ΔH on the temperature dependency of the equilibrium will be further studied in section 6.4.3.

Using MM, it was found that the energy minimum for the interaction of the acidic proton of 3-bromophenol is deeper for interaction with the nitrogen atom of the pyridine-group than with the cyano-group, see Figure 5a. This implies that the interaction with the pyridine group of 4-cyanopyridine is favored, although a statistical distribution between both interactions is expected because of the small differences and also in case of overloading.

Figure 5 Energy profile of the intermolecular interactions calculated using the Hartree-Fock 6-31G* level of calculation and SM8 model for solvation in toluene of *n*:1 3-bromophenol:4-cyanopyridine complexes. The indicated distance is always the intermolecular distance between the OH group of the *n*th phenol with the respective nitrogen atom of 4-cyanopyridine or (for sequentially interacting phenols) with the OH group of the previously interacting phenol. **a**) 3-bromophenol with cyano-group of 4-cyanopyridine (closed symbol) and pyridine-N of 4-cyanopyridine (open symbol), **b**) phenols with the pyridine-group of 4-cyanopyridine, ● phenol, □ 4-ethylphenol, × 4-pentylphenol, ▲ 2-bromophenol and ◆ 3-bromophenol, and **c**) 4-cyanopyridine with ■ 3-bromophenol to the pyridine-N of 4-cyanopyridine, ● trimolecular complex with one 3-bromophenol molecule to each of the nitrogen atoms in 4-cyanopyridine, ▲ tetramolecular complex where the third 3-bromophenol interacts sequentially with the 3-bromophenol on the pyridine-N-side of the complex and ◆ pentamolecular complex where the fourth 3-bromophenol interacts sequentially with the 3-bromophenol on the cyano-N-side of the complex. The lines are added to guide the eye.

For all types of phenols the interactions with the pyridine-group of the 4-cyanopyridine were computed by MM, see Figure 5b. Phenol, 4-ethylphenol and 4-pentylphenol show almost the same curve, indicating a minimal effect of the length of the para substituted alkyl group. Thus, for 4-nonylphenol similar results are expected. Compared to phenol, 3-bromophenol shows a deeper energy minimum and 2-bromophenol shows a smaller energy minimum. These MM results only support the findings based on ITC data that p-substitution of a phenol with a bromide group increases the acidity. The energy minimum of 2-bromophenol is not as deep as that of phenol in the modeling results, while a slightly stronger interaction was measured with ITC and expected based on the decreased pK_a of 2-bromophenol. Apparently the effect of the steric hindrance of the bromine atom on the energy level of the complex is overestimated in MM. Simulations may be improved by incorporating water molecules in the complexes or including complexes of larger stoichiometry.⁵⁹ Simulations with larger complexes, see Figure 5c, show an energy minimum for the interaction with the second, third and fourth 3-bromophenol, although the energy minimum is becoming less pronounced. This means that it is very likely that, although depending on the concentrations in a specific liquid-liquid-equilibrium, also complexes with a higher stoichiometry are formed. For the interaction of the third 3-bromophenol, with the 3-bromophenol that is hydrogen bonded to the pyridine nitrogen in a (2,1)-complex, lowering the distance below 1.8 Å resulted in replacement of the second 3-bromophenol by the third (identical) 3-bromophenol, while the intermolecular distance between these two 3-bromophenols remained 1.8 Å, therefore no lower values are shown in the figure for complexations between 3-bromophenol and (2,1)-complexes of 3-bromophenol and 4-cyanopyridine.

The differences in the parameters determined with ITC are relatively small, which may be (partially) caused by the low K and ΔH values. Nevertheless, with the combination of ITC and MM it is possible to predict trends in affinity and ΔH of complexation based on electron densities on the aromatic ring, taking into account the effect of substituents. Calculations on steric hindrance using MM are delicate and simple 1:1 complexations may be oversimplified. Improvement of these calculations is possible by modeling larger sets of molecules, and the possibility of complexes with a higher stoichiometry should always be considered and examined.

6.4.3 Temperature dependency of the liquid-liquid equilibrium

The ratio K_D/K'_D , based on LLE at 20 °C (K_D) and 60 °C (K'_D) was calculated to study the effect of ΔH on the temperature dependency of the equilibrium that is expected based on eq (6)-(8).²³ For the first case on tertiary amines and aminopyridines at an initial acid concentration of 2 wt% in the aqueous phase K_D indeed decreases with increasing temperature, see Table 2. For the different tertiary amines, TDDA shows a higher K_D/K'_D than TOA and also DDAP with the longer carbon chains shows a slightly higher K_D/K'_D than DOAP, although the differences are small. Moreover, TOA and TDDA show larger K_D/K'_D than their carbon chain length equivalent aminopyridines DOAP and DDAP, respectively. For TOA and TDDA, LLE measurements at an initial acid concentration of 5 wt% showed both lower K_D and K_D/K'_D . Similar effects are calculated by Krzyzaniak et al.²³ for DDAP.

Table 2 also includes the results for the temperature effect on LLE for the case with 4-cyanopyridine and (substituted) phenols, as well as results of Bokhove et al.²⁰ based on an initial concentration of 4.8 mM 4-cyanopyridine and a concentration of 0.1 M of substituted phenols in toluene. A higher K_D is obtained for 3-bromophenol than for phenol, and 2-bromophenol shows a lower K_D than phenol. The K_D values found by Bokhove et al.²⁰ (see Table 2) show deviations from those in this work, although they also show the clear difference between 2-bromophenol and 3-bromophenol. Phenol and 3-bromophenol show the highest K_D/K'_D at an initial 4-cyanopyridine concentration of 4.8 mM. Extraction with pure toluene shows no significant change in K_D with increased temperature, which is expected when there is no complex formation reaction and no critical solution temperature boundary is observed. Also for these components, at a higher initial 4-cyanopyridine concentration ($c_0 = 95$ mM), both K_D and K_D/K'_D are reduced and the differences between the extractants are smaller, although 3-bromophenol still shows the highest value for K_D/K'_D .

Table 2 Liquid-liquid-equilibria at 20 °C and 60 °C and their ratio K_D/K'_D of (top) acetic acid ($c_0 = 2$ wt% and 5 wt%) with 0.24 M tertiary amine and aminopyridine extractants in water-saturated 1-octanol and (bottom) 4-cyanopyridine ($c_0 = 4.8$ mM and 95 mM) with a solvent consisting of 0.1 M (substituted) phenols in toluene.

	K_D (T = 20 °C)		K_D (T = 60 °C)		K_D (T = 20 °C)/ K'_D (T = 60 °C)	
	2 wt%	5 wt%	2 wt%	5 wt%	2 wt%	5 wt%
In water saturated 1-octanol						
TOA	2.70 ± 0.074	1.18 ± 0.044	1.63 ± 0.053	1.12 ± 0.043	1.66 ± 0.10	1.05 ± 0.082
DOAP	2.66 ± 0.074		1.84 ± 0.057		1.45 ± 0.087	
TDDA	2.83 ± 0.077	1.13 ± 0.043	1.52 ± 0.051	1.05 ± 0.041	1.86 ± 0.12	1.08 ± 0.086
DDAP	2.86 ± 0.078		1.84 ± 0.057		1.55 ± 0.093	
MOAP	2.27 ± 0.066		1.91 ± 0.059		1.19 ± 0.073	
2MDDAP	3.19 ± 0.085		2.27 ± 0.066		1.40 ± 0.080	
	K_D (T = 20 °C)		K_D (T = 60 °C)		K_D (T = 20 °C)/ K'_D (T = 60 °C)	
	Results from Bokhove ²⁰ ($c_0 = 4.8$ mM)	Results from this work	Results from this work		$c_0 = 4.8$ mM	$c_0 = 95$ mM
In toluene						
PhOH	6.8	7.6 ± 0.86	5.8 ± 0.64		1.3 ± 0.17	1.1 ± 0.051
2-BrPhOH	6.9	6.0 ± 0.66	5.6 ± 0.62		1.1 ± 0.15	1.1 ± 0.051
3-BrPhOH	9	9.3 ± 1.0	7.1 ± 0.78		1.3 ± 0.17	1.2 ± 0.059
Pure toluene	5	6.0 ± 0.66	6.0 ± 0.66		1.0 ± 0.13	1.0 ± 0.046

6.4.3.1 Acetic acid interaction with amines and aminopyridines

The natural logarithm of the ratio of K_D/K'_D measured in the LLE experiments for the forward (T = 20 °C) and backward (T = 60 °C) extraction step is plotted as a function of the fitted ΔH from ITC measurements (T = 20 °C) in Figure 6a, for the tertiary amines and aminopyridines in 1-octanol. Similar results are displayed in Figure 6b for several combinations of extractants (i.e. TOA, TDDA and the phosphorous based extractants tributylphosphate (TBP) and trioctylphosphine oxide (TOPO)) and diluents (i.e. toluene, methyl isobutyl ketone (MIBK), 1-octanol and heptane).

a

b

Figure 6 Natural logarithm of the ratio of forward ($T = 20\text{ }^{\circ}\text{C}$) and backward ($T = 60\text{ }^{\circ}\text{C}$) extraction distribution coefficients $\ln K_D/K'_D$ versus the enthalpy of complex formation ΔH at $T = 20\text{ }^{\circ}\text{C}$ determined by ITC for acetic acid with **a**) 0.24 M tertiary amines (see Figure 1) in water saturated 1-octanol, and **b**) 0.24 M $\blacksquare$ TOA, $\bullet$ TDDA, $\blacktriangle$ TBP and $\blacklozenge$ TOPO in toluene (open symbols), MIBK (half-open symbols), heptane (closed symbols) and 1-octanol (cross symbols). The error in ΔH equals 2.5 %. The ratio K_D/K'_D was determined in liquid-liquid equilibrium experiments with 2 wt% acetic acid in the aqueous phase and 0.23 M TOA or TDDA, 1.1-2.4 M TBP, or approx. 0.22 M TOPO in the organic phase.

The ITC data in Figure 6b were taken from Sprakel and Schuur.⁴⁸ For the inactive diluents, the low K_D resulted in larger deviations in K_D/K'_D . Because the model of just eq (2)-(3) is not suitable for complexes with a higher stoichiometry or large differences in the interaction of sequentially binding acids,⁴⁷ for TOA and TDDA the extended model of eq (2)-(5) was applied and the ΔH of the most dominant complex was plotted, i.e. $\Delta H_{1,1}$ for 1-octanol and $\Delta H_{n+1,1}$ for the other diluents. In Figure 6 a negative trend of $\ln K_D/K'_D$ is observed with reducing magnitude of ΔH , which is in agreement with the linear decrease expected based on eq (8). This would imply that indeed a larger negative ΔH is advantageous for LLX processes. However, the error margins are too significant to allow for a direct conclusion based on only these experiments. Moreover, for eq (8) temperature independent values of ΔH and ΔS are assumed which is a simplification. To further study and substantiate the complexation of acid and complexating agent, also ΔS and the temperature effect on the thermodynamic parameters should be taken into account, especially since enthalpy-entropy compensation (EEC) may play a role,⁶⁰⁻⁶⁴ *vide infra*.

6.4.3.1.1 Effect of chain length

The (1,1) and (n+1,1)-complex formation between acetic acid and tertiary amines with carbon chains of 2, 4, 6, 8 and 12 atoms in toluene and in 1-octanol at 20 °C is depicted in Figure 7a and b, respectively, by the fitted enthalpy-entropy data. The lines for a Gibbs energy of complexation of -9 and -12 kJ/mol complex, corresponding to a K of 40 and 140, are also shown in the figure. The slope of these lines depends only on the temperature.

Figure 7 Fitted ΔH and ΔS per mole of complex from ITC at 20 °C for (graph **a**) and **b**) acetic acid and $\blacksquare$ TEA, $\bullet$ TBA, $\blacktriangle$ THA, $\star$ TOA and $\blacklozenge$ TDDA in toluene (open symbols) and 1-octanol (closed symbols) with **a**) (1,1)-complex based on eq (2) and (3) and **b**) the (n+1,1)-complex based on eq (4)-(5) and stoichiometry in 1-octanol of $n + 1 \approx 1.8 - 2.5$ and toluene of $n + 1 \approx 2.5 - 2.6$; and (graph **c**) and **d**) $\Delta H_{1,1}$ and $\Delta S_{1,1}$ based on eq (2) and (3) for **c**) acetic acid and 0.24 M tertiary amines and aminopyridines in water saturated 1-octanol and **d**) (substituted) phenols with 0.75 M 4-cyanopyridine in toluene (3.0 M 4-nonylphenol, 3.1 M phenol, 3.1 M 2-bromophenol and 3.2 M 3-bromophenol). Straight lines correspond to a Gibbs energy of complexation of -9 and -12 kJ/mol complex, i.e. a complexation constant K of 40 and 140, respectively.

Figure 7a and b show clear differences for 1-octanol and toluene considering the location of the data points around the lines with constant ΔG and the visibility of the linear trend in the data points. For the less favorable complexes for each diluent, i.e. the (n+1,1)-complex for 1-octanol and the (1,1)-complex for toluene,^{10,48} lower K and ΔG are found, therefore these points are located more towards the top of the figure. For toluene, all

data points of the most favorable (n+1,1)-complex are within the area between these lines (Figure 7b). The parameters belonging to the dominant complexes for toluene, $\Delta H_{n+1,1}$ and $\Delta S_{n+1,1}$, are clearly larger negative for the extractants with larger carbon chains, see Figure 7b. The increased chain length induces a larger entropic penalty in the complexation, which could have been expected from increased steric hindrance. On the other hand, for the (1,1)-complex ΔH and ΔS tend to get smaller negative with increasing chain length of the tertiary amine in toluene. This may be a result of weaker hydrogen bonding of the first acid in toluene with increasing chain length. In 1-octanol, where a stronger interaction based on proton transfer is expected, this effect is not visible.¹⁰ Also for 1-octanol all data points of the more stable (1,1)-complex are within the area within $\Delta G = -9$ and -12 kJ/mol (Figure 7a), indicating that the differences in Gibbs energy of complexation are small for varying the chain length of the tertiary amine. This effect could be interpreted as enthalpy-entropy compensation (EEC).^{60-62,65}

EEC is the phenomenon that entropic and enthalpic contributions to the total binding energy vary in an opposite way when small changes to ligand, protein or solvent are applied.^{60,61} EEC is a common topic in the field of protein-ligand binding,^{60,65} but also related to other chemical reactions.⁶²⁻⁶⁴ Although there is still debate on the existence of EEC and whether there is actual (full) compensation, there is experimental evidence that indicates at least a weak form of EEC.^{60,64,66-69} EEC may also be (partly) induced by experimental errors, since ΔG and $T\Delta S$ are computed from the values for K and ΔH that are directly obtained from fitting of the data, and thereby the resulting error in $T\Delta S$ is opposite to the error in ΔH .⁶⁰ The standard deviation of 2.5 % in $\Delta H_{1,1}$ (see also section 6.3.2) from a fit based on a sequential reaction mechanism, for a system of tertiary amines similar to those in Figure 7a and b, would induce an error of 6.4 % in $T\Delta S_{1,1}$ ⁴⁷ and the standard deviation of 4 % in $\Delta H_{1,1}$ (see also section 6.4) for the system of tertiary amines and aminopyridines in 1-octanol (Figure 7c), would induce an error of 14 % in $T\Delta S_{1,1}$ ⁴⁷. Figure 7 shows EEC over a significantly large range of ΔH and ΔS values. The phenomenon of EEC implies that if the enthalpy of complexation is improved by molecular design, this will always be interfered by (partially) compensating changes in the entropy of complexation and therefore does not necessarily influence the Gibbs energy of complexation and equilibrium constant K .⁶⁰ This can be interpreted as the reduction of the degrees of freedom of the complex as a result of tighter bonding.

6.4.3.1.2 Effect of addition of pyridine ring to tertiary amine extractants

The relation between the thermodynamic parameters ΔH and ΔS for the complexation of tertiary amines and aminopyridines with acetic acid is shown in Figure 7c. Although DPPA and DPMDAP are far from the line corresponding to $\Delta G = -10$ kJ/mol, the other extractants are all around the line of $\Delta G = -10$ kJ/mol, showing the trend of EEC. From the decreased ΔG for DPPA and DPMDAP it can be concluded that addition of two extra benzyl-groups to the pyridine ring, either strongly reduces the basicity of the extractant or results in formation of a frustrated Lewis pair as a result of steric hindrance.⁷⁰ Comparing the derived parameters for ΔS (Figure 7c) it is clear that the effect of the molecular structure on ΔH is also accompanied by compensating changes in ΔS . Comparing the results of 2MDDAP with DDAP (Figure 7c) shows that adding a methyl group next to the nitrogen atom in the pyridine of DDAP does not significantly change the thermodynamic parameters.

The trend in the relation between K_D/K'_D and ΔH in Figure 6 may also be less clear than expected based on eq (8) because of the fact that ΔH and ΔS are not necessarily constant with temperature. Therefore, the effect of increasing temperature on ΔH and ΔS , and thereby on ΔG , was studied with ITC experiments at an elevated temperature of 60 °C, see Figure 8.

Figure 8 ΔH and ΔG of complex formation with acetic acid for 0.24 M TOA, TDDA, DOAP and DDAP; in water saturated 1-octanol at $T = 20$ °C (closed symbols) and $T = 60$ °C (open symbols). Lines are added to guide the eye and connect data points at 20 °C and 60 °C.

From a comparison of the results at 60 °C (open symbols) with those at 20 °C (closed symbols) in Figure 8, indeed ΔG decreases and therefore the complexation constant decreases as well. Additionally, especially for the amines without a pyridine ring ΔH is larger negative with increasing temperature. The increase of ΔH is stronger for the extractants with longer carbon chains, when comparing TDDA and TOA, as well as DDAP and DOAP. The differences in the change in ΔH with temperature can explain why the results in Figure 6 do not show a clear direct relation between ΔH at $T = 20$ °C and K_D/K'_D . Thus, next to the ΔH at $T = 20$ °C, also the change in ΔH with temperature should be taken into account when the temperature effect on the complexation equilibrium and K_D/K'_D is studied.

6.4.3.2 4-Cyanopyridine interactions with phenolic compounds

Also for 4-cyanopyridine with phenolic compounds the relation between ΔH and ΔS of complexation and the temperature dependency of the complexation equilibrium was studied in a combined approach using ITC and MM. The ΔH that was found for interaction with phenol (Table 1) is about 2 kJ/mol lower than that for 2-bromophenol, which better supports the K_D/K'_D results for a higher initial concentration (Table 2). The ITC and LLE results for phenol compared to 3-bromophenol (Table 1 and Table 2) do not match, since compared with phenol the shift in K_D is equal to that of 3-bromophenol although 3-bromophenol has a higher ΔH . MM does support the LLE results and does show comparable ΔH for phenol and 3-bromophenol (Figure 5b). For 3-bromophenol the ratio of K_D/K'_D (Table 2) is higher than with 2-bromophenol which can be related to the higher ΔH (see Table 1) that was found in ITC experiments and confirmed by MM (Figure 5b). This would not be expected based on the lower pK_a of 2-bromophenol, but may be explained by increased steric hindrance in the complexation. However, in this case also the negative ΔS calculated with eq (6)-(7) is smaller for 2-bromophenol, which means that there is no indication for additional steric hindrance. The concentrations for the phenol titrant and 4-cyanopyridine sample in ITC were both higher than applied in the LLE experiments which was required for fitting of the data at these low K -values. Therefore it has to be taken into account that increasing the concentration will in general decrease $K_{1,1}$,^{47,71,72} which may also result in a lower measured value of ΔH . This emphasizes the importance of the concentrations applied in ITC in order to link the results with LLE.⁴⁷

Bokhove et al.⁵⁹ included 15 different complexes in their study on the complexation equilibrium of 4-cyanopyridine with 4-nonylphenol. The dominant stoichiometry was found to depend on the aqueous phase

concentration of 4-cyanopyridine. According to their results, at the low concentration that was used in the current study, the (2,1)-complex between 4-nonylphenol and 4-cyanopyridine is dominant ($\pm 35\%$ of the complexes), but the (1,1)-complex ($\pm 20\text{--}30\%$) and (3,1)-complex ($\pm 20\text{--}25\%$) are also present. For the samples with a high concentration that were applied in the LLE, the (1,1)-complex is still dominant according to their results ($\pm 35\text{--}45\%$), followed by the (2,1)-complex ($\pm 35\%$) and only low concentrations of higher complexes are present ($< 20\%$).⁵⁹

Also for the (substituted) phenols with 4-cyanopyridine, the relation of ΔH and ΔS of complexation (see Figure 7d) appears to show EEC, however, the differences in the parameters that are determined are small despite the higher concentrations used in ITC. Based on the larger standard deviation of 7 % in $\Delta H_{1,1}$, see also section 6.4.2, induced by fitting of the data without a properly S-shaped isotherm as a result of low K-values and concentrations limited by solubility, a standard deviation of 17 % in $T\Delta S_{1,1}$ is obtained. Nevertheless, it can be concluded that EEC is likely, based on the trend in the $\Delta H_{1,1}$ and $\Delta S_{1,1}$ values for the complexation with (substituted) phenols, of which for nonylphenol the difference in $\Delta H_{1,1}$ and $T\Delta S_{1,1}$ with the other phenols is larger than the standard deviation.

6.4.4 Implications for future directions in solvent selection

Based on the rather constant ΔG in Figure 7, that is visible as a linear relation between ΔH and ΔS , the presence of EEC for the extractant families studied is likely. This implies that e.g. varying the amine chain length has little effect on the forward extraction step, as ΔG and therefore K are constant. On the other hand, ΔH and ΔS can be varied, which may be used in the back-extraction step. To study the implications of EEC for extractant families, and identify possibly achievable K_D/K'_D once the ΔG of such a family of extractants is known, K_D/K'_D was calculated as a function of ΔG for a range of ΔH and ΔS combinations. The calculations were done using eq (2),(3) and (8) for the equilibrium constants, a solvent-to-feed ratio of 1:1, assuming ΔH and ΔS are not affected by temperature, including only (1,1)-complexes and for an initial extractant concentration of 0.24 M.

Figure 9 Effect of enthalpy of the complexation reaction ΔH on the relation between the ratio of the forward and backward extraction K_D/K'_D and the Gibbs energy ΔG of complexation. Curves from bottom to top are for $\Delta H = -10, -20, -30, -40, -50$ and -60 kJ/mol and at a temperature difference of $\Delta T = 40$ K (left) and 70 K (right) between forward and backward extraction, an initial acid concentration of 0.34 M (**a**, **b**, **c**, **d**) and increased initial acid concentration of 0.84 M (**e**+**f**), and a K_m of 0.4 (**a**, **b**, **e**, **f**) and an increased K_m of 2.5 (**c**+**d**).

For an initial acid concentration of 0.34 M, a physical extraction constant (see Figure 2) $K_m = 0.4$ and a temperature difference between forward and backward extraction of $\Delta T = 40$ K, see Figure 9a the ratio of the forward and backward distribution coefficient K_D/K'_D increases with increasing enthalpy of complexation ΔH , for a given value of ΔG . In Figure 9a, at low ΔG the effect of ΔH is less significant and there is an optimum with respect to ΔG in the curves. It follows that a higher equilibrium constant does not always result in the highest K_D/K'_D . With hydrogen bonding the maximum ΔH that can be obtained is around $\Delta H = -50$ kJ/mol. This implies that for these conditions the highest K_D/K'_D would be obtained for an optimum ΔG of around -10 kJ/mol, a typical value for tertiary amine extractants, see Table 1. Increasing the temperature difference between the forward and backward extraction step to 70 K (Figure 9b) increases K_D/K'_D , which can be expected based on eq (8). Moreover, the increased temperature step shifts the maxima of the curves towards a more negative value of ΔG . This implies that stronger complexing agents can be used when the temperature step in the backward extraction is increased. In most of these cases the loading of the organic phase is above one and only a complex stoichiometry of $n = 1$ is taken into account, so the non-temperature dependent physical extraction constant K_m should play a significant role. Increasing the physical extraction K_m (Figure 9c for $\Delta T = 40$ K and Figure 9d for $\Delta T = 70$ K) from 0.4 to 2.5, makes K_D less dependent on the complexation reaction. As a result the ratio K_D/K'_D indeed decreased significantly, accompanied by a small shift of the optimal ΔG to a less negative ΔG .

A stronger effect on K_D/K'_D is observed when the initial acid concentration is increased to 0.84 M (Figure 9e for $\Delta T = 40$ K and Figure 9f for $\Delta T = 70$ K). The obtained values for K_D/K'_D are significantly lower at the higher initial acid concentration, especially for the larger shift in temperature, and there is a shift of the optimal ΔG to less negative values. The effects of the increased temperature-swing and physical extraction on the relation between K_D/K'_D and ΔG are small compared to the effect of initial acid concentration. This implies that in the case of a multistage extraction - back-extraction system in which also higher concentrations are obtained, complexation reactions with a higher ΔG become less favorable.

For the design of the molecular structure of new solvents these findings imply that it is important to aim for the most negative ΔH and not only a high equilibrium constant or largely negative ΔG . Combining this with the results from Figure 8 in which it was shown that ΔH is not (always) independent of temperature, it can be concluded that for molecular design the temperature dependency of ΔH itself should also be considered. This is

especially of importance when only a small temperature step is applied or when solute concentrations are higher, as in those cases a less (negative) ΔG can be favorable.

6.5 Conclusion

An approach combining isothermal titration calorimetry (ITC) and molecular modeling (MM) has been shown to be useful in the search of compounds for complexation based extraction. It offers a way to carry out molecular design and engineering of solvents for liquid-liquid extraction (LLX) of polar compounds. Aiming at a maximum temperature dependency for temperature-swing solvent regeneration, understanding the relation between the molecular structure of the extractant and the temperature dependency of the extractant-solute interactions is of great importance for solvent design. For two cases, i.e. the interaction of acetic acid with tertiary amines and of 4-cyanopyridine with (substituted) phenols, solvent-solute interactions were studied.

It was confirmed that increased (negative) enthalpy of complexation as measured by ITC and predicted by MM correlates well with the temperature dependency of the liquid-liquid equilibrium, thereby showing that MM is a perfect tool to engineer molecules, which can be checked by ITC. The dependency of the enthalpy of complexation on the molecular structure was found to pair with a compensating dependency of ΔS of complexation, i.e. enthalpy-entropy compensation (EEC). Knowledge on EEC can aid in the optimization of ΔH and thereby improve the temperature dependency by making small changes to extractant structures. It was also shown that for a typical system there is an optimum in K_D/K'_D with respect to varying ΔG for every ΔH i.e. the largest negative ΔG is not necessarily the optimum for a temperature-swing regeneration.

References

- (1) Blahušiak, M.; Kiss, A. A.; Kersten, S. R. A.; Schuur, B. *Energy* 2016, *116*, 20-31.
- (2) Blahušiak, M.; Kiss, A. A.; Babic, K.; Kersten, S. R. A.; Bargeman, G.; Schuur, B. *Sep Purif Technol* 2018, *194*, 301-318.
- (3) López-Garzón, C. S.; Straathof, A. J. J. *Biotechnol Adv* 2014, *32*, 873-904.
- (4) McConvey, I. F.; Nancarrow, P. *Pharmaceutical Process Development: Current Chemical and Engineering Challenges*; The Royal Society of Chemistry, 2011, pp 209-237.
- (5) Blumberg, R.; Gonen, D.; Meyer, D. *Recent Advances in Liquid-Liquid Extraction*; Hanson, C., Ed.; Pergamon, 1971, pp 93-111.
- (6) Chen, J.; Duan, L. P.; Mi, J. G.; Fei, W. Y.; Li, Z. C. *Fluid Phase Equilib* 2000, *173*, 109-119.
- (7) Reyhanitash, E.; Brouwer, T.; Kersten, S. R. A.; van der Ham, A. G. J.; Schuur, B. *Chem Eng Res Des* 2018, *137*, 510-533.
- (8) Sprakel, L. M. J.; Schuur, B. *Sep Purif Technol* 2019, *211*, 935-957.
- (9) Wasewar, K. L. *Int J Chem Eng Appl* 2012, *3*, 249-255.
- (10) Tamada, J. A.; King, C. J. *Ind Eng Chem Res* 1990, *29*, 1327-1333.
- (11) Hano, T.; Matsumoto, M.; Ohtake, T.; Sasaki, K.; Hori, F.; Kawano, Y. *J Chem Eng Jpn* 1990, *23*, 734-738.
- (12) Matsumoto, M.; Otono, T.; Kondo, K. *Sep Purif Technol* 2001, *24*, 337-342.
- (13) Rasrendra, C. B.; Girisuta, B.; van de Bovenkamp, H. H.; Winkelman, J. G. M.; Leijenhurst, E. J.; Venderbosch, R. H.; Windt, M.; Meier, D.; Heeres, H. J. *Chem Eng J* 2011, *176-177*, 244-252.
- (14) Uslu, H.; Datta, D.; Bamufleh, H. S. *J Mol Liq* 2015, *212*, 430-435.
- (15) Hong, Y. K.; Hong, W. H. *Korean J Chem Eng* 2004, *21*, 488-493.
- (16) Aşçi, Y. S.; İnci, İ. *J Ind Eng Chem* 2012, *18*, 1705-1709.
- (17) Kaur, G.; Elst, K. *RSC Adv* 2014, *4*, 45029-45039.
- (18) Krzyzaniak, A.; Schuur, B.; Sukumaran, M.; Zuilhof, H.; De Haan, A. B. *Chem Engineer Trans* 2011, *24*, 709-714.
- (19) Krzyzaniak, A.; Leeman, M.; Vossebeld, F.; Visser, T. J.; Schuur, B.; de Haan, A. B. *Sep Purif Technol* 2013, *111*, 82-89.
- (20) Bokhove, J.; Schuur, B.; de Haan, A. B. *Sep Purif Technol* 2012, *98*, 410-418.
- (21) Brouwer, T.; Blahusiak, M.; Babic, K.; Schuur, B. *Sep Purif Technol* 2017, *185*, 186-195.
- (22) Tamada, J. A.; King, C. J. *Extraction of Carboxylic Acids by Amine Extractants*. Berkeley, CA, 1989.
- (23) Krzyzaniak, A.; Schuur, B.; de Haan, A. B. *Chem Eng Sci* 2014, *109*, 236-243.

- (24) Castro-Aguirre, E.; Iñiguez-Franco, F.; Samsudin, H.; Fang, X.; Auras, R. *Adv Drug Deliver Rev* 2016, *107*, 333-366.
- (25) Bozell, J. J.; Moens, L.; Elliott, D. C.; Wang, Y.; Neuenschwander, G. G.; Fitzpatrick, S. W.; Bilski, R. J.; Jarnefeld, J. L. *Resour Conserv Recy* 2000, *28*, 227-239.
- (26) Gadipelly, C.; Pérez-González, A.; Yadav, G. D.; Ortiz, I.; Ibáñez, R.; Rathod, V. K.; Marathe, K. V. *Ind Eng Chem Res* 2014, *53*, 11571-11592.
- (27) Lim, J. C. L.; Lee, K. E. *Nat Environm Pollut Technol* 2017, *16*, 591-597.
- (28) Shah, V. H.; Pham, V.; Larsen, P.; Biswas, S.; Frank, T. *Ind Eng Chem Res* 2016, *55*, 1731-1739.
- (29) Shan, X.; Qin, W.; Dai, Y. *Chem Eng Sci* 2006, *61*, 2574-2581.
- (30) Athankar, K. K.; Wasewar, K. L.; Varma, M. N.; Shende, D. Z. *J Chem Eng Data* 2016, *61*, 2335-2345.
- (31) Qin, W.; Li, Z.; Dai, Y. *Ind Eng Chem Res* 2003, *42*, 6196-6204.
- (32) Procházka, J.; Heyberger, A.; Volaufová, E. *Sep Sci Technol* 2005, *39*, 1073-1091.
- (33) Matsumoto, M.; Takahashi, T.; Fukushima, K. *Sep Purif Technol* 2003, *33*, 89-93.
- (34) Inci, I. *J Sci Ind Res* 2002, *61*, 817-822.
- (35) Kamlet, M. J.; Abboud, J. L. M.; Abraham, M. H.; Taft, R. W. *J Org Chem* 1983, *48*, 2877-2887.
- (36) Eckert, F.; Klamt, A. *AIChE J* 2002, *48*, 369-385.
- (37) Laurence, C.; Graton, J.; Gal, J.-F. *J Chem Educ* 2011, *88*, 1651-1657.
- (38) Aono, S.; Kato, S. *J Comput Chem* 2010, *31*, 2924-2931.
- (39) Chagnes, A.; Moncomble, A.; Cote, G. *Solvent Extr Ion Exch* 2013, *31*, 499-518.
- (40) Cuypers, R.; Burghoff, B.; Marcelis, A. T. M.; Sudhölter, E. J. R.; de Haan, A. B.; Zuilhof, H. *J Phys Chem A* 2008, *112*, 11714-11723.
- (41) Cuypers, R.; Murali, S.; Marcelis, A. T. M.; Sudhoelter, E. J. R.; Zuilhof, H. *ChemPhysChem* 2010, *11*, 3465-3473.
- (42) Kabiri, M.; Unsworth, L. D. *Biomacromolecules* 2014, *15*, 3463-3473.
- (43) Falconer, R. J. *J Mol Recognit* 2016, *29*, 504-515.
- (44) Damian, L. *Methods Mol Biol* 2013, *1008*, 103-118.
- (45) Ladbury, J. E.; Chowdhry, B. Z. *Chem Biol* 1996, *3*, 791-801.
- (46) Cuypers, R.; Sudhoelter, E. J. R.; Zuilhof, H. *ChemPhysChem* 2010, *11*, 2230-2240.
- (47) Sprakel, L. M. J.; Schuur, B. *Ind Eng Chem Res* 2018, *57*, 12574-12582.
- (48) Sprakel, L. M. J.; Schuur, B. *J Ind Eng Chem* 2018, *72*, 364-373.

- (49) Barrow, G. M.; Yerger, E. A. *J Am Chem Soc* 1954, *76*, 5211-5216.
- (50) Reyhanitash, E.; Egor Fufachev; Kaspar D. van Munster; Michael B.M. van Beek; Lisette M.J. Sprakel; Carmen N. Edelijn; Bert M. Weckhuysen; Sascha R.A. Kersten; Pieter Bruijninx; Schuur, B. Carboxylic acid recovery from phosphonium phosphinate ionic liquid. *submitted*.
- (51) Liu, Y.; Sturtevant, J. M. *Biophys Chem* 1997, *64*, 121-126.
- (52) Boyce, S. E.; Tellinghuisen, J.; Chodera, J. D. *bioRxiv, Biochem* 2015, 23796/23791-23796/23797.
- (53) Tellinghuisen, J. *Anal Biochem* 2005, *343*, 106-115.
- (54) Schalley, C. A. *Analytical methods in supramolecular chemistry*; Wiley: Weinheim; 2007.
- (55) Cramer, C. J.; Truhlar, D. G. *Acc Chem Res* 2008, *41*, 760-768.
- (56) Gilli, P.; Pretto, L.; Bertolasi, V.; Gilli, G. *Acc Chem Res* 2009, *42*, 33-44.
- (57) Krishtalik, L. I. *BBA-Bioenergetics* 2000, *1458*, 6-27.
- (58) Lide, D. R. *CRC handbook of chemistry and physics*; 74th ed.; CRC Press: Boca Raton, 1993.
- (59) Bokhove, J.; Schuur, B.; de Haan, A. B. *Chem Eng Sci* 2012, *82*, 215-222.
- (60) Chodera, J. D.; Mobley, D. L. *Ann Rev Biophys* 2013, *42*, 121-142.
- (61) Dragan, A. I.; Read, C. M.; Crane-Robinson, C. *Eur Biophys J* 2017, *46*, 301-308.
- (62) Freed, K. F. *J Phys Chem B* 2011, *115*, 1689-1692.
- (63) Laurence, C.; Berthelot, M.; Graton, J. *The Chemistry of Phenols*; John Wiley & Sons, Ltd, 2003, pp 529-603.
- (64) Arnett, E. M.; Joris, L.; Mitchell, E.; Murty, T. S. S. R.; Gorrie, T. M.; Schleyer, P. v. R. *J Am Chem Soc* 1970, *92*, 2365-2377.
- (65) Gallicchio, E.; Kubo, M. M.; Levy, R. M. *J Am Chem Soc* 1998, *120*, 4526-4527.
- (66) Starikov, E. B.; Nordén, B. *Chem Phys Lett* 2012, *538*, 118-120.
- (67) Sharp, K. *Protein Sci* 2001, *10*, 661-667.
- (68) Ryde, U. *MedChemComm* 2014, *5*, 1324-1336.
- (69) Christian Laurence; Gal, J.-F. *Lewis Basicity and Affinity Scales*; John Wiley & Sons, Ltd, 2009.
- (70) Stephan, D. W. *Org Biomol. Chem.* 2008, *6*, 1535-1539.
- (71) Li, Z.; Qin, W.; Dai, Y. *Tsinghua Sci Technol* 2002, *7*, 41-45.
- (72) Tamada, J. A.; Kertes, A. S.; King, C. J. *Ind Eng Chem Res* 1990, *29*, 1319-1326.

Swing processes for solvent
regeneration in liquid-liquid extraction
of succinic acid

Abstract

Solvent regeneration processes for liquid-liquid extraction of succinic acid (HSuc) from aqueous streams were investigated. Tri-n-octyl amine (TOA) and tri-n-octyl phosphine oxide (TOPO) in methyl isobutyl ketone (MIBK) showed good extraction. For 20 vol% TOA in MIBK, addition of pentane at an anti-solvent/solvent ratio of 1 (vol/vol) decreased K_D from 10.2 to 0.46, whereas applying ethane at 30 bar decreased K_D to 0.45 and increasing the temperature to 60 °C decreased K_D to 1.6. Evaporation of MIBK from a solvent of 40 vol% TOA in MIBK decreased K_D from 10.2 to 4.0. For these processes including regeneration, capital investments and energy requirements were calculated for a production of 10 kiloton per year at a concentration factor of 5. Costs of all processes to obtain the product at maximum solubility are less than evaporation (2600 kJ/kg product at maximum solubility). A combination of a swing in diluent and in temperature results in higher product concentrations after back-extraction, and reduces the energy input to obtain the pure HSuc to 19 MJ/kg. The ethane based process is the most effective with 13 MJ/kg to obtain the pure HSuc product. Although additional capital investments for compressors and pumps are required, only 110 days of production are required for a return on the additional investments.

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7.1 Introduction

Liquid-liquid extraction (LLX) can be an efficient, environmentally friendly and economical process for the separation of acids from aqueous streams,¹⁻³ e.g. to recover organic acids from aqueous waste streams and fermentation broths.⁴ LLX can be an efficient alternative to distillation, especially in the case of low solute concentrations, similar boiling points of components or thermal decomposition of one (or more) of the components.

For an efficient process based on LLX, not only a good extraction but also an effective and easy recovery of the solvent is required.^{5,6} The step that can be made in the distribution coefficient K_D between the extraction and regeneration step is even more important than a high K_D in the extraction step.⁷ There are various options for solvent regeneration. Evaporation of the acid would be the easiest solution in the case of an acid with a sufficiently low boiling point. However, when the boiling point of the acid is too high, as is the case for succinic acid (HSuc), other options for regeneration must be applied, typically through back-extraction. In the case of HSuc this can be followed by a crystallization step through evaporation of water to obtain the final product. Two possible options to enhance the back-extraction are diluent-swing regeneration and temperature-swing regeneration, or combinations of these.⁵ Diluent-swing may be realized by either adding or removing (a part of) a diluent, which results in a decrease of the acid distribution. Next to adding a liquid diluent, also a pressure-swing regeneration may be applied, in which a pressurized gas is applied as an anti-solvent. The addition of a diluent aims at decreasing the polarity and solvating abilities of the solvent mixture to decrease the acid distribution.

To study the use of diluent-swing or temperature-swing for solvent regeneration, extraction of HSuc was selected as a case study, because HSuc is an example of a carboxylic acid that can be produced via green routes in a fermentation based process in which glucose is consumed.^{8,9} Next to that, being derived from renewable sources, HSuc is a potential green platform chemical¹⁰⁻¹² and it is an important raw material for several products in industry, such as plastics, solvents and products for the food and pharmaceutical industry.¹³ The price of HSuc is roughly 1500 € per ton.¹⁴ Due to the low acid concentration in the fermentation broth,¹⁵ the costs for the downstream processing of the HSuc product stream can be up to 50-70 % of the total costs for the production,¹⁵ indicating the industrial relevance of this example.

In this research various solvent regeneration strategies have been investigated, all resulting in aqueous solutions of HSuc that are to be further purified by crystallization, and regenerated solvent that can be sent back to the LLX process to recover HSuc from the aqueous feed stream. The general process scheme, displayed in Figure 1, consists of the extraction column, the regeneration column and the crystallization column to further purify the concentrated acid stream. In this study the crystallization step is left out of consideration as it will be the same for all processes, and in all processes the final product is a concentrated acid solution that is ready for the crystallization operation.

For several temperature and diluent-swing based processes the swing in the distribution ratio between the extraction and back-extraction step was studied by determining liquid-liquid equilibria (LLE) before and after the swing in conditions. Processes based on the most promising solvent systems with the largest swing in acid distribution were modeled with Aspen Plus to compare their predicted capital investments and required energy input.

Figure 1 Schematic overview of a separation process based on liquid-liquid extraction with an extraction column and a regeneration column. The concentrated product of acid in water is further purified by crystallization.

7.2 Theory

In liquid-liquid extraction (LLX) of acids, where the aqueous phase that contains a low concentration of acid is contacted with a solvent phase, the acid distribution K_D between the solvent phase and the aqueous phase is defined in eq (1), where the overbar indicates compounds in the organic solvent phase.

$$K_D = \frac{\overline{[HA]}}{[HA]} \quad (1)$$

To regenerate the acid from the solvent, a difference in the acid-distribution between the extraction step and the regeneration step as large as possible is desired, see eq (2).

$$\frac{K_D}{K'_D} = \frac{K_{D, \text{extraction step}}}{K'_{D, \text{back-extraction step}}} \quad (2)$$

Complexating agents (B), such as long-chain tertiary amines,¹⁶⁻¹⁹ phosphine oxides and phosphates^{2,20,21} are typically added to the solvent to increase the distribution of acid by complex formation with the acid molecules. Complex formation strongly depends on the temperature and medium in which it takes place,^{16,19,22} therefore a temperature-swing or a diluent-swing of active and inactive diluents may be applied to achieve a high K_D/K'_D .

7.3 Materials and methods

7.3.1 Chemicals

All chemicals were used without further purification and purchased from Sigma Aldrich (HSuc, $\geq 99\%$, trioctylamine (TOA, 98 %), trioctylphosphine oxide (TOPO, 99 %), 1-octanol ($>99\%$), heptane (99 %), pentane ($\geq 99\%$) and MIBK ($\geq 99\%$)).

7.3.2 Experimental methods

7.3.2.1 Unpressurized liquid-liquid equilibria (LLE)

Unpressurized LLE experiments were performed in 10 or 20 mL glass vials. The aqueous phase and organic phase were mixed in these vials for at least 6 hours in the shaking bath. After the equilibration, the phases were allowed to settle and samples were taken from the aqueous phase and analyzed with HPLC.

7.3.2.2 Pressurized liquid-liquid equilibria (LLE)

The setup to perform LLE experiments under high gas pressures consisted of a vessel (0.25 L, maximum pressure of 60 bar) with a heating/cooling jacket and a mechanical stirrer. Before the experiment the aqueous and organic phase were loaded in the vessel which was then closed. The vessel was connected through a pressure regulator to a gas supply vessel within the setup that can be refilled from the gas supply vessel that is located outside, to maintain the pressure. Before a sample was taken, the mechanical stirrer was stopped and the mixture was allowed to settle for 30 minutes. Samples of the aqueous phase were taken through a tap that is connected to the bottom of the vessel.

7.3.3 Analytical methods

7.3.3.1 HPLC

The concentration of acid in the aqueous phase was determined using High-Performance Liquid Chromatography (HPLC) on an HPLC Agilent 1200 series with RI detector (accuracy > 99 %) and a Hipler-H column. The mobile phase was an aqueous solution of 5 mM H_2SO_4 at a flowrate of either 0.6 or 1 mL/min.

7.3.4 Simulation methods

The modeled processes can be described with four types of process configurations. For the process of temperature-swing regeneration no additional equipment is required and this process can be described by the process configuration in Figure 1. The process of diluent-swing regeneration in which a part of the active diluent is distilled before the regeneration column is shown in Figure 2a and the process in which an inactive diluent is added to the solvent before the regeneration column and distilled off after the regeneration column is shown in Figure 2b. In both diluent-swing processes an extra distillation column is required to distill off a part of the diluent.⁵ For the process of pressure-swing regeneration in which a gas is applied as an anti-solvent, the conceptual process scheme is shown in Figure 2c. In this case the solvent regeneration column is replaced by a vessel to reduce the pressure of the stream leaving the regeneration column to be able to recycle the gas. For this process also additional compressors and a pump are required for the pressurization of the streams.

a

b

c

Figure 2 Schematic overview of diluent-swing based LLX processes with *a*) diluent-swing by evaporation of a part of the diluent, *b*) diluent-swing by addition of a liquid anti-solvent and *c*) diluent-swing by pressurized gaseous anti-solvent.

To evaluate and compare the processes, the required energy is calculated relative to a base case in which the water is evaporated through a process of quadruple-effect evaporation to increase the concentration of acid in the product stream. The initial acid concentration c_0 is assumed to be 0.012 in mass fraction and a commercial scale production of 10 kta is assumed. The raffinate mass fraction of the extraction columns equaled 0.001. If allowed by the acid distribution ratios, the product stream contained the maximum concentration of HSuc that is soluble at 20 °C, i.e. a mass fraction of 0.061.²³ At 60 °C, the temperature in the temperature-swing, the maximum solubility is a mole fraction of 0.042 (mass fraction = 0.22). These concentrations were taken for the product streams of the designed LLX processes.²³ Further upgrading of the product is performed by crystallization, which was not included in the modeling because crystallization is also part of the reference process based on evaporation of the water. However, for an equal final comparison of the energy required in each of the processes, the energy requirement for evaporation and crystallization to obtain a pure product (weight fraction of 0.995) from the product after extraction and back-extraction is included in the economic evaluation.

The acid fraction remaining in the organic phase after the back-extraction (and sent back to the extraction) was assumed to be 0.005. The ingoing and outgoing concentrations of the streams of both the extraction and regeneration columns were calculated as well as the minimum solvent-to-feed ratio $(S'/F')_{\min}$, making use of short-cut calculations. $(S'/F')_{\min}$ of an extraction process can be determined using eq (3)-(5) that were taken from De Haan et al.²⁴ In these equations $X_{\text{in}} = (x_{\text{in}}/(1-x_{\text{in}}))$, with x the mass fraction) is the weight ratio in the feed stream, X_{out} the weight ratio in the raffinate and Y_{in} the ingoing weight ratio of the extract stream. The apostrophes indicate solute free phase flows. The number of theoretical equilibrium stages N_{ts} was calculated with the Kremser equation, eq (6), assuming low concentrations and constant K_D .²⁴ In this equation the extraction factor E is defined as $E = K_D * S'/F'$.

For the reference case it is assumed that a quadruple-effect evaporator can be applied to save 75 % of the energy duty for evaporation.²⁵⁻²⁷ For the energy calculations no heat integration was assumed for these processes and the price of a MWh of energy based on natural gas was estimated to be 35 €, ²⁸ which is based on data from the year 2016 but still a reasonable assumption for the current situation considering the low inflation of the past two years.

$$\frac{S'}{F'_{\min}} = \frac{X_{\text{in}} - X_{\text{out}}}{Y_{\text{out,max}} - Y_{\text{in}}} \quad (3)$$

$$Y_{\text{out}} = \frac{X_{\text{in}} - X_{\text{out}}}{\frac{S'}{F'}} + Y_{\text{in}} \quad (4)$$

$$Y_{\text{out,max}} = K_D \cdot X_{\text{in}} \quad (5)$$

$$N_{\text{ts}} = \frac{\ln \left[\left(\frac{X_{\text{in}} - \frac{y_{\text{in}}}{K_D}}{X_{\text{out}} - \frac{y_{\text{in}}}{K_D}} \right) \left(1 - \frac{1}{E} \right) + \frac{1}{E} \right]}{\ln E} \quad (6)$$

Aspen Plus V10 modeling software was applied to model the three processes as well as the reference case in which the NRTL method was applied for the calculation of the distillations and flash columns for the evaporators. The required solvent flows, number of theoretical stages and product concentrations of the extraction operations were calculated with the shortcut calculations of eq (3)-(6) using the distribution ratios that were measured in this work and not using Aspen Plus. The capital expenses required for these extraction columns were estimated with the Aspen Plus Aspen Process Economic Analyzer based on the calculated flows and required number of stages in combination with a default packed column. Distillations were simulated using RadFrac and the 'bottoms-to-feed ratio' was adjusted to obtain the correct bottom flow that was calculated based on the measured K_D values and minimum solvent-to-feed ratios. For the modeling of the distillation of water from the aqueous solutions of HSuc only 3 stages were applied and no reflux (i.e. simple evaporation of the water), for the reference case and the additional distillation required for upgrading of the product in case a too low product concentration was obtained, i.e. the maximum solubility was not reached after regeneration. For evaporation of MIBK and pentane distillation was applied using a column with 10 stages and a reflux ratio of 1.5. For the reference case of water evaporation from the aqueous HSuc feed stream to obtain the concentrated product, multi-effect four-stage evaporators were modeled. This process was modeled as a series of flash columns (Flash2) and connected heat exchangers over a decreasing pressure range from 1.7 to 0.3 bar. By defining the vapor fraction of the first flash column, the fraction of water evaporating in the multi-stage evaporator could be adjusted. Flash2 and Flash3 columns were applied for the splitting

of the aqueous and organic phase in the modeling of the extraction and back-extraction columns. The capital investments for each process were calculated with the Aspen Process Economic Analyzer.

7.4 Results and discussion

7.4.1 Effect of solvent composition on succinic acid distribution

Applications of long-chain tertiary amine mixtures in MIBK and 1-octanol have been reported for the extraction of HSuc from aqueous streams,^{5,16,29} and also long-chain phosphine oxides, e.g. trioctylphosphine oxide (TOPO), are used for carboxylic acids extraction in general, including for HSuc.^{2,30} Therefore, the initial mapping of solvent effects to identify possibilities for diluent-swing was performed with solvents based on trioctylamine (TOA) and trioctylphosphine oxide (TOPO). Some diluents commonly applied in carboxylic acid extractions, such as chloroform and toluene, were avoided because of their negative environmental impact. The effect of solvent composition on the distribution of HSuc was studied with MIBK and 1-octanol.

For extraction of carboxylic acids, generally a maximum distribution of acid is observed for solvents with a tertiary amine composition around a volume fraction of 0.3,^{19,31,32} thus in this research the full range of compositions was covered for the TOA based solvents. Since TOPO is a solid at room temperature and therefore problematic solubility and third phase formation can be expected at higher concentrations, experiments are performed at mass fractions of TOPO of up to 0.4. The results for LLE experiments using 1-octanol as a diluent at 20 °C at an initial acid concentration c_0 of 0.1 M and a volume based solvent-to-feed ratio S/F of 1/3, are displayed in Figure 3a.

a

b

Figure 3 Effect of composition of extractant on the distribution of HSuc ($c_0 = 0.1$ M) at (closed symbols) 20 °C and an elevated temperature (open symbols) of 60 °C in figure **a**) or 55 °C in figure **b**), with a volume based solvent-to-feed ratio of 1/3 for TOA (squares, based on vol%) and TOPO (circles, based on wt%) in **a**) 1-octanol and **b**) MIBK.

For TOA in 1-octanol (Figure 3a) high maximum distribution ratios of 42.6 and 42.1 were obtained at 20 and 40 vol%, respectively, similar to distribution ratios obtained for lactic acid.^{16,33-35} For TOPO in 1-octanol (Figure 3a) the distribution ratios were much lower, i.e. 0.5 and 0.8 at 20 and 40 wt%, respectively. The observed values for K_D of HSuc for TOA and TOPO in MIBK are displayed in Figure 3b. Also here there is a clear maximum in the K_D of HSuc with increasing TOA concentration in MIBK and these values for MIBK are lower compared to those previously discussed for 1-octanol. Previously reported K_D -values by Tamada et al.¹⁶ are approximately 6, for HSuc extraction with the commercially available long-chain tertiary amine mixture Alamine 336 (2-25 vol%) in MIBK at a free aqueous acid concentration of 0.1 M. These values are comparable to those in Figure 3b. A reduction in the K_D was observed for increasing temperature, which is in line with earlier work by Tamada and King,⁵ who extracted HSuc ($c_0 = 0.3$ M) with 13 vol% Alamine 336 in MIBK.

Based on the strong temperature and compositional dependency of the HSuc distribution, and the knowledge that inert diluents strongly reduce the distribution of acids, approaches were investigated for both a temperature-swing and two types of diluent-swing, i.e. evaporation of a part of the diluent or addition of a second, inert diluent as an anti-solvent. The success of a temperature-swing process is determined by the dependency of K_D on the temperature and similarly the success of a diluent-swing process is determined by the dependency of K_D on the volume fraction of extractant in the solvent and the ease of evaporation of the diluent or anti-solvent. Moreover, the existence of a maximum in K_D with varying extractant composition is important for the application of a diluent-swing process. With a diluent-swing process by evaporation the volume fraction of TOA is increased, therefore a solvent with an extractant concentration above the maximum should be used as the starting solvent, e.g. 40 vol% TOA in MIBK. Then, upon evaporation of a part of the MIBK, K_D decreases as can be seen for higher concentrations of TOA in Figure 3. This is a good approach for a diluent-swing process and based on these results it can be concluded that TOA in MIBK is a promising solvent for a process based on evaporation of a part of the diluent.

7.4.2 Diluent-swing by addition of anti-solvent

For diluent-swing by addition of anti-solvent, both addition of liquid anti-solvents (section 7.4.2.1) and gaseous anti-solvents (section 7.4.2.2) have been investigated.

7.4.2.1 Addition of liquid anti-solvent

The effect of the volume based anti-solvent/solvent ratio on the HSuc distribution ratio for a solvent consisting of 20 vol% TOA in 1-octanol is shown in Figure 4a. These experiments are performed at an elevated temperature of 55 °C because it is expected that otherwise the distribution ratios obtained with TOA in 1-octanol are too high to allow for a sufficient step in K_D in the regeneration step for a viable process.^{6,36} Based on Figure 4a it is clear that, even at this elevated temperature, the K_D for 1-octanol indeed only decreases from 10 to approximately 2 with the addition of an anti-solvent to the solvent at a 1:1 volume ratio. The values for K_D at 20 °C are significantly higher (Figure 3a) and thus a regeneration process based on a diluent-swing alone is not expected to be feasible for this system, in line with statements reported for similar systems.^{6,36}

Figure 4 Effect of anti-solvent/solvent ratio on the succinic acid distribution of (initial acid concentration $c_0 = 0.1$ M and volume based solvent-to-feed ratio S/F of 1/3) for addition of the anti-solvent heptane to a solvent consisting of 20 vol% TOA in 1-octanol (open symbols) and MIBK (closed symbols) at 55 °C, with **a**) the succinic acid distribution K_D and **b**) the ratio of the distribution with and without anti-solvent K_D / K'_D .

Figure 4b shows the ratio of the acid distribution with and without anti-solvent K_D / K'_D , from which it is clear that the effect of anti-solvent/solvent ratio is stronger for MIBK compared to 1-octanol at an elevated temperature of 55 °C, as for MIBK the K_D is decreased from approximately 2.5 to 0.5 already at a volume based anti-solvent/solvent ratio of 0.5.

To study if addition of an anti-solvent is a feasible regeneration process for HSuc extraction with the diluent MIBK, distribution ratios were measured at 20 °C for various (volume based) anti-solvent/solvent ratios and different compositions of the MIBK based solvent. The results are displayed in Figure 5 in which the absolute K_D (Figure 5 a-c) and the ratio between the distribution coefficients with and without the anti-solvent are shown (Figure 5 d-f). Especially for a solvent consisting of 20 vol% TOA in MIBK there is a strong decrease of K_D , already at a low anti-solvent/solvent ratio (Figure 5a and d). The difference between applying pentane or heptane is only small. For mixtures of TOPO (Figure 5b and c), the absolute values of K_D are lower and also the decrease with increasing anti-solvent/solvent ratio is less strong than with TOA based solvents (Figure 5e and f). In this case, a mass based composition is applied because TOPO is a solid. The effect of anti-solvent addition on K_D is similar for solvents that contain either 10 wt% or 20 wt% TOPO.

Figure 5 Effect of anti-solvent/solvent ratio on succinic acid distribution ($c_0 = 0.1$ M) at 20 °C with heptane (open symbols) and pentane (closed symbols) as anti-solvents, with in the top row (a, b and c) K_D and in the bottom row (d, e and f) the ratio of acid distribution with and without an anti-solvent K'_D/K_D , for a solvent-to-feed ratio of 1/3 and the solvent phase consisting of a+d) 20 vol% TOA in MIBK, b+e) 20 wt% TOPO in MIBK and c+f) 10 wt% TOPO in MIBK.

7.4.2.2 Addition of gaseous anti-solvent

Three types of gases were investigated as potential anti-solvents, i.e. methane, ethylene and ethane. There is no data available for their solubility in either TOA or MIBK so for an estimate of their solubility in the solvent phase the solubility in the organic solvent 1-octanol as well as water based on literature is shown in the first two columns of Table 1. Ethane and ethylene show a significantly higher solubility in 1-octanol, but also an increased water solubility which especially for ethylene may have a countereffect.

The composition of the liquid phase of 1-octanol and MIBK upon pressurization with methane and ethane at 1 or 30 bar was predicted at 20 °C using Aspen Plus V10 and the UNIFAC model, see Table 1. The calculated mass fractions for the gas solubility are overpredicted, compared to the literature values for 1-octanol, but ethane clearly shows a larger solubility for both methods and is thus expected to be more promising as an anti-solvent. As expected, the calculated mass fractions for the gas solubility in the diluent at the elevated pressure of 30 bar are significantly higher than at 1 bar. For both methane and ethane the solubility in MIBK is relatively similar to that in 1-octanol. The solubility of ethane of 634 g/kg MIBK is comparable with an anti-solvent/solvent ratio of approximately 2, and when related to the results of Figure 4, a significant effect of a diluent-swung with the gaseous anti-solvent may be expected.

Table 1 Solubility and critical point of selected gases.^{37,38}

Gas	Solubility in water (g/kg) at 1 atm ^a	Solubility in 1-octanol (g/kg) at 1 atm ^a	Modeled solubility in 1-octanol (g/kg) at 1 bar	Modeled solubility in 1-octanol (g/kg) at 30 bar	Modeled solubility in MIBK (g/kg) at 1 bar	Modeled solubility in MIBK (g/kg) at 30 bar	Critical temperature (K)	Critical pressure (bar)
Methane	0.023	0.35	4.1	135	3.7	127	190.56	45.99
Ethylene	0.14	2.8					282.35	50.4
Ethane	0.057	4.1	12.6	565	11.4	634	305.32	48.7

LLE experiments were performed for each of the solvent mixtures based on TOA and TOPO in MIBK with methane at a pressure of 30 bar as the anti-solvent, see Figure 6. A sample of the composition of the aqueous phase was taken directly after liquid-liquid equilibration, just before applying the methane pressure of 30 bar ($t = 0$ h). Then, after $t = 2, 4$ and 6 hours of pressurization the concentration of the aqueous phase was also determined. The measured initial K_D (7.9, see Figure 6a) for 20 vol% TOA in MIBK without an anti-solvent is lower, than that reported in Figure 5 ($K_D = 10.2$). This may be a result of small differences in the solvent-to-feed ratio, room temperature or

equilibration/settling time for the experiments with gases since all samples had to be taken in the course of one day. The results in Figure 6 clearly indicate that equilibrium was always achieved within 2h. The effect of methane on K_D is stronger for TOA based solvents (Figure 6a and b) than for TOPO based solvents (Figure 6c and d). The relative change in K_D is similar for 20 vol% TOA in MIBK (Figure 6a) and 10 vol% TOA in MIBK (Figure 6b). When ethylene was applied as an anti-solvent for the TOPO based solvent (Figure 6c) there was no significant increase in K_D compared to methane, while for the TOA based solvent (Figure 6a) the effect on K_D with ethylene pressurization was significantly stronger than with methane. Upon applying ethane, the decrease in K_D is the strongest (Figure 6a) and even comparable to the effect of the anti-solvents pentane and heptane (Figure 5a), when an anti-solvent/solvent ratio based on the maximum solubility of approximately two (Table 2) is assumed.

Figure 6 Effect of applying a pressure of 30 bar of methane (closed symbols), ethane (half open symbols) and ethylene (open symbols) on the succinic acid distribution ratio ($c_0 = 0.1$ M) in LLE at 20 °C and a solvent-to-feed ratio of 1/3 with solvents consisting of **a)** 20 vol% TOA in MIBK, **b)** 10 vol% TOA in MIBK, **c)** 20 wt% TOPO in MIBK (note that the x-axis value is shifted for graph readability, the data points are at 0, 2, 4 and 6 h), and **d)** 10 wt% TOPO in MIBK.

7.4.3 Combined effect of pressure-swing and temperature-swing

In an attempt to improve the performance of the methane based pressure-swing regeneration this process was combined with a temperature-swing in which the temperature was increased from 20 °C to 60 °C in the regeneration step, see Figure 7. The effect of temperature itself is strong (time = 0 h) for both TOPO based and TOA based solvents, as was also seen in Figure 3 and the additional effect of the applied methane pressure is only very small (time = 6 h). Therefore, it can be assumed that combining a pressure-swing process with a temperature-swing based process is not worth the additional investment costs required for pressurization.

Figure 7 Effect of temperature on the succinic acid distribution ratio ($c_0 = 0.1$ M) at 20 °C (closed symbols) and 60 °C (open symbols) at an applied methane pressure of 30 bar ($t > 0$), a solvent-to-feed ratio of 1/3 and the solvent phase consisting of **a)** 20 vol% TOA in MIBK and **b)** 20 wt% TOPO in MIBK.

7.4.4 Process considerations

Four swing based LLX processes, i.e. one process based on a temperature-swing and three based on a diluent-swing, were modeled and compared with each other and with the base case of water evaporation to concentrate the feed stream. The first two diluent-swing processes are both based on a diluent-swing by addition of an anti-solvent (see Figure 2b) and both processes use a solvent consisting of 20 vol% TOA in MIBK in the extraction step. In process 1, based on the results in Figure 5, the anti-solvent pentane is added to the solvent mixture at a volume based anti-solvent/solvent ratio of 1, before entering the regeneration column. After the regeneration

column the stream of solvent and anti-solvent is distilled in order to recycle both the solvent and the anti-solvent to the extraction and regeneration step, respectively. In process 2, based on the results in Figure 6, the gaseous ‘anti-solvent’ ethane with a pressure of 30 bar is added to the solvent mixture at a volume based anti-solvent/solvent ratio of 1 before entering the regeneration column. After the regeneration column, the pressure of the stream containing solvent and ethane is reduced to recycle the ethane that will require repressurization. The value of $K_D = 7.9$ (Figure 6) was applied for the extraction step in the calculations of process 2, in order to have a fair comparison with the measurements after applying ethane as an anti-solvent. In process 3, based on the results of Figure 3, a diluent-swing is applied by evaporating a large part of the MIBK (see Figure 2b) from the solvent mixture that consists of 40 vol% TOA in MIBK in the extraction step, in order to reach a TOA volume fraction of 80 vol% before the regeneration column. In process 4, a temperature-swing is applied between the extraction column and the regeneration column, based on the results of Figure 7. This process is also based on a solvent that consists of 20 vol% TOA in MIBK.

For each of the processes the energy input and output was modeled as well as the investment costs for a commercial scale production plant of 10 kta of pure HSuc, with an HSuc mass fraction of 0.012 in the feed. The input data and the modeling results are given in Table 2. The last column in Table 2 shows the reference case that is based on quadruple-effect evaporation of water from the feed stream to obtain the same product. In case $Y_{out,max}$ was larger than the maximum solubility of HSuc, the maximum solubility of HSuc was applied in the calculations with the corresponding product flow. This means that a lower amount of stages could theoretically be applied in process 1 and 2. This has however only a marginal effect on the economic evaluation.

Table 2 Energy requirements and product specifications to evaluate the four different processes and compare with the base case of evaporation. The extraction factor E is defined as $E = K_D \cdot S'/F'$, for which K_D was converted to a mass fraction based ratio. N_{ts} is the number of theoretical stages in the column, see eq (6). All processes are based on a commercial scale production of 10 kta of pure succinic acid and a succinic acid mass fraction of 0.012 in the feed.

		Unit	Process 1	Process 2	Process 3	Process 4	Base case (evaporation)
		Process:	anti-solvent pentane	‘anti-solvent’ ethane	evaporation of diluent	temperature- swing	
			20 % TOA in MIBK	20 % TOA in MIBK	40 % TOA in MIBK	20 % TOA in MIBK	
Model input	Extraction column						
	K_D		10.2	7.9	10.2	10.2	
	$(S'/F')_{\min}$		0.076	0.099	0.077	0.076	
	Extraction factor E		1.45	1.45	1.45	1.45	
	N_{ts}		6	6.2	6	6	
	Back-extraction column						
	$1/K_D$		2.2	2.2	0.2	0.63	
	S (water) (kg/s)		6.91	6.91	16.7	13.3	
	Extraction factor E		1.52	2.24	1.5	1.5	
	N_{ts}		8.6	5.4	11.7	10.3	
	Distillation column						
	Feed		4.5 kg/s (TOA + MIBK) 3.5 kg/s pentane		4.5 kg/s (TOA + MIBK)		1 L/s water
	Product details						
	Mass fraction succinic acid		0.061	0.061	0.028	0.033	0.061
	Flow (kg/s)		6.91	6.91	16.7	13.3	6.91
Model output	Equipment cost (installed)						
	Extraction column		470 k€	470 k€	470 k€	470 k€	
	Regeneration column		140 k€	120 k€	165 k€	130 k€	
	Distillation column		830 k€		760 k€		
	Flash column			120 k€			740 k€ (= total of 4 columns)
	Compressors			1900 k€			

		Unit	Process 1	Process 2	Process 3	Process 4	Base case (evaporation)
		Process:	anti-solvent pentane	‘anti-solvent’ ethane	evaporation of diluent	temperature- swing	
			20 % TOA in MIBK	20 % TOA in MIBK	40 % TOA in MIBK	20 % TOA in MIBK	
Model output	Coolers		75 k€	110 k€	155 k€	180 k€	895 k€
	Pump			19 k€			
	Total		1500 k€	2900 k€	1600 k€	780 k€	1600 k€
	Distillation		(anti-solv. pentane)		(MIBK to 20 vol%)		(water)
	Reboiler duty Q_{reb}		4500 kW		3000 kW		1950 MW (simple dist.)
	Condenser duty Q_{cond}		3500 kW		1960 kW		1820 MW (simple dist.)
	Duty (4-stage evaporator)						18 MW
	Duty to incr. conc. (4-stage evap.)				5525 kW		
	Energy input						
	Pump			75 kW			
	Compressor			0.65 kW			
	Recycle compressor			250 kW			
	Cooler/heater		960 kW	270 kW	1050 kW	4800 kW	
	Flash vessel			105 kW			
	Regen. column		12 kW	95 kW	74 kW	60 kW	
	Total energy input		8970 kW	800 kW	6085 kW (with further evaporation 11600 kW)	4900 kW	160 MW (18 MW based on 4-stage evap.)

						Base case (evaporation)
Unit		Process 1	Process 2	Process 3	Process 4	
Process:		anti-solvent pentane	‘anti-solvent’ ethane	evaporation of diluent	temperature- swing	
		20 % TOA in MIBK	20 % TOA in MIBK	40 % TOA in MIBK	20 % TOA in MIBK	
Energy calcu- lations	Energy for production					
	Energy per kg product at max. solubility (no heat int.)	1300 kJ/kg	120 kJ/kg	360 kJ/kg (w. further evap. 1680 kJ/kg)	370 kJ/kg (w. further evap. 1230 kJ/kg)	2600 kJ/kg
	Duty cost per ton product at maximum solubility	13 €	1.10 €	3.6 € (w. further evap. 16 €)	3.5 € (w. further evap. 12 €)	26 €
	Total energy per kg pure acid incl. crystallization	36 MJ/kg (58 % of evaporation)	13 MJ/kg (21 % of evaporation)	44 MJ/kg (70 % of evaporation)	35 MJ/kg (56 % of evaporation)	62 MJ/kg
	Production re- quired for return on investments compared to quadruple-effect evaporator		50 kton, 2000 h, 110 days (80 % production)	-		

From Table 2 it is clear that for process 1 and 3, as well as for the base case of evaporation, the required capital investments are similar. For process 2 the required compressors and pumps strongly increase the capital investments for the process. For the temperature-swing process, process 4, no extra solvent or equipment is required and the required capital investment is thus lower than for the other processes. The energy input required for all unit operations is low compared to the energy input of the distillation columns in process 1 and 3 and extremely low compared to the energy input that would be required if the evaporation would be performed by simple distillation, with a reboiler duty of 1950 MW and a condenser duty of 1820 MW. For processes 3 and 4 the product concentration is lower than that of the other processes, and thus the required energy input for additional evaporation of water to obtain the same product is also taken into account and shown in Table 2. Based on all these results the energy per kg of pure HSuc product was calculated in which the additional crystallization and evaporation of the water was also included, showing that the energy input per kg product is very low for the ethane based pressure-swing process (process 2), only 21 % of the energy input of the quadruple-effect evaporation process.

Although K_D was reduced from 10.2 to 1.6 for the temperature-swing process, process 4, (see Figure 3b) and thus a $1/K_D$ of 0.63 is applied, this only resulted in a product concentration of 0.033 at a production rate of 13.4 kg/s based on a solvent-to-feed ratio of 1.5 times $(S/F)_{\min}$. In the temperature-swing process there is no increased concentration in the solvent stream by evaporation. This process therefore also requires additional evaporation of water and the required energy input is similar to that based on evaporation, process 3, although the required capital investments for process 4 are lower. The return on investments was defined as the number of days of production required at which the additional investments of capital required for compressors and pumps compared to the quadruple-effect evaporation process are paid back by the decreased operational costs. No depreciation was assumed as the return on investment was reached within one year. For the diluent-swing regeneration process with pressurized ethane (process 2) 50 kttons of production, i.e. 110 days based on 80 % operation, are required to fully return all additional capital invested, making the other two cases more interesting for the short-term as their capital investments are similar to that of the base case. However, as industrial processes are not designed for operation of less than a year, the ethane based process with the lowest price per kg of pure product has a high potential as it will save a large amount of energy and operational costs on the long-term. For processes 1 and 3 no significant additional capital investments are required and process 4 requires less capital investments (see Table 2), hence no return on investments was calculated.

As no study on solvent and anti-solvent losses in the process was performed, the prices of solvents and gases are not included in the calculations. Furthermore, the solubility of anti-solvent in the aqueous phase is very low and therefore it was assumed that solvent losses do not influence the comparison of the four processes as they will affect all four studied processes in a similar way. For the base case of evaporation of a part of the water to obtain the more concentrated acid solutions also no thorough study was performed. The rough estimate that was calculated can however be used to compare the other processes with, since this is just a reference case and the advantage of the diluent-swing processes compared to the case of evaporation is clearly shown.

All swing based regeneration processes are economically feasible and based on these calculations the ethane based process is the most promising process. Comparing the other processes, the process based on evaporation of pentane seems more viable than those based on evaporation of MIBK and a swing in temperature, as those processes result in lower product concentrations and extra distillation or evaporation is required to obtain the same product.

7.4.4.1 Opportunities for process improvement

There is an opportunity for improvement of process 3 and 4 by combining both types of swing, since in these calculations process 3 is performed without a temperature-swing in the regeneration. To improve this process, the heat that is required to evaporate the MIBK can be kept in the system to also apply a temperature-swing regeneration. With this increased temperature in the regeneration step, which is basically obtained by less cooling of the streams after the MIBK distillation, there is an increased $1/K_D$ of 6.7 (the inverse of the K_D in Figure 3b) in the regeneration step, and a water feed in the regeneration of 1.57 kg/s, resulting in a product with a HSuc mass fraction of 0.22. The duty of the regeneration column is 585 kW and the column has 3.8 stages. For the overall process there is a similar total energy input of 6050 kW (17 MJ/kg pure HSuc) and the required equipment is the same, except that there is no need for an extra cooler (95 k€) after the distillation column. The advantage of production at a higher temperature is that the maximum solubility of the HSuc is increased to a mass fraction of 0.22 and thus less water needs to be evaporated in the crystallization step. Including the crystallization step, the energy requirement for this combined diluent-swing and temperature-swing process is 6700 kW (19 MJ/kg pure HSuc), which is 31 % of the energy input per kg of pure HSuc product required for the benchmark process based on quadruple-effect evaporation. Thus, combining the evaporation of diluent with a temperature-swing by making use of the heat that is already applied in the MIBK distillation, does increase the viability of the process. Nevertheless, this process still requires more energy than the ethane based process that requires only 21 % of the energy input of the quadruple-effect evaporation benchmark.

The process of diluent-swing by addition of pentane could theoretically also easily be combined with a temperature-swing by increasing the temperature of the anti-solvent and thereby the temperature in the regeneration column. However, the improvement based on this will only be small and result in similar process economics, since the K_D of HSuc is already strongly decreased by the addition of pentane.

7.5 Conclusion

Swing processes using a temperature-swing and/or a diluent-swing for the regeneration of solvents in liquid-liquid extraction processes were compared. In the case of a solvent consisting of 20 vol% TOA the effect of addition of pentane as an anti-solvent was stronger than for 20 wt% TOPO in MIBK in liquid-liquid equilibria measurements for LLX of succinic acid (HSuc) from aqueous streams, reducing K_D from 10.2 to 0.46 already at a volume based anti-solvent/solvent ratio of 1. Applying a gaseous anti-solvent is promising because of the easy removal by reducing the pressure and no requirement of an additional distillation column. Extra equipment in the form of compressors and pumps is however required. Applying ethane at a pressure of 30 bar with 20 vol% TOA in MIBK decreased K_D from 7.9 to 0.45. This is comparable to the effect of the liquid anti-solvent pentane. An increase of temperature to 60 °C without a diluent-swing decreased K_D to 1.6.

A temperature-swing based process and three diluent-swing based processes were compared and their capital investments and energy required for operation were predicted using Aspen Plus. All processes, based on either a temperature-swing, evaporation of the diluent MIBK, or addition of pentane or ethane as anti-solvents, were more promising than the benchmark process based on quadruple-effect evaporation of the water. Combining a temperature-swing with a diluent-swing strongly improves the process and results in higher product concentrations and for this process the calculated energy input per kg pure acid product is only 31 % (19 MJ/kg pure acid) of that of benchmark process. The process based on an ethane pressure-swing requires only 110 days of production to fully return the additional capital invested for compressors and a pump. This is the most effective process considering the reduction of the energy demand, since the energy required for operation is 21 % (13 MJ/kg) of what would be required for the quadruple-effect evaporation of the water.

References

- (1) Eyal, A. M.; Canari, R. *Ind Eng Chem Res* 1995, *34*, 1789-1798.
- (2) Hano, T.; Matsumoto, M.; Ohtake, T.; Sasaki, K.; Hori, F.; Kawano, Y. *J Chem Eng Jpn* 1990, *23*, 734-738.
- (3) López-Garzón, C. S.; Straathof, A. J. J. *Biotechnol Adv* 2014, *32*, 873-904.
- (4) Shan, X.; Qin, W.; Dai, Y. *Chem Eng Sci* 2006, *61*, 2574-2581.
- (5) Tamada, J.; King, C. *Ind Eng Chem Res* 1990, *29*, 1333-1338.
- (6) Shah, V. H.; Pham, V.; Larsen, P.; Biswas, S.; Frank, T. *Ind Eng Chem Res* 2016, *55*, 1731-1739.
- (7) Sprakel, L. M. J.; Schuur, B. *Sep Purif Technol* 2019, *211*, 935-957.
- (8) Cok, B.; Tsiropoulos, I.; Roes, A. L.; Patel, M. K. *Biofuel Bioprod Bior* 2014, *8*, 16-29.
- (9) Shen, N.; Qin, Y.; Wang, Q.; Liao, S.; Zhu, J.; Zhu, Q.; Mi, H.; Adhikari, B.; Wei, Y.; Huang, R. *Lett Appl Microbiol* 2015, *60*, 544-551.
- (10) Cukalovic, A.; Stevens, C. V. *Biofuel Bioprod Bioref* 2008, *2*, 505-529.
- (11) Bechthold, I.; Bretz, K.; Kabasci, S.; Kopitzky, R.; Springer, A. *Chem Eng Technol* 2008, *31*, 647-654.
- (12) Werpy, T.; Petersen, G. Top Value Added Chemicals from Biomass: Results of Screening for Potential Candidates from Sugars and Synthesis Gas; National Renewable Energy Laboratory - Pacific Northwest National Laboratory, 2014.
- (13) Zeikus, J. G.; Jain, M. K.; Elankovan, P. *Appl Microbiol Biot* 1999, *51*, 545-552.
- (14) ICIS. In *Indicative Chemical Prices A-Z*, www.icis.com, 2018.
- (15) Sheng, Z.; Tingting, B.; Xuanying, C.; Xiangxiang, W.; Mengdi, L. *J Chem Eng Data* 2016, *61*, 856-864.
- (16) Tamada, J. A.; Kertes, A. S.; King, C. J. *Ind Eng Chem Res* 1990, *29*, 1319-1326.
- (17) Tung, L. A.; King, C. J. *Ind Eng Chem Res* 1994, *33*, 3217-3223.
- (18) Wasewar, K. L.; Yawalkar, A. A.; Moulijn, J. A.; Pangarkar, V. G. *Ind Eng Chem Res* 2004, *43*, 5969-5982.
- (19) Rasrendra, C. B.; Girisuta, B.; van de Bovenkamp, H. H.; Winkelman, J. G. M.; Leijenhorst, E. J.; Venderbosch, R. H.; Windt, M.; Meier, D.; Heeres, H. J. *Chem Eng J* 2011, *176-177*, 244-252.
- (20) Matsumoto, M.; Otono, T.; Kondo, K. *Sep Purif Technol* 2001, *24*, 337-342.
- (21) Malmay, G. H.; Monteil, F.; Molinier, J. R.; Hanine, H.; Conte, T.; Mourgues, J. *Bioresour Technol* 1995, *52*, 33-36.
- (22) Ladesov, A. V.; Kosyakov, D. S.; Bogolitsyn, K. G.; Gorbova, N. S. *Russ J Phys Chem A* 2015, *89*, 1814-1820.
- (23) Yu, Q.; Black, S.; Wei, H. *J Chem Eng Data* 2009, *54*, 2123-2125.

- (24) Haan, A. B.; Bosch, H. *Industrial separation processes: fundamentals*; Walter de Gruyter, GmbH, & Co., KG: Berlin; 2013.
- (25) Sorour, M. A. *Am J Energy Eng* 2015, 3, 6-11.
- (26) Earle, R. L. *Unit operations in food processing*; 1st ed. ed.; Pergamon: Oxford, 1966.
- (27) Cortes, M. G.; Verelst, H.; Gonzales, E. *Chem Engineer Trans* 2010, 21, 277-282.
- (28) Katharina Grave, B. B., Jose Ordonez, Jakob Wachsmuth, Sil Boeve, Matthew Smith, Torben Schubert, Nele Friedrichsen, Andrea Herbst, Katharina Eckartz, Martin Pudlik, Marian Bons, Mario Ragwitz, Joachim Schleich. Prices and costs of EU energy; European Commission: Ecofys, 2016.
- (29) Procházka, J.; Heyberger, A.; Volaufová, E. *Sep Sci Technol* 2005, 39, 1073-1091.
- (30) Wasewar, K. L. *Int J Chem Eng Appl* 2012, 3, 249-255.
- (31) Wardell, J. M.; King, C. J. *J Chem Eng Data* 1978, 23, 144-148.
- (32) Malmay, G.; Albet, J.; Putranto, A.; Hanine, H.; Molinier, J. *J Chem Eng Data* 1998, 43, 849-851.
- (33) Krzyzaniak, A.; Schuur, B.; Sukumaran, M.; Zuilhof, H.; De Haan, A. B. *Chem Engineer Trans* 2011, 24, 709-714.
- (34) Li, Z.; Qin, W.; Dai, Y. *J Chem Eng Data* 2002, 47, 843-848.
- (35) Brouwer, T.; Blahusiak, M.; Babic, K.; Schuur, B. *Sep Purif Technol* 2017, 185, 186-195.
- (36) Amruta Magdum, S. G. G., P. J. Patil, A. V. Patil. *Int J Eng Res Technol* 2017, 10.
- (37) Boyer, F. L.; Bircher, L. J. *J Phys Chem* 1960, 64, 1330-1331.
- (38) Haynes, W. M.; Lide, D. R.; Bruno, T. J. *CRC handbook of chemistry and physics: a ready-reference book of chemical and physical data*; CRC Press: Boca Raton, Florida, 2017.

Solvent selection for extractive
distillation processes to separate
close-boiling polar systems

Abstract

Solvent selection is key in extractive distillation process development and solvent effects are often predicted based on the activity coefficients at infinite dilution. For close-boiling polar systems with strong or specific interacting species, standard simulation tools, e.g. using UNIFAC or COSMO-RS, often predict poor as the activity coefficients at infinite dilution do not always reflect the selectivity in the process. For these systems, a heuristic solvent selection method in which molecular properties such as acidity, hydrogen bonding and polarity are applied is desired as a first estimate in the solvent selection. To explore the key parameters for such a first selection, solvent effects on the relative volatility (α) were measured for three different industrially relevant polar mixtures; valeric acid - 2-methylbutyric acid, diethylmethylamine - diisopropylether, and 2-butanone - 2-butanol. For each of the cases the effect of potential solvents on α was measured in an ebulliometer. For the acids, the difference in pK_a of 0.1 was too small to separate based on acidity with a moderately basic solvent. Stronger basic solvents resulted in thermal and chemical instability. Although the solvent methyl-2-methyl butyrate is not suitable as a solvent because of reactivity, this structurally similar solvent showed selectivity, indicating that also in extractive distillation the like dissolves like phenomenon can be applied to induce selectivity. A larger difference in basicity of the mixture components (amine - ether mixture) and a difference in hydrogen bonding affinity between the mixture components (ketone - alcohol mixture) allowed for increasing α based on differences in acidity and hydrogen bonding, respectively.

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8.1 Introduction

The climate target of the European Union for the year 2030 involves 40 % cuts in greenhouse gas emissions and a 27 % improvement in energy efficiency.¹ In 2016 roughly 25 % of the total energy within the EU was used for industrial purposes.² Hence, to reach the goals for 2030, reducing the industrial energy demand has an enormous potential. Distillation is the most widely applied separation process for homogeneous fluid separations,³ including many mixtures that are difficult to separate by distillation due to pinch-points or close boiling points. Therefore, energy-saving opportunities include improving these difficult distillation processes. Extractive distillation is a technology that can potentially improve the separation of close-boiling mixtures and enable separation of azeotropic mixtures.^{4,6} In extractive distillation a solvent is applied that interacts with a preferred affinity for one of the mixture components, by which the relative volatility of the mixture is changed or an azeotrope is ‘broken’.⁶ For a wide range of mixtures from very polar to apolar, extractive distillation has been used, e.g. ethanol - water mixtures using either ethylene glycol (EG)⁷ or ionic liquids as entrainers,^{8,9} ethyl acetate - ethanol mixtures,^{10,11} mixtures of monochloroacetic acid and dichloroacetic acid,¹² mixtures of ethylbenzene and styrene¹³ and mixtures of aromatics/aliphatics.¹⁴

The choice of solvent is key for the viability of an extractive distillation process, and solvent selection can be an expensive and time-consuming procedure. Next to manipulating the relative volatility in the extractive distillation process, it is essential that the solvent is regenerated easily to recycle the solvent back to the extractive distillation column. In apolar systems the solvent typically induces positive deviations from Raoult’s law, whereas in polar systems, such as monochloroacetic acid and dichloroacetic acid,¹² the solvent induces negative deviations. In this work the focus is on polar close-boiling mixtures, and solvents that have an attractive effect on the high-boiling component, thereby inducing negative deviations from Raoult’s law. The combination of being effective in the extractive distillation and being regenerable requires a certain affinity window that is unfortunately not straight forward to define. Ideally, extensive experimental screening of solvents is avoided, which might be realized by making use of known solvent scales to characterize intermolecular affinity between a solvent and the mixture constituents. An example is the proton affinity scale, which is a scale that describes the basicity of solvents, where the proton affinity is equal to the enthalpy that is measured during the deprotonation reaction of the base in the gas phase.¹⁵ Stronger bases therefore have a larger proton affinity. For this scale, as well as for other scales applied for solvent characterization, the databases that are created list properties of

the solvents based on their interactions with a (scale-)specific component. Other scales often applied for solvent characterization are the BF_3 -affinity-scale^{15,16} and the hydrogen bond basicity scale pK_{BHX} .^{15,16} For most of these scales the properties or interactions of solvents with the components need to be determined experimentally, but also parametrizations based on the linear solvation energy relationship (LSER)^{17,18} are applied, using solvatochromic and/or Kamlet-Taft parameters.^{19,20}

The direct prediction of the solvent effect on the relative volatility of a mixture that is to be separated can also be based on infinite dilution activity coefficients.²¹⁻²³ These predictions are mainly applied on apolar systems of alkanes/alkenes or alkane/aromatics, but also on acetone/methanol mixtures^{24,25} and separation of hydrocarbons with ionic liquids.²⁶ Software for solvent selection and prediction of VLE behavior in extractive distillation is also widely applied in which different types of chemical calculations can be combined. Examples are COSMO-RS,²⁷ UNIFAC²⁸ and Computer Aided Molecular Design (CAMD) on the basis of the selectivity at infinite dilution with software packages ProCAMD®, a tool that is a part of the ICAS® framework.²⁹ These predictive methods based on activity coefficients are successfully applied for solvent selection for separation of various mixtures, including C_8 - aromatics mixtures, C_4 mixtures, aromatics and non-aromatics, ethanol-water, ILs, acids, oxychemicals, and systems of ketones, esters and alcohols.^{23,30-32}

The consideration of thermodynamics, such as the selectivity at infinite dilution, does however not always lead to selection of the right solvent as the selectivity at infinite dilution is not in all cases related to the selectivity at finite dilution and a comparison is problematic in case the distillate product changes.²⁴ The selectivity only focuses on the extractive distillation column, but for a viable process the regeneration column, e.g. the enthalpy of evaporation of the solvent, should also be included.²⁴ Predictions based on group contribution methods are also limited by the database their fits are based on and therefore the design of new solvents is not straight forward. There are also other cases in which application of methods based on infinite dilution activity coefficients or group contribution methods is not straight forward, especially in the case of very strong interactions and in the case of specific interactions or formation of azeotropes, which are all common in close-boiling systems of polar compounds. For these polar systems the prediction of VLE behavior is challenging, although a first indication for selecting the right type of solvent for a specific separation is desired. Therefore, in this work an experimental study is described that focuses on solvent effects in extractive distillation of close-boiling polar compounds.

Three specific industrially relevant binary mixtures were chosen that cover a significant part of the field of polar compounds in terms of functional groups and each show different behavior regarding their relative volatility, i.e. the mixture of a) diethylmethylamine (DEMA) and diisopropylether (DIPE), b) valeric acid (HVal) and its isomer 2-methylbutyric acid (2MBA) and c) 2-butanone (2-BuO) and 2-butanol (2-BuOH). Next to differences in functional groups, for each case there are other differences regarding boiling point T_b , melting point T_m , octanol-water partitioning coefficient $\log P_{O/W}$ and acidity pK_a (or basicity) of the components, see Table 1.

Table 1 Physical properties (boiling point T_b , melting point T_m , acidity pK_a and octanol-water partitioning coefficient $\log P_{O/W}$ of components of the three binary mixtures applied in this study.

Substance	Abbreviation	T_b (°C)	T_m (°C)	Structure	Density (g/mL)	pK_a	$\log P_{O/W}$
Valeric acid	HVal	187	-34		0.938	4.71	1.39
2-methylbutyric acid	2MBA	177	-90		0.936	4.8	1.05
Diethylmethylamine	DEMA	63 - 65	-196		0.72	3.65 (pK_b)	0.958
Diisopropylether	DIPE	68.5	-60		0.725	≈ 17 (pK_b)	1.52
2-butanol	2-BuOH	99.1	-115		0.806	≈ 16	0.683
2-butanone	2-BuO	79.5	-86.7		0.805	≈ 20	0.29

The case with HVal and 2MBA was chosen to study the limiting ΔpK_a for separation based on extractive distillation, in which results were compared to the separation of monochloroacetic and dichloroacetic acid reported by Jongmans et al.¹² (ΔT_b of 5 °C, and ΔpK_a of 1.6). HVal is an important industrial building block³³ that is produced from 1-butene, where impurities lead to the production of 2MBA.³³⁻³⁵ The components in the case with DEMA - DIPE are widely applied in industry as building blocks³⁶ and as solvents.³⁷ DEMA and DIPE involve an ether and an amine with therefore

different acidity. This case was chosen because of the very low relative volatility of the mixture which makes distillation infeasible. The case with 2-BuO - 2-BuOH (relatively large ΔT_b) involves two components with different functional groups (hydrogen bond donating and accepting for 2-BuOH, and only hydrogen bond accepting for 2-BuO).

For each of these cases solvents were selected from different classes and the effect on the relative volatility was measured and related to the molecular structures, interactions and activity coefficients of the components in the mixtures. Aiming at further increasing the understanding of affinities in the systems, isothermal titration calorimetry (ITC) was applied to measure the heat of interaction and excess enthalpies of mixing.

8.2 Materials and methods

8.2.1 Chemicals

Chemicals were obtained from Sigma-Aldrich, unless mentioned otherwise, i.e. acetic acid ($\geq 99.5\%$), Acetone Lichrosolv® ($\geq 99.8\%$, Merck KGaA), beta-cyclodextrin ($\geq 98\%$, Acros Organics), 1,8-bis(dimethylamino)naphthalene (Proton Sponge® 99%), butanoic acid (HBu, 99%), 2-butanol (2-BuOH, $> 99.5\%$), 2-butanone (2-BuO, $> 99.5\%$), m-cresol ($\geq 98\%$), 18-Crown-6 (TCI-GR), cyclohexanol ($\geq 99\%$), cyrene (99.0%), dibutylamine (DBA, $\geq 99.5\%$), dibutylether (DBE, $\geq 99.3\%$), diethylene glycol (DEG, $\leq 100\%$, Merck KGaA), diethylene glycol dibutylether (DEGDBE, $\geq 99\%$), diethylene glycol dimethyl ether (diglyme, $\geq 99.5\%$), N,N-diethylmethylamine (DEMA, $\geq 98\%$, Acros Organics and TCI-GR), diisopropylether (DIPE, $\geq 99\%$), DMSO (99.9%), dodecane ($\geq 99\%$), ethylbenzene (98% , Fluka), ethylene glycol (EG, $\geq 99.8\%$), glycerol (99.0%), n-heptane anhydrous ($99+\%$, Alfa Aesar), isovaleric acid (isoHVal, 99%), itaconic acid ($\geq 99\%$), 2MBA ($\geq 98\%$), 5-methyl-2-hexanone (5-m-2-one, 98.0%), methyl isobutyl ketone (MIBK, $\geq 99.7\%$), methyl-2-methylbutyrate (MeMeBu, $\geq 98\%$), methyl levulinate (MeLev, 98.0%), octanoic acid (HOct, $\geq 98\%$), 1-octanol ($\geq 99\%$), oleic acid ($\geq 99.5\%$, Fischer Scientific), phenol (PhOH, $\geq 99.5\%$), 1,2-propane diol ($\geq 99\%$), propylene glycol (PG, 99.0%), tribenzylamine (TBzA, $\geq 99\%$), tributylphosphate (TBP, $99+\%$), 2,2,4-trimethylpentane (iso-octane, $\geq 99.5\%$), trioctylamine (TOA, 98%), HVal ($\geq 99\%$) and p-xylene (99% , Honeywell).

8.2.2 Experimental methods

8.2.2.1 Ebulliometer

Fischer Labodest VLE602 ebulliometers were used for the VLE experiments. The equilibrium temperature of the mixtures was measured with a Pt-100 thermocouple after setting the pressure. For each experiment the measurement cell was filled with 80 mL of sample. Equilibration required between 30-90 minutes, depending on the mixture and the temperature of the previous measurement. After equilibration, 1 mL aliquots were taken from the liquid phase and the condensed vapor phase to determine the compositions. Solvent regeneration was investigated by measuring binary VLE data of the high-boiling component of the mixture and the solvent. For each case, the measurement and analysis errors were determined as they also depend on the temperature and pressure at which the measurement is carried out.

8.2.3 Analytical methods

8.2.3.1 GC and GC-MS

For the DEMA - DIPE mixture samples were analyzed with a Varian CP-3800 GC with FID (accuracy > 98 %) and Agilent DB-WAX column (60 m * 0.25 mm * 0.25 μ m), using 100 μ L sample and 100 μ L internal standard (dodecane), diluted in acetone to a total of 1.7 mL. The temperature profile is as follows: injection and FID at 280 °C, initial measurement temperature of 40 °C with a linear ramp of 5 °C/min after 1 minute to 50 °C, and after 1 minute at 50 °C, again a ramp in 3 minutes to 250 °C at which the temperature was kept constant for 3 minutes. Analysis was also performed with 7890A Ms 5975C Agilent GC-MS with FID and helium as carrier gas (accuracy > 98 %) and Agilent HP-5Ms, HP19191S-433 column. The sample concentration was approximately 5 % in methylisobutylketone (MIBK). The injection and FID were kept at 280 °C, the initial column temperature was 45 °C with a linear increase after 4 minutes to 160 °C at a measurement time of 32 minutes, and after 2 minutes again a linear increase to 250 °C at 47 minutes, after which it was kept constant for 2 minutes. For the HVal - 2MBA mixture samples of binary VLE experiments were analyzed with a HPLC 1200 series with RID (accuracy > 99 %), with either an Agilent Hi-plex H+ Column (300 * 7.7 mm) or GROM Resin H+ IEX (250*8 mm) and a 0.6 mL/min 5 mM H₂SO₄ mobile phase. Samples of pseudo-binary VLE experiments were analyzed with a Varian CP-3800 GC with FID (accuracy > 98 %) and VF1701ms (60 m * 0.25 mm * 0.25 μ m) column. The temperature of injection and FID were 280 °C, initial column temperature 50 °C with a linear increase after 1 minute to 130 °C at 14 minutes, and after 1 minute again a linear increase to 180 °C in 1.3 minutes after which it was increased linearly to 190 °C in 3.3 minutes and then kept constant for 2 minutes. For the samples that also contain

octanoic acid (HOct) the procedure was extended with a linear temperature increase from 190 °C to 235 °C in 1.2 minutes followed by a last linear increase to 245 °C in 3.3 minutes where the temperature was kept constant for 2 minutes. For the 2-BuO - 2-BuOH mixture samples were analyzed with the previously mentioned method with the Varian GC, using heptane as an internal standard in this case. The injection and FID temperature were at 280 °C, and the initial column temperature was 45 °C with a linear increase after 4 minutes to 150 °C at 15.5 minutes, after which there was a second linear increase to 250 in 4.5 minutes.

8.2.3.2 Isothermal titration calorimetry (ITC)

ITC was performed using a TA Instruments TAM III Microcalorimeter with 1 or 4 mL stirred sample vials at 20 °C. The automatic syringe was filled with 300 μ L of titrant and connected with the sample cell through a cannula. The titrant was injected periodically. For complex formation between HVal and TOA, the sequential reaction model as described in chapter 5 was applied for fitting of the experimental data from which the stoichiometry, enthalpy and equilibrium constant of the reaction could be determined. The experimental data were corrected with the heat of injection of the last injection of a measurement series.

8.2.3.3 Error analysis

For the study on HVal, the error in the equilibrium temperature measured was 0.4 °C. Based on results of experiments in triplo, standard deviations were calculated for the composition of the vapor and liquid phase. At 300 mbar the standard deviation in the liquid composition was $1.5 \cdot 10^{-3}$ and $1.8 \cdot 10^{-3}$ in the vapor composition. At 900 mbar this was $2.1 \cdot 10^{-3}$ and $3.1 \cdot 10^{-3}$, respectively. For the solvent screening VLE measurements the standard deviation of the GC analysis that was performed in triplo was 3.2 % for α . For the case with DEMA - DIPE, the standard deviation in the temperature equaled 0.4 °C at 1000 mbar and 0.7 °C at 300 mbar. For α the standard deviation equaled 0.024 (GC) and 0.052 (GC-MS) at 1000 mbar and 0.013 (GC) and 0.060 (GC-MS) at 300 mbar. The resulting standard deviation based on GC-MS experiments was larger since in GC a triple injection was performed on each sample. For the 2-BuO - 2-BuOH mixture, the absolute error in the equilibrium distillate temperature was 0.4 °C and 0.2 kPa in the pressure of the system. The absolute error in α was calculated to be 0.2, which is next to errors in the sample preparation (0.001 g error in mass) and in the GC analysis (0.5 % in weight fraction), mainly a result of a significant error in the solvent-to-feed ratio of ± 10 % that was calculated based on feed samples that were also analyzed with GC.

8.3 Results and discussion

8.3.1 The system N,N-diethylmethylaniline (DEMA) - diisopropylether (DIPE)

8.3.1.1 Verification of ebulliometry measurements

The equilibration and temperature measurement of the ebulliometer was verified by measuring the pure component boiling temperatures of DEMA and DIPE at various pressures, see Figure 1. From the figure it can be concluded that the experimental data correspond well with the theoretical values calculated with the Antoine equation.³⁹

Figure 1 Pure component boiling temperatures for DIPE (■) and DEMA (□), lines are calculated with the Antoine equation and parameters for the pure components.³⁹

8.3.1.2 Binary mixture VLE measurements

Binary mixture VLE data measured for DEMA and DIPE at 300 and 1000 mbar are displayed in Figure 2, in which it is clear that α of this mixture is very low. At 1000 mbar the average α of DEMA over DIPE equals 1.05 ± 0.024 . A decrease in pressure increased the average α to 1.09 ± 0.013 at 300 mbar. An ideal equilibrium curve with $\alpha = 1.09$ is shown in Figure 2a. Furthermore, although no clear azeotrope can be observed at this low relative volatility, there is a possibility of a minimum boiling azeotrope based on the Txy-diagrams (Figure 2b and d). In this separation case ΔT_b is very small, but the difference in acidity (basicity) and molecular structure between the components is large.

Figure 2 Binary VLE data for DEMA and DIPE at 300 mbar **a)** xy -diagram from Sprakel et al.,⁴⁰ dotted line represents an ideal curve with $\alpha = 1.09$, **b)** Txy -diagram from Sprakel et al.,⁴⁰ and at 1000 mbar **c)** xy -diagram and **d)** Txy -diagram. In figure **b)** and **d)**: ■ equilibrium composition and temperature of the vapor phase and □ of the liquid phase. The error in x_{DEMA} , y_{DEMA} equals 0.0027 at 300 mbar and 0.0056 at 1000 mbar, see also section 2.3.3.

For this case solvents are selected with the aim to achieve a high selectivity, see eq (1). The solvent selectivity can be written as the ratios of the activity coefficients of both components with and without the presence of the solvent.⁶ In this equation P_i^{sat} is the saturated vapor pressure of a component at a given temperature, y_i is the vapor mole fraction and x_i is the liquid mole fraction.

$$S_{ij} = \frac{(\alpha_{ij})_S}{\alpha_{ij}} = \frac{\left(\frac{\gamma_i P_i^{\text{sat}}}{\gamma_j P_j^{\text{sat}}} \right)_S}{\frac{\gamma_i P_i^{\text{sat}}}{\gamma_j P_j^{\text{sat}}}} \cong \frac{\left(\frac{\gamma_i}{\gamma_j} \right)_S}{\frac{\gamma_i}{\gamma_j}} \quad (1)$$

For DEMA - DIPE, the separation is complicated due to α being close to unity. In those cases, generally there are positive deviations from Raoult's law (i.e. both activity coefficients are greater than or equal to 1) and the ratio of activity coefficients is larger than the ratio of saturated vapor pressures. Thus, see eq (1), a solvent is desired that interacts ideally with the high-boiling component and repels the low-boiling component (or interact ideally with the low-boiling component and attracts the high-boiling component).⁶ Next to improving α of the binary mixture, the solvent should be chemically and thermally stable, non-toxic and non-corrosive, inexpensive, readily available and not reacting with one of the mixture components.^{5,6} Furthermore, it should be possible to regenerate the solvent so it can be recycled to the process.¹² For the regenerability of the solvent moderate interactions are favored over very strong interactions.¹² Also, the solvent should not form an azeotrope with one of the components,⁶ which can in general be achieved by keeping a boiling point difference of at least 30 °C and for the economic viability a relatively low heat of evaporation is favored. For binary mixtures with a low α it is in general easier to respect the natural difference in vapor pressure of the components and not select a solvent that will invert the relative volatility of the low-boiling and high-boiling component.^{6,22}

Different types of solvents were applied, several solvents were selected based on similarity and homologues (dibutylether (DBE), diglyme, dibutylamine (DBA), dipropylamine (DPA)), others on acidity (acetic acid (HAc), HVal, oleic acid), polarity or the potential of hydrogen bond formation. Hydrogen bonding is expected to play an important role as both DEMA and DIPE contain significantly different hydrogen bond accepting groups that will most likely show different affinity with a solvent. This potential of differences in hydrogen bond formation was also studied based on qualitative predictions of deviations from Raoult's law for interactions of different classes of compounds, see Table 2.⁴¹ Ideally, the solvent shows a different effect on the deviations of Raoult's law to induce an increase in α , as is the case for acids, alcohols, secondary amines, and paraffins. Solvents in each of these categories were selected. Especially for the alcohols, positive deviations from Raoult's law are expected for interaction with the ether and ideal behavior with the amine making this an interesting group of solvents. Also for glycols

interesting solvent properties in terms of hydrogen bonding possibilities are expected, and in addition they are cheap and commercially available on large scales.

Table 2 Predicted qualitative deviations (positive +, negative - or none (0)) from Raoult's law based on functional groups and hydrogen bonding interactions for the selected case of tertiary amine and ether, data are adapted from Robbins.⁴¹

	Solvent	Solute	
		Tertiary amine	Ether
Hydrogen bonding donors	Phenol	-	-
	Acid	-	0
	Alcohol	0	+
acceptors	Ketones	+	+
	Tertiary amines	0	0
	Secondary amines	+	0
	Primary amines	+	+
	Ether, oxides	0	0
	Esters	+	+
	Aromatics and olefins	0	0
none	Paraffins	0	+

Pseudo-binary VLE data were measured for all selected solvents at a S/F ratio of 1, the results for the effect on the relative volatility in the system are displayed in Figure 3, based on only the fractions of the mixture components and not the solvent. For the carboxylic acids the interactions with the mixture of DEMA and DIPE were too strong and no equilibrium could be obtained in the experiments. When m-cresol was applied as a solvent, a miscibility gap was observed, so for this solvent no α could be measured at S/F = 1. For all other solvents except when diglyme was applied, the measured volatility of DIPE was larger than that of DEMA.

a

b

Figure 3 Pseudo-binary VLE data for DEMA - DIPE, relative volatility α of DIPE over DEMA at 300 mbar (black, data was previously reported in Sprakel et al.⁴⁰) and 1000 mbar (grey), with **a**) S/F of 1 and **b**) S/F of 3.

The secondary amines, alkanes and ethers had no to little effect on α , indicating that for these solvents the difference in affinity for the two components is too small to have a significant effect on α . Secondary amines are able to form hydrogen bonds, nevertheless it can be concluded that the hydrogen bond basicity of the secondary amines is too weak to affect α . The alcohols cyclohexanol, PhOH and propylene glycol (PG) each have a positive effect on α . Interaction with each of these solvents is based on

hydrogen bonding and the increased α confirms the positive deviations from Raoult's law that were expected for interaction with the ether and ideal behavior with the amine (see Table 2). These differences are a result of the difference in electronegativity between the nitrogen and oxygen atom. The effect of PhOH is significantly larger than that of the other two solvents, which is a result of the more acidic proton of PhOH.

The increased relative volatility of DIPE over DEMA indicates that there is a larger hydrogen bonding basicity of the tertiary amine as compared to the ether, which can be expected based on the nitrogen atom in DEMA. Increasing the solvent-to-feed ratio (Figure 3b) also increases the relative volatility, although based on that also for PhOH at 1000 mbar a higher α would be expected. The α at increased S/F-ratio for PhOH may be influenced by more pronounced self-aggregation of the PhOH at higher S/F-ratios instead of hydrogen bonding with the amine. Moreover, at 1000 mbar the equilibrium temperature is increased, resulting in less strong hydrogen bonding in general. Because of the possibility of a minimum boiling azeotrope in the binary VLE data (Figure 2), for the three solvents that successfully increased the relative volatility (cyclohexanol, PhOH and PG), VLE data were also measured at x_{DEMA} of 0.05 and 0.95 and all showed a relative volatility above 1 (see Table 3, data was previously reported in Sprakel et al.⁴⁰). Based on this the presence of an azeotrope in the pseudo-binary system could be excluded. Also in these results, the solvent effect of PhOH is more pronounced. At a higher S/F-ratio miscibility gaps appeared, because of which no equilibrium data could be measured. The most straightforward method to test the regeneration is by measuring the binary VLE data of the high-boiling component (DEMA) and the solvent. For all three solvents a very high or infinite relative volatility was obtained as either no or only a very small signal was obtained for DEMA in the GC chromatogram. Based on this the recovery of the solvents is not expected to be problematic.

Table 3 VLE data (relative volatility α) for the three most promising solvents for separation of DEMA and DIPE. (n.e. = no equilibrium achievable). Data was previously reported in Sprakel et al..⁴⁰

		α							
Pressure (mbar)		1000				300			
S/F		1		3		1		3	
Solvent	x_{DEMA}	0.05	0.95	0.05	0.95	0.05	0.95	0.05	0.95
-		1.3	1			1.1	1.1		
Propylene glycol		3.7	n.e.	n.e.	n.e.	4	n.e.	n.e.	n.e.
Cyclohexanol		1.5	1.6	n.e.	1.1	1.8	1.9	n.e.	1.8
Phenol		7.6	3.6	8	n.e.	15	5	58	n.e.

From the results on DEMA - DIPE, it can be concluded that even for mixtures of components with (almost) equal volatility, a large difference in hydrogen bonding affinity offers opportunities for hydrogen bond donating solvents to increase α . An advantage of a mixture of components with (almost) equal volatility is that the natural difference in volatility is not important and solvents may be selected to target either of the mixture components, based on the most appropriate attractive or repulsive interactions.

8.3.1.3 Interaction between DEMA and DIPE

With isothermal titration calorimetry (ITC) two different experiments were performed with the aim to obtain more insight in the interactions between DEMA and DIPE, as well as with the solvent HVal, because no equilibrium could be reached in experiments with HVal. In the first ITC experiment HVal was titrated to a mixture of DEMA in the apolar and inactive diluent dodecane, whereas in the second experiment HVal was titrated to a mixture of DEMA in DIPE as a diluent. The integrated ITC results are shown in Figure 4.

Figure 4 Integrated ITC data for interaction of HVal with DEMA (0.13 M) at 20 °C in diluent ■ DIPE and ● dodecane, with the isotherms fitted by the sequential reaction model (dotted lines, $\cdot \cdot \cdot$).³⁸ Fitted parameters for the sequential reaction model are: in dodecane $K_{1,1} = 21$, $\Delta H_{1,1} = -19.5$ kJ/mol, $K_{n+1,1} = 112$, $\Delta H_{n+1,1} = -12.5$ kJ/mol and $n = 1.58$; and in DIPE $K_{1,1} = 9.5$, $\Delta H_{1,1} = -21.1$ kJ/mol, $K_{n+1,1} = 11$, $\Delta H_{n+1,1} = -16.4$ kJ/mol and $n = 1.59$.

Based on the integrated data and the sequential reaction model described by Sprakel and Schuur³⁸ the parameters that describe the interactions and complex formation between the mixture components were fitted. For interaction of HVal with DEMA diluted in dodecane the calculated fit parameters are $K_{1,1} = 21$, $\Delta H_{1,1} = -19.5$ kJ/mol, $K_{n+1,1} = 112$, $\Delta H_{n+1,1} = -12.5$ kJ/mol and $n = 1.58$; and in DIPE $K_{1,1} = 9.5$, $\Delta H_{1,1} = -21.1$ kJ/mol, $K_{n+1,1} = 11$, $\Delta H_{n+1,1} = -16.4$ kJ/mol and $n = 1.59$. These parameters indicate that the stoichiometry of the complexes is not affected by the choice of diluent. Furthermore, the moderate (exothermic) reaction enthalpies (< 25 kJ/mol) indicate hydrogen bonding, there is no indication of the stronger proton-transfer in the carboxylic acid-amine complex.^{42,43} The enthalpy of reaction is higher in the case where the complexes are diluted in DIPE, indicating a more favorable environment for complexation in the polar and hydrogen bond accepting DIPE and therefore suggesting interactions between DEMA and DIPE. The experimental stability problems and not obtaining a vapor-liquid equilibrium can therefore not be explained by too strong interactions and may be a result of the formation of a second liquid phase.

8.3.2 The system valeric acid (HVal) and 2-methylbutyric acid (2MBA)

Figure 5 shows the binary VLE data for the system of HVal and 2MBA at both 300 and 900 mbar. The average α is low and equals 1.35 ± 0.02 at 300 mbar and 1.30 ± 0.03 at 900 mbar. At all pressures the xy-diagrams (Figure 5a and c) show the typical shape of ideal binary data. The Txy-diagrams (Figure 5b and d) show a narrow plateau in the region around an equimolar composition, this effect is stronger at the lowest pressure of 300 mbar.

Figure 5 Binary VLE data of mixture of HVal and 2MBA at 300 mbar (standard deviation in $x_{2MBA} = 0.0015$ and $y_{2MBA} = 0.0018$) **a)** xy diagram from Sprakel et al.⁴⁰ and **b)** Txy diagram, and 900 mbar (standard deviation in $x_{2MBA} = 0.0021$ and $y_{2MBA} = 0.0031$, see section 2.3.3. for more information) **c)** xy diagram and **d)** Txy diagram. In figure **b)** and **d)**: ■ equilibrium composition and temperature of the vapor phase and □ of the liquid phase. The lines added to guide the eye.

The narrow plateau in Figure 5b may be caused by the dimerization of acids in the vapor phase.⁴⁴ In literature, similar xy and Txy-diagrams are reported for binary mixtures of HBu and isobutyric acid, and as well for HBu and isoHVal.⁴⁵ Also in those cases, the relative volatility is low and the slopes in the temperature profile are flattening close to equimolar compositions.

Also for this case, potential solvents for improving α were selected based on different aspects, i.e. a group of basic solvents, acidic solvents, solvents based on similarity with one of the components of the mixture and apolar solvents. With both the acidic and basic solvents the aim is to induce negative deviations from Raoult's law by double hydrogen bonding or acid-base interactions, respectively. On the other hand, for the apolar solvents and the solvents based on similarity that may induce steric hindrance, the aim is to induce positive deviations from Raoult's law. Because of the structural difference between HVal and 2MBA also other solvents were selected based on steric hindrance, e.g. for tribenzylamine (TBzA) that contains three aromatic rings a difference in affinity is expected with the linear HVal and the branched structure of 2MBA. A similar effect may be expected for the Proton Sponge® where the cavity for interaction with the solvent is also relatively narrow based on the molecular structure. Pseudo-binary VLE experiments to determine the solvent effect on the relative volatility of the system were performed with all selected solvents at 300 and 900 mbar, see Figure 6.

Figure 6 Pseudo-binary VLE data for HVal and 2MBA at 300 mbar (black, data from Sprakel et al.⁴⁰) and 900 mbar (grey), $S/F = 1/1$ for all cases except 18-Crown-6 ether and Proton Sponge® ($S/F = 0.2$), and tribenzylamine ($S/F = 0.1$).

With both the acidic and basic solvents the aim is to induce negative deviations from Raoult's law by double hydrogen bonding or acid-base interactions, respectively. On the other hand, for the apolar solvents and the solvents based on similarity that may induce steric hindrance, the aim is to induce positive deviations from Raoult's law. However, most solvents (Figure 6) have no or only limited effect on α . For the apolar solvents, apparently the difference in affinity with HVal that has a longer carbon chain is too small to increase α . Moreover, at 900 mbar the temperature is increased which results in more ideal behavior, as the activity coefficients with dodecane are expected to be > 1 , a decreased α is expected at 900 mbar. The expected difference in hydrogen bonding ability between the mixture components is also not strong enough for increased α with the ether based solvents. For tribenzylamine (TBzA) that contains three aromatic rings a difference in affinity could be expected based on differences in steric hindrance with the linear HVal and the branched structure of 2MBA, however α is not increased. For tributylphosphate (TBP) no color change was visible, however additional peaks appeared in the GC chromatogram, indicating decomposition or instability.

The two solvents increasing α are Proton Sponge® and MeMeBu. MeMeBu was selected based on steric hindrance because of the structural difference between HVal and 2MBA and also because of structural resemblance with 2MBA, which results in either increased interaction between the solvent and 2MBA or positive deviations from Raoult's law for HVal. An effect based on steric hindrance may also be expected for the Proton Sponge®, a solvent that is also strongly basic, where the cavity for interaction with the solvent is relatively narrow based on the molecular structure. For the experiments with Proton Sponge® (as well as with trioctylamine (TOA)) the color of the mixture significantly changed and after the experiments the sample was completely dark, indicating a low thermal stability which is most likely a result of too strong interactions with the acids, as was previously also reported for monochloroacetic acid and dichloroacetic acid.¹² Thermal instability may also be the reason that no increased α was measured at 900 mbar for Proton Sponge®, as the equilibrium temperature is approximately 30 °C higher at 900 mbar.

Applying the solvent MeMeBu increased α to 1.84 ± 0.18 at 300 mbar. Especially in the range of low relative volatility this is an increase that can strongly reduce the heat duty in extractive distillation processes.⁴⁶ The solvent is an ester with a lower boiling point than the mixture components and will therefore be leaving an extractive distillation process with the distillate stream. Because 2MBA is also a product of the hydrolysis of

MeMeBu additional validation was performed to exclude that the increased α measured is not a result of that. The maximum water content in the initial sample was 0.5 wt% and therefore the increased relative volatility cannot be a result of the hydrolysis, since even if based on this all the formed 2MBA would hypothetically end up in the vapor phase without being a part of the equilibrium, the relative volatility would only increase to 1.6. However, at 900 mbar at which the temperature is higher, which results in more ideal behavior based on which no significant decrease in α is expected, the measured value for α is lower for the solvent MeMeBu. The decreased α is most likely a result of transesterification of the solvent with HVal, which means that MeMeBu is not a good solvent because of reactivity. Nevertheless, there is still an effect of MeMeBu on α , as the additional 2MBA that is formed is simply part of the equilibrium and only slightly decreases the S/F-ratio.

From the observations with the various solvents investigated for HVal and 2MBA, it can be concluded that the difference of 0.1 in pK_a is too small to induce a significant increase in the relative volatility through attractive interactions by acid-base pairing or hydrogen bonding. Although applying an even stronger basic solvent may possibly increase α , as observed with the Proton Sponge®, the interactions with the mixture components are so strong that in those cases thermal and chemical stability is compromised. Jongmans et al.¹² also report that solvents with the strongest interactions with the mixture components could not be regenerated, but in their case the difference in pK_a (1.6) was large enough to apply moderately strong solvents to increase the relative volatility by inducing negative deviation from Raoult's law. Further study of mixtures with differences in acidity is required to determine the minimum difference in pK_a that allows for applying moderately strong solvents that can be regenerated.

8.3.2.1 Interaction between valeric acid and TOA

The heat of interaction in the system of HVal, 2MBA and TOA was measured with ITC by performing titrations of the acids on samples with compositions that resemble the sample composition in the extractive distillation process, see Figure 7. Figure 7a shows the interaction of HVal with a mixture of 2MBA and TOA in a polar environment (1-octanol), where the molar ratio is the ratio of total acid concentration over the amine concentration (and since there was already acid in the sample, the curves do not start at zero). The energy released upon interaction is between 10 and 20 kJ/mol, which is a moderate interaction energy in the range of values typically reported for hydrogen bonding interactions.^{38,43} In a second experiment, see Figure 7b where the molar ratio is the ratio of total acid concentration over

amine concentration, the stronger acid lactic acid (50 vol% in 1-octanol) was titrated to a sample consisting of HVal, TOA and 1-octanol. This type of experiment is called a displacement experiment, because the acid-base interaction for the stronger acid is preferred over the interaction of the base with the weaker acid, and complexes with the weaker acid are displaced by complexes with the stronger acid. These experiments may be used to distinguish plateaus in the isotherm, a method that can be applied in ITC of higher affinity interactions.⁴⁷ For this experiment however there is only one step (two plateaus) in the measured energy instead of the three expected plateaus that are expected as a result of 1) additional loading of the complexes with acid titrant, 2) the replacement of acid that was already present with acid titrant, and 3) the solvation of acid titrant in the sample with fully loaded complexes. The single step indicates that there is similar interaction energy of the stronger lactic acid and HVal upon interaction with TOA. Moreover Figure 7b shows a steep decrease in the energy around a stoichiometry of 2, indicating the formation of complexes with overloading of acid, which also confirms the hydrogen bonding that was concluded based on the results in Figure 7a. The spread in the first few data points is most likely a result from errors in the injection volume as a consequence of the high viscosity of the lactic acid - 1-octanol mixture. Thus, the interactions in the mixtures are (mainly) based on hydrogen bonding and the formed complexes are overloaded with acid compared to amine.

Figure 7 Heat of interaction at 20 °C, of **a)** titrating HVal to a sample containing 2MBA (1.4 mmol), TOA (4.3 mmol) and 1-octanol (6.2 mmol) and **b)** titrating lactic acid in 1-octanol (50 vol%) to a sample containing HVal (0.49 mmol), TOA (0.91 mmol) and 1-octanol (0.92 mmol).

8.3.3 The system 2-butanone (2-BuO) and 2-butanol (2-BuOH)

Figure 8 shows the binary VLE data for the system of 2-BuO and 2-BuOH at 1000 mbar, with an average α of 1.9 at 1000 mbar. The xy-diagram as well as the Txy-diagram have the typical shape of those of an ideal mixture and the average α is not very low in this case. Because of this relative volatility, distillation is an intrinsically feasible process for this separation case, however the required energy input can still be significantly reduced if α could be increased to above 3.⁴⁸ Therefore the application of extractive distillation is also potentially interesting in this case. The xy-diagram of the VLE data (Figure 8a) measured in this study was compared with the data of Miller et al.⁴⁹ and Tanaka et al.⁵⁰ that were not consistent with each other, although measured at almost equal pressure of 1 atm and 1000 mbar, respectively. The data in this study are in good agreement with the data of Tanaka et al.⁵⁰ The differences with the work of Miller et al.⁴⁹ may be a result of the presence of impurities in their system that affect the relative volatility.

For this case there is a significant difference in functional groups as one of the components is an alcohol and one a ketone. Although the average α is already 1.9 for the case of 2-BuO - 2-BuOH, partly induced by the relatively large ΔT_b of approximately 20 °C, solvents were selected with the aim to further increase α , in which the effect of different types of solvents could be compared. In the mixture of 2-BuO and 2-BuOH, the activity coefficient of 2-BuOH is around 1 and that of 2-BuO is larger than one 1.⁴⁹ Thus, a good solvent should increase the ratio of the activity coefficients of 2-BuO and 2-BuOH to improve α . This is achieved by making the interaction with the -OH group stronger or more probable and/or the interaction with the >C=O group weaker or less probable.

Figure 8 VLE data of the mixture of 2-BuO and 2-BuOH **a)** binary xy -diagram $\bullet$ this work, 1000 mbar $\circ$ data from Miller and Huang,⁴⁹ 1 atm and $\square$ data from Tanaka et al.,⁵⁰ 1000 mbar, **b)** binary Txy -diagram, data from this work ($\square$ boiling points and $\blacksquare$ dew points), **c)** (pseudo-binary) relative volatility α (± 0.2 , see section 8.2.3.3 for more information) in the presence of solvent ($S/F = 1$) at 1000 mbar, for x_{2-BuO} of 0.4 (black bars) and 0.6 (grey bars), and **d)** detailed VLE data for $\circ$ binary system and pseudo-binary with $\blacksquare$ ethylene glycol and $\blacktriangle$ DMSO. Dashed curves are a guide for the eye.

Because of the $-OH$ group in the higher-boiling 2-BuOH, the solvent should have attracting interaction with this OH group (hydrogen bond acceptor), therefore oxides (DMSO), alcohols (EG, PG, 1-octanol, glycerol), esters (methyl levulinate (MeLev)), ethers (diglyme, DBE), acids (HBu) and ketones (5-m-2-one, cyrene) were selected. Especially for the components

with a larger functional group density a strong effect is expected, as for example in the case of the di-alcohol EG the probability of hydrogen bonding is increased compared to 2-BuOH itself, whereas for 1-octanol with a lower functional group density the probability is decreased. DMSO and HBu are expected to have strong effects as they are able to form stronger hydrogen bonds with their C=O group in comparison to the oxygen atoms in 2-BuO and 2-BuOH. The π -bond in aromatic rings creates a quadrupole that interacts with the dipoles of the alcohol and ketone groups. Since the dipole moment of 2-BuO is larger than that of 2-BuOH, a stronger interaction between the aromatic ring and 2-BuO is expected. Therefore p-xylene and ethylbenzene are predicted to show attractive interaction with 2-BuO and in order to be suitable as solvents a strong difference in affinity is required to invert the relative volatility of the binary mixture and have 2-BuOH as the top stream (considering the relative volatility of the binary mixture).²⁴

The effect on the relative volatility of the systems was tested for all solvents in pseudo-binary VLE experiments of which the results are shown in Figure 8c, except for the solvent glycerol that appeared to be not fully miscible with the binary mixture. As expected based on the interaction with the aromatic ring, p-xylene and ethylbenzene decrease α . However, the difference in solvent affinity with the mixture components is not large enough to allow for a top stream of 2-BuOH, a result of the interaction between the aromatic ring of the solvent and the alcohol group. A decreased α is also observed for MeLev, diglyme, DBE and 5-methyl-2-hexanone, which means their affinity towards 2-BuOH is not sufficiently larger than the affinity towards 2-BuO. For 1-octanol and HBu there is no or only a very small effect, indicating similar affinity with the mixture components. For 1-octanol this may be a result of the low functional group density. The interaction of HBu may be not specific enough because of the strongly interacting acid group. EG, PG and DMSO all increase α , indicating their larger affinity for (hydrogen bond) interaction with 2-BuOH than with 2-BuO. VLE data over the whole range of compositions are required for a more detailed process design of extractive distillation. To further explore the solvent effect on the relative volatility of the mixture, the pseudo-binary xy-diagram was measured over the whole range of compositions for EG and DMSO, see Figure 8d. Both solvents appear to be successful and EG is suggested as the best solvent because of price, availability and the larger effect on α compared to PG. Solvents were selected with their boiling points between 130-200 °C with the aim to ensure recoverability by having a boiling point difference of more than 30 °C with the mixture components. The recoverability of the solvent EG was investigated in the same way as for case b and full recovery of EG is possible, as no solvent could be detected in the condensed vapor

phase of the VLE measurements covering the range of (initial) EG volume fractions of 0.19 - 0.93. By optimizing the solvent-to-feed ratio an even further improvement of α can be expected compared to the α of approximately 3 that was obtained with EG at a volume based ratio of 1, although there is a limitation as a two phase system occurred in experiments with a 5:1 solvent-to-feed ratio. For the industrial process the stream of 2-BuO and 2-BuOH that requires purification will most likely not have an equimolar composition. For a more realistic feed stream with a larger concentration of 2-BuO the effect of the extractive distillation process on the energy input of the process is expected to be smaller.

The results for this system indicate that improving α is possible based on differences in hydrogen bonding affinity of the solvent and mixture components. As the differences between the mixture components are larger for this system and also the binary VLE data show a moderate relative volatility, interactions with the solvent are required to be less strong. However, another consequence is that the natural difference in volatility, i.e. 2-BuO being the most volatile component, should be taken into account in the solvent selection. Therefore attractive interactions with the least volatile component and/or repulsive interactions with the most volatile component are required.

8.3.3.1 Interaction between 2-BuO and 2-BuOH

As the interaction energy between the solvents that are selected for this separation case and the mixture components is relatively low compared to the acid-base interactions of the other cases, the mixing interaction of the two mixture components was measured with ITC instead of their interaction with a solvent. The heat of mixing of 2-BuOH and 2-BuO (Figure 9), is relatively low and positive in sign, i.e. endothermic, which means that the energy of intermolecular interactions is similar for both compounds and the combination of compounds. This also implies that the components do not (strongly) attract each other and a successful solvent may be found based on moderate or even weak repulsion of 2-BuO or attraction of 2-BuOH. For very large mole fractions of either of the two components, the heat effects are more strongly endothermic.

Figure 9 Energy of mixing interaction upon mixing of 2-BuOH and 2-BuO over the full range of concentrations at 20 °C, data represent ■ titrating of 2-BuO to 2-BuOH and □ titrating of 2-BuOH to 2-BuO.

8.4 Conclusion

Solvent effects on the relative volatility were measured for three different industrially relevant cases, that are separation of a) diethylmethylaniline and diisopropylether ($\Delta T_b = 3 - 5$ °C, α DEMA over DIPE of 1.05 ± 0.028 at 1000 mbar, $\alpha = 1.20 \pm 0.036$ at 300 mbar), b) valeric acid and 2-methylbutyric acid ($\Delta T_b = 10$ °C, $\Delta pK_a = 0.1$, $\alpha = 1.35 \pm 0.02$ at 300 mbar and 1.30 ± 0.03 at 900 mbar) and c) 2-butanol and 2-butanone ($\Delta T_b = 20$, $\alpha = 1.9$ at 1000 mbar). For each of the cases potential solvents were selected based on different aspects, including acidity/basicity, structural similarity, steric hindrance, polarity and predicted differences in hydrogen bonding affinity.

For DEMA - DIPE, although ΔT_b is very small, the difference in acidity and molecular structure of the components could be used to find suitable solvents. At a solvent-to-feed ratio of 3 and 300 mbar, PhOH ($\alpha > 5$), cyclohexanol ($\alpha = 2$) and PG ($\alpha = 3.1$) each increase α of the binary mixture. For HVal - 2MBA the solvent MeMeBu increased α ($\alpha = 1.84 \pm 0.18$ at 300 mbar), a solvent based on structural similarity with the mixture components. However, experiments at 900 mbar and thus at a higher temperature showed reactivity of the solvent in the form of transesterification. The difference of 0.1 in pK_a in combination with the small ΔT_b is too small to allow for separation using a moderately basic solvent, and applying a stronger basic solvent resulted in chemical instability. For this specific case crystallization would be a promising alternative process. For the case with 2-BuO - 2-BuOH, ΔT_b is relatively large and a difference in functional group allowed for separation through hydrogen bonding with the solvent. All successful solvents are hydrogen bond acceptors that show a larger affinity for 2-BuOH than for 2-BuO.

Generalizing, for mixtures of very similar components in terms of acidity, boiling point and structure, stronger interaction with the solvent is required (e.g. complex formation, proton transfer), which may be problematic in terms of chemical stability. Therefore, before applying a solvent in the actual pseudo-binary VLE measurements, the thermal and chemical stability with the mixture should be checked. For less similar components, weaker interactions with the solvent such as hydrogen bonding are sufficient to affect α . Solvents should be selected for which specific attractive or repulsive interactions with the mixture components are expected, taking into account the extent of the natural difference in volatility of the mixture components. Knowing this, isothermal titration calorimetry (ITC) may be applied for initial prediction of the solvent effects based on measurements of the excess enthalpy of mixing.

References

- (1) European-Council. 2030 Climate and energy policy framework; 2014.
- (2) Eurostat. Energy statistics - an overview, European Council, 2018.
- (3) Smith, R.; Jobson, M. *Encyclopedia of Separation Science*; Wilson, I. D., Ed.; Academic Press: Oxford, 2000, pp 84-103.
- (4) Graczova, E.; Vavrusova, M. *Chem Engineer Trans*, 2018, *70*, 1189-1194.
- (5) Kockmann, N. *ChemBioEng Reviews* 2014, *1*, 40-49.
- (6) Doherty, M. F.; Knapp, J. P. *Distillation, Azeotropic, and Extractive*. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 2004.
- (7) Kiss, A. A.; Ignat, R. M. *Sep Purif Technol* 2012, *98*, 290-297.
- (8) Kulajanpeng, K.; Suriyapraphadilok, U.; Gani, R. *Chem Engineer Trans*, 2014, *39*, 517-522.
- (9) Quijada-Maldonado, E.; Aelmans, T. A. M.; Meindersma, G. W.; de Haan, A. B. *Chem Eng J* 2013, *223*, 287-297.
- (10) Li, Q.; Zhang, J.; Lei, Z.; Zhu, J.; Zhu, J.; Huang, X. *Ind Eng Chem Res*, 2009, *48*, 9006-9012.
- (11) Berg, L.; Ratanapuech, P.; Google Patents - US4569726(A), 1986.
- (12) Jongmans, M. T. G.; Londoño, A.; Mamilla, S. B.; Pragt, H. J.; Aaldering, K. T. J.; Bargeman, G.; Nieuwhof, M. R.; Kate, A. t.; Verwer, P.; Kiss, A. A.; van Strien, C. J. G.; Schuur, B.; de Haan, A. B. *Sep Purif Technol* 2012, *98*, 206-215.
- (13) Jongmans, M. T. G.; Hermens, E.; Raijmakers, M.; Maassen, J. I. W.; Schuur, B.; de Haan, A. B. *Chem Eng Res Des* 2012, *90*, 2086-2100.
- (14) Canales, R. I.; Brennecke, J. F. *J Chem Eng Data* 2016, *61*, 1685-1699.
- (15) Christian Laurence; Gal, J.-F. *Lewis Basicity and Affinity Scales*; John Wiley & Sons, Ltd, 2009.
- (16) Laurence, C.; Graton, J.; Gal, J.-F. *J Chem Educ* 2011, *88*, 1651-1657.
- (17) Kamlet, M. J.; Abboud, J. L. M.; Abraham, M. H.; Taft, R. W. *J Org Chem* 1983, *48*, 2877-2887.
- (18) Taft, R. W.; Abboud, J.-L. M.; Kamlet, M. J.; Abraham, M. H. *J Solution Chem* 1985, *14*, 153-186.
- (19) Bízek, V.; Horáček, J.; Koušová, M. *Chem Eng Sci* 1993, *48*, 1447-1457.
- (20) Meyer, P.; Maurer, G. *Ind Eng Chem Res*, 1995, *34*, 373-381.
- (21) Bastos, J. C.; Soares, M. E.; Medina, A. G. *Ind Eng Chem Proc Des Dev*, 1985, *24*, 420-426.
- (22) Seader, J. D.; Henley, E. J.; Roper, D. K. *Separation process principles: chemical and biochemical operations*; 3rd ed.; Wiley:

- Hoboken, N.J., 2011.
- (23) Lei, Z.; Li, C.; Chen, B. *Sep Purif Rev* 2003, *32*, 121-213.
- (24) Kossack, S.; Kraemer, K.; Gani, R.; Marquardt, W. *Chem Eng Res Des* 2008, *86*, 781-792.
- (25) Schult, C. J.; Neely, B. J.; Robinson, R. L.; Gasem, K. A. M.; Todd, B. A. *Fluid Phase Equilib* 2001, *179*, 117-129.
- (26) Zhu, J.; Yu, Y.; Chen, J.; Fei, W. *Front Chemical Eng Chi*, 2007, *1*, 190-194.
- (27) Eckert, F.; Klamt, A. *AIChE J* 2002, *48*, 369-385.
- (28) Fredenslund, A.; Jones, R. L.; Prausnitz, J. M. *AIChE J* 1975, *21*, 1086-1099.
- (29) Harper, P. M.; Gani, R. *Comput Chem Eng* 2000, *24*, 677-683.
- (30) Brignole, E. A.; Bottini, S.; Gani, R. *Fluid Phase Equilib* 1986, *29*, 125-132.
- (31) Pretel, E. J.; López, P. A.; Bottini, S. B.; Brignole, E. A. *AIChE J* 1994, *40*, 1349-1360.
- (32) Lek-utaiwan, P.; Suphanit, B.; Douglas, P. L.; Mongkolsiri, N. *Comput Chem Eng* 2011, *35*, 1088-1100.
- (33) DOW. Product Safety Assessment: Valeric Acid; 2014.
- (34) Kubitschke, J.; Lange, H.; Strutz, H. *Carboxylic Acids, Aliphatic*. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA, 2000.
- (35) Bahrmann, H.; Frohning, C. D.; Heymanns, P.; Kalbfell, H.; Lappe, P.; Peters, D.; Wiebus, E. *J Mol Catal A: Chem* 1997, *116*, 35-37.
- (36) Roose, P.; Eller, K.; Henkes, E.; Rossbacher, R.; Höke, H. *Amines, Aliphatic*. In *Ullmann's Encyclopedia of Industrial Chemistry*.
- (37) Sakuth, M.; Mensing, T.; Schuler, J.; Heitmann, W.; Strehlke, G.; Mayer, D. *Ethers, Aliphatic*. In *Ullmann's Encyclopedia of Industrial Chemistry*, 2010.
- (38) Sprakel, L. M. J.; Schuur, B. *Ind Eng Chem Res* 2018, *57*, 12574-12582.
- (39) J. Gmehling, U. O., W. Arlt, P. Grenzheuser, U. Weidlich, B. Kolbe, J. Rarey. In *Vapor-Liquid Equilibrium Data Collection*, 1991 - 2014.
- (40) Sprakel, L. M. J.; Kamphuis, P.; Nikolova, A. L.; Schuur, B. *Chem Engineer Trans*, 2018, *69*, 529-534.
- (41) Robbins, L. A. *Chem Eng Prog* 1980, *76*, 58-61.
- (42) Tamada, J. A.; King, C. J. *Ind Eng Chem Res* 1990, *29*, 1327-1333.
- (43) Tamada, J.; King, C. *Ind Eng Chem Res* 1990, *29*, 1333-1338.
- (44) Miyamoto, S.; Nakamura, S.; Iwai, Y.; Arai, Y. *J Chem Eng Data*, 1999, *44*, 48-51.
- (45) Sewnarain, R.; Ramjugernath, D.; Raal, J. D. *J Chem Eng Data*, 2002, *47*, 603-607.

- (46) Blahušiak, M.; Kiss, A. A.; Babic, K.; Kersten, S. R. A.; Bargeman, G.; Schuur, B. *Sep Purif Technol* 2018, *194*, 301-318.
- (47) Krainer, G.; Keller, S. *Methods*, 2015, *76*, 116-123.
- (48) Blahušiak, M.; Kiss, A. A.; Kersten, S. R. A.; Schuur, B. *Energy*, 2016, *116*, 20-31.
- (49) Miller, K. J.; Huang, H.-S. *J Chem Eng Data*, 1972, *17*, 77-78.
- (50) Tanaka, H.; Muramatsu, T.; Kato, M. *J Chem Eng Data*, 1992, *37*, 164-166.

Predicting solvent effects on relative
volatility behavior in extractive
distillation

Abstract

A solvent screening approach for extractive distillation, combining isothermal titration calorimetry (ITC) and molecular modeling (MM), was investigated based on three close-boiling mixture cases. The investigated mixtures are 1) octanoic acid (HOct) and levulinic acid (HLev), 2) diethylmethylaniline (DEMA) and diisopropylether (DIPE), and 3) 2-butanol (2-BuOH) and 2-butanone (2-BuO). Solvent effects were predicted based on ITC and MM, instead of a solvent screening based on a full set of time-consuming vapor-liquid equilibrium (VLE) experiments. The correlation between the interaction energy of the solvent and the constituents of the mixture was shown, as well as the effect on the relative volatility α of the mixture. The effect on α was validated with VLE experiments. For solvents that increase α and are regenerable, moderate interactions of the mixture components with the solvent were calculated using MM, i.e. an interaction energy between the intermolecular interaction of the binary mixture and -60 kJ/mol). For mixtures without strong intermolecular interactions, for example 2-BuO and 2-BuOH, a preferential interaction with the high-boiling component is needed, i.e. a larger exothermic interaction energy than with the low-boiling component. In ITC measurements successful solvents show a weak exothermic heat of mixing (> -10 kJ/mol) with the preferred high-boiling component, and a smaller exothermic or even endothermic heat of mixing with the low-boiling component. Solvents with interactions too close to 0 kJ/mol lack effect on the relative volatility and exothermic interactions larger than 60 kJ/mol compromise regeneration, and both should be avoided. The developed method and solvent selection guidelines offer a reduced time, labor and material approach for solvent screening when group contribution methods and COSMO-RS are less reliable due to strong non-idealities.

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9.1 Introduction

Extractive distillation is a promising separation technique in cases where ordinary distillation is hindered by for example the presence of an azeotrope or a close-boiling system.¹ The solvent (entrainer) interacts with the components in the mixture and may change their activity coefficients. Thereby the relative volatility may be improved and/or it may lead to breaking of an azeotrope. This may enable a separation or reduce the energy demand of a conventional distillation process.¹ Extractive distillation is for example applied to separate close-boiling point hydrocarbons,² non-aromatics and aromatics,³ azeotropic mixtures of butanes, butenes and butadiene,⁴ and mixtures of acetone and methanol.⁵

The choice of applied solvent is key for a successful and viable process. In the ideal case a type of solvent screening would be performed that avoids extensive and time-consuming vapor-liquid equilibrium investigations with a range of solvents for each mixture of components. Several scales and methods have been developed for theoretical solvent screening approaches, e.g. affinity scales such as the BF_3 -affinity and hydrogen bond basicity $\text{p}K_{\text{BHX}}$,⁶ and predictive software based on quantum-chemical calculations such as COSMO-RS.⁷ Methods based on COSMO-RS for screening of organic solvents and ionic liquids followed by modeling in Aspen Plus were successful for the solvent screening for the process of dehydration of tert-butanol by extractive distillation,⁸ and for separation of mixtures of hydrocarbons and ethanol/water.⁹ Computer Aided Molecular Design (CAMD) can also be performed with the software packages ProCAMD®,¹⁰ based on activity coefficients. This was successfully applied for solvent selection for e.g. mixtures of C_8 -aromatics,¹¹ separation of hexane - methanol mixtures,¹² separation of several binary mixtures of alcohols, acetone, esters and water,¹³ separation of C_4 and 1,3-butadiene as well as other hydrocarbon systems and polar mixtures.²

Furthermore, predictions based on infinite dilution activity coefficients defining the selectivity at infinite dilution^{2,14,15} and parametrizations based on the linear solvation energy relationship (LSER) model^{16,17} have been used. Preselection of possible solvents to reduce the number of experiments can also be approached with computer-aided molecular design (CAMD), in which potential solvent molecules are formulated based on building blocks and functional groups, mostly based on the UNIFAC group contributions.² Because in most cases multiple solvents are suggested based on CAMD additional screening of the solvents based on other factors (e.g. availability, toxicity) is required.²

For solvent selection, straightforward requirements are related to availability, price, stability, toxicity, flammability, reactivity, corrosivity, safety and the possibility of azeotrope formation with one of the mixture components.^{1,2,18} Moreover, for the overall process optimization, consideration of just thermodynamics or the selectivity at infinite dilution, does not always lead to the selection of the right solvent as these parameters mainly focus on the extractive distillation step.¹⁹ For a viable process the regeneration efficiency should be included which can be assessed through entrainer flow rate and reflux or reboil ratio in the regeneration step.^{18,19} This was for example successfully applied by Kossack et al.²⁰ by evaluating the solvents based on minimum flowrate and energy demand, followed by an optimization of the flowsheet structure.

Nevertheless, none of the aforementioned methods are able to successfully predict the solvent effects on the relative volatility for the complete range of available solvents and all types of mixtures that are to be separated in (industrial) applications. This is partially a result of the required data for the solvent screening analysis, such as phase diagrams, equilibrium data and other solvent specifications. In particular, non-ideality resulting in azeotropes and the potential of a solvent to overcome the azeotrope can be difficult to predict. For systems where the common approaches are inaccurate due to significant non-ideality because of affinity between the solvent and components in the mixture, measuring or calculating that affinity may be a powerful approach to predict the effect of a solvent on the relative volatility behavior in extractive distillations.

In this work we explore the applicability of the experimental technique isothermal titration calorimetry (ITC), the theoretical molecular modeling (MM) approach, and the combination of the two methods to predict solvent effects on relative volatility behavior. It is possible to set up a typical ITC experiment within half an hour per solvent, after which the measurement time may vary from 6 to 24 hours, depending on the number of data points required. Typical ITC experiments require only up to 2 mL of the solvent and mixture components. Initiating the MM calculations typically takes up to 5 minutes per solvent, after which the calculation time is strongly dependent on the complexity of the molecular structure and may vary from several minutes to several hours. Both techniques are thus not labor intensive, reasonably fast (using commercial MM software) and do not require large amounts of chemicals. Thermodynamics of interactions can be studied experimentally with ITC. ITC is widely applied in the fields of biomolecular chemistry and ligand-protein interactions,²¹ and also for the study of solvent-solute interactions in separation processes.²²⁻²⁴ Examples of

isotherms and an accuracy analysis of the thermodynamic data obtained with ITC for extraction processes were published in previous work.²⁴⁻²⁶ Insights on the effects of molecular structure on the thermodynamics of the interaction for acid-base interactions in separation processes were published by Sprakel and Schuur,²⁶ based on which also solvent selection approaches may be improved. Another application of ITC is that it can accurately measure the heat of mixing of two liquids,²⁷ which may be applied for interactions of liquids that are applied in extractive distillation, also in cases where no strongly bonding complexes are expected.

With MM the interaction energy of the interaction between a solvent and solute can be modeled,^{22,25,26,28,29} and solvent selection can be based on the strength of interaction. Furthermore, the geometry and interactions of groups of solvent and solute molecules can be studied.^{22,26,28} For a full and detailed analysis of the interactions based on quantum mechanics, additional molecular dynamics simulations would be required in which large numbers of molecules are involved and the computation time is extensive. This work focuses on simulation as a quick screening tool and therefore it was chosen to apply simple and fast MM calculations with a small number of molecules.

Three close-boiling binary mixtures were selected based on their polarity and associating behavior, i.e. a) octanoic acid (HOct) and levulinic acid (HLev), b) diethylmethylaniline DEMA and diisopropylether (DIPE) and c) 2-butanol (2-BuOH) and 2-butanone (2-BuO). Table 1 shows the most important properties of the mixture components that are all different types of polar components. The case of HOct - HLev ($\Delta pK_a = 0.4$, $\Delta T_b = 6$ °C) was chosen because the extent of the difference in acidity is in between that of the cases of monochloroacetic acid (MCA) and dichloroacetic acid (DCA) ($\Delta pK_a = 1.6$, $\Delta T_b = 5$ °C) reported by Jongmans et al.³⁰ and HVal and its isomer 2-methylbutanoic acid ($\Delta pK_a = 0.1$, $\Delta T_b = 10$ °C) reported in earlier studies by us.^{31,32} For the MCA-DCA case studied earlier by Jongmans et al.³⁰ moderate bases were found to be successful solvents that both increase the relative volatility and are regenerable, whereas strong bases were thermally unstable and unsuitable as solvents. However, for separation of the valeric acids moderate bases did not have a significant effect on the relative volatility.^{31,32} Valeric acids are less strong than MCA and DCA, and in addition the smaller ΔpK_a of 0.1 might have caused the more difficult resolution. Applying stronger bases was problematic in terms of operational stability and regeneration. This implies that for separation of weak acids by extractive distillation a ΔpK_a larger than 0.1 is required to allow for a successful separation based on a difference in acidity. To further investigate on the minimum ΔpK_a for extractive distillation of weak

acids using basic solvents, a further study was performed with the case of HOct - HLev ($\Delta pK_a = 0.4$). The mixture of DEMA - DIPE ($\Delta pK_a \approx 14$, $\Delta T_b = 3-6$ °C) consists of an ether and amine base with a very low relative volatility but a large difference in basicity and therefore there is a large potential for extractive distillation, possibly with acidic entrainers. The mixture of 2-BuO - 2-BuOH is industrially relevant since most of the 2-BuO worldwide produced is through dehydrogenation of 2-BuOH, after which a purification step is required,³³ moreover with this case an alcohol and ketone are added to the family of mixtures investigated, thereby covering a more extensive part of the group of polar compounds. In this case, the hydrogen bonding ability is the most pronounced difference between the compounds in the mixture.

For all three cases, first the relevant intermolecular interactions were modeled with MM, then ITC was performed and finally the solvent effects on the VLE behavior were measured to validate the screening approach based on MM and ITC. For comparison purpose, also traditional VLE predictions were performed with the UNIFAC method using Aspen Plus software.

Table 1 *Physical properties of the mixture components.*

Acid	Octanoic acid	Levulinic acid	Diethyl methylamine	Diisopropylether	2-Butanol	2-Butanone
T_b (°C)	239	245	63-65	68.5	99.1	79.5
T_m (°C)	16.5	33	-196	-60	-115	-86.7
pK_a	4.9	4.5	3.65 (pK_b)	≈ 17 (pK_b)	≈ 16	≈ 20
$\log P$	3.05	-0.49	0.958	1.52	0.683	0.29
ρ (g/mL)	0.91	1.13	0.72	0.725	0.806	0.805
Functional groups	Acid	Acid. ketone	Tertiary amine	Ether	Alcohol	Ketone

9.2 Materials and methods

9.2.1 Chemicals

All chemicals were used without further purification and purchased from Sigma-Aldrich (acetic acid (>99.5 %), butanoic acid (HBu, 99.0 %), 2-butanol (2-BuOH, >99.5 %), 2-butanone (2-BuO, >99.5 %), m-cresol (>98 %), cyclohexanol (>99 %), cyrene (99.0 %), dibutylamine (DBA, >99.5 %), dibutylether (DBE, >99.3 %), diethylene glycol dibutyl ether (DEGDBE, >99 %), diethylene glycol dimethyl ether (diglyme, >99.5 %), diisopropylether (DIPE, >99 %), dimethyl sulfoxide (DMSO, 99.9 %), dodecane (>99 %), ethyl levulinate (EtLev, 99 %), ethylene glycol (EG, >99.8 %), glycerol (99.0 %), glycol (99.8 %), heptane (99 %), hexadecane (HexD, 99 %), isovaleric acid (isoHVal, 99 %), itaconic acid (>99 %), levulinic acid (HLev, 98 %), 5-methyl-2-hexanone (5-m-2-one, 98.0 %), 2-methylbutyric acid (2MBA, >98 %), methyl isobutyl ketone (MIBK, >99.7 %), methyl levulinate (MeLev, >98.0 %), methyl-2-methylbutyrate (MeMeBu, >98 %), methyl octanoate (MeOct, 99 %), octanoic acid (HOct, >98 %), 1-octanol (>99 %), octyl octanoate (OctOct, >98 %), phenol (PhOH, >99.5 %), 1,2-propane diol (>99 %), propylene glycol (PG, 99.0 %), sulfolane (99 %), tribenzylamine (TBzA, >99 %), 2,2,4-trimethylpentane (>99.5 %), trioctylamine (TOA, 98 %), trioctylphosphine oxide (TOPO, 99 %), valeric acid (HVal, >99 %), Acros Organics (tributylphosphate (TBP, 99 %), beta-cyclodextrin (>98 %), N,N-diethylmethylaniline (DEMA, >98 %)), TCI-GR (18-Crown-6 (>98 %), N,N-diethylmethylaniline (DEMA, >98 %)), Fischer Scientific (oleic acid (>99.5 %), tridodecylamine (TDDA, 95 %)), VWR International (toluene (>99.5 %)), Merck KGaA (diethylene glycol (DEG, 99 %), acetone Lichrosolv® (>99.8%)), Alfa Aesar (n-heptane anhydrous (99+ %)), Honeywell (p-xylene (99 %)), BASF (Dehypon G162) and Fluka (ethylbenzene (90 %)).

9.2.2 Molecular modeling

Molecular modeling (MM) was applied using Wavefunction Spartan'16 Parallel software to model the heat of interaction between the solvent molecules and the components of the mixtures studied. The geometry of the molecules or groups of molecules was optimized using the DFT- ω B97X-D-6-31G* level of calculation and parametrization. A conductor-like polarizable continuum model (CPCM) using a high dielectric constant of 37 (default value for a polar component) was used to model solvation in order to incorporate the effect of the polar environment. By combining the molecules with individually optimized structures, and minimizing the energy of their ensemble, the interaction energies were calculated.

It is unrealistic to assume that solvent molecules are always freely accessible, and interactions on a 1:1 basis typically yielded large interaction energies with the solutes for a range of solvents. Therefore, rather than basing solvent selection criteria on 1:1 complexations, to distinguish between solvents calculations based on the third molecule interactions with two solvent molecule ensembles were used. Thus, next to a calculation of the interaction energy between the solvent and each of the two components in the mixture, the interaction energy of two solvent molecules was also calculated, as well as the interaction energy of these solvent-solvent ensembles with a third component, being either a solvent molecule or one of the molecules of the mixture studied. The interaction energy of the solvent-solvent ensemble with a third component from the binary mixture that is to be separated was then determined relative to the interaction with a third solvent molecule, as is schematically shown in Figure 1. Including even more molecules in the model may possibly further improve the calculations, although at the cost of a strongly increased computational time which is not intended for this quick screening method.

Figure 1 Schematic description of the MM calculation of the energy of interaction of 2 solvent molecules (methyl levulinate, MeLev) with a third molecule of a mixture component (octanoic acid, HOct) relative to the interaction energy with a third solvent molecule. Calculations were performed using Wavefunction Spartan Parallel'16 software with DFT- ω B97X-D-6-31G* level of calculation and CPCM solvation with a polar solvent.

9.2.3 Isothermal titration calorimetry (ITC)

ITC experiments were performed in a TA Instruments TAM III Microcalorimeter operated at 20 °C based on dynamic correction. In each experiment a reference cell was used that contained water with a heat capacity equal to that of the sample cell including sample. A total of 283 μL of titrant was titrated in 20 subsequent periodical injections into the sample cell. Golden stirrers operated at 1.33 Hz were used to mix the sample. An injection interval of 55 minutes was applied to ensure that the signal was back at the baseline. Interval injection was preferred over continuous injection, because the measurement of the heat of mixing is subject to several errors that are induced by temperature differences between sample and titrant, variations of sample volume and viscosity affecting the heat released from stirring and variations in the stirring speed itself.²⁷ These variations are expected to have less effect when ITC is operated with periodical injections, as in that case the absolute signal is stronger and the time intervals allow for baseline stabilization. The heat of interaction as a result of each injection was measured for the combinations of solvents and components of the mixtures studied, from which the accumulated heat of mixing versus the mixture composition could be derived.

9.2.4 Vapor-liquid equilibria (VLE)

Vapor-liquid equilibria (VLE) were obtained using Fischer Labodest VLE602 ebulliometers in which a magnetically stirred equilibrium cell is present that is connected to a Cottrell circulation pump. The cell is heated with an immersion heater. The pressure can be set between 100 mbar and atmospheric pressure using either an Edwards E2M1.5 or Pfeiffer DUO 3 vacuum pump. The power supplied to the reboiler and the heating mantle temperature can be set. The equilibrium temperature of the mixture as well as the liquid temperature in the reboiler were measured using Pt-100 thermocouples. For each sample composition, the equilibrium cell was filled with 80 mL of sample (including the solvent). When the equilibrium temperature was reached after 30-90 minutes, samples of both the liquid phase and the condensed vapor phase were taken and analyzed.

9.2.5 GC and GC-MS

Samples from the VLE-experiments were dissolved in acetone and analyzed in triplo by gas chromatography (GC) with a Varian CP-3800 with FID detector (280 °C, accuracy >99 % for liquid phase samples and accuracy >97 % for vapor phase samples of lower concentration) and an Agilent DB-WAX column (60 m * 0.25 mm * 0.25 μm). For the DEMA - DIPE case the internal standard of dodecane was applied, for the other cases heptane was

applied as the internal standard. The temperature profiles of the GC oven for the different cases are shown in Table 2. For the DEMA - DIPE case some of the samples were analyzed with a 7890A Ms 5975C Agilent GC-MS (accuracy >99 % and accuracy >97 % for vapor phase samples of lower concentration) with FID and an Agilent HP-5Ms, HP19191S-433 column with helium as the carrier gas.

Table 2 *Oven temperature of GC and GC-MS for analysis of the liquid phase and condensed gas phase composition of ebulliometer experiments (only the plateaus are given, all intermediate temperature increases have linear profiles).*

DEMA - DIPE (GC)		DEMA - DIPE (GC-MS)		HOct - HLev		2-BuO - 2-BuOH	
Time (min)	T (°C)	Time (min)	T (°C)	Time (min)	T (°C)	Time (min)	T (°C)
0-1	40	0-4	45	0-5	45	0-4	45
3-4	50	32-34	160	19-29	250	14.50-15.50	150
7-10	250	47-49	250			18-20	250

9.3 Results and discussion

9.3.1 Binary VLE data

Binary VLE data for the three studied cases are shown in Figure 2. For the case of HOct - HLev (Figure 2a) the relative volatility is rather high up to $x = 0.8$ considering the small difference in natural boiling points ($\Delta T_b = 6^\circ\text{C}$, see Table 1). The equilibrium line does however show a tangent pinch, making it more difficult to obtain highly pure HOct, and application of a solvent based separation can be beneficial. In contradiction to what would normally be expected, at a lower pressure the relative volatility is lower. This may be a result of non-ideal dimerization behavior in the vapor phase, with the high-boiling HLev being the stronger acid and therefore having a lower compressibility factor. For DEMA - DIPE (Figure 2b) the relative volatility (average $\alpha = 1.05$) is very low as most of the points are almost on the $y = x$ line. Based on this VLE behavior, it is clear that ordinary distillation cannot be applied to separate this mixture and a solvent based approach is suggested. For the case of 2-BuO - 2-BuOH (Figure 2c) the equilibrium line shows the shape of ideally behaving liquids (average $\alpha = 1.9$ at 1000 mbar). Based on the VLE-behavior of the 2-BuO - 2-BuOH mixture, ordinary distillation is certainly technically feasible. However, based on the work of Blahusiak et al.³⁴ energy efficiencies in distillation processes may be significantly reduced upon increasing the selectivity up to $\alpha = 3$. Thus also in this case, applying a solvent may be beneficial for the overall economics of the separation.

Figure 2 Binary VLE data for **a)** octanoic acid (HOct) and levulinic acid (HLev) at 500 mbar (open symbols) and 200 mbar (closed symbols), **b)** diethylmethylamine (DEMA) and diisopropylether (DIPE) with an average $\alpha = 1.05$ at 1000 mbar, data from Sprakel et al.,^{31,32} and **c)** 2-butanone (2-BuO) and 2-butanol (2-BuOH) with an average $\alpha = 2.0$ at 1000 mbar, data from Sprakel et al..^{31,32} The lines are added to guide the eye.

9.3.2 Initial solvent selection

A first selection of the solvents applied in each case was made based on a variety of different solvent types containing different functional groups and covering the full range of solvents, i.e. from highly polar and active solvents that specifically interact with the components through e.g. hydrogen bonding, to apolar and inactive solvents. In each of the cases the boiling point T_b of the solvent was also considered as it should not be too close to that of the mixture components. Table 3 shows the total list of solvents applied in the three cases studied, including properties such as pK_a/pK_b , the BF_3 -affinity and the hydrogen bond basicity pK_{BHX} .^{6,35} However, as can be seen in the table, the data available within these scales is far from complete and although several solvents will have comparable values because of structural resemblance, it is difficult to select solvents purely based on these data. Therefore promising results in literature for related separation processes were also used to form the group of selected solvents, as well as qualitative functional group based predictions on deviations of Raoult's law,¹ complemented with a selection of solvents based on different functional groups, e.g. alcohols, acids, bases, alkanes and ethers.

9.3.2.1 Octanoic acid - levulinic acid

In the HOct - HLev mixture, HOct is the most volatile component, therefore a high-boiling solvent should either attract HLev, or repel HOct more than HLev in order to increase the relative volatility of HOct. In case a low-boiling solvent is applied the opposite holds. Because of the difference in the pK_a of the acids, a group of basic solvents was selected (i.e. trioctylamine (TOA), tridodecylamine (TDDA), tribenzylamine (TBzA), tributylphosphate (TBP), trioctylphosphine oxide (TOPO)), next to solvents with other functional groups (i.e. alcohols (glycerol and Dehypon G162, a C_{16} Guerbet alcohol with 2 ethylene oxide groups)), an alkane (hexadecane), sulfolane and an ether (18-Crown-6). Because of promising results with applying esters having molecular structures similar to the mixture components for separation of valeric acid and its isomers,^{31,32} several esters were also investigated (methyl levulinate (MeLev), methyl-2-methylbutyrate (MeMeBu), methyl octanoate (MeOct), ethyl levulinate (EtLev) and octyl octanoate (OctOct)).

Table 3 Solvent properties^{6,35} for solvents applied in the three separation cases studied.

Solvent	Abbreviation	T _b (°C)	pK _a	BF ₃ -affinity	pK _{BHX}
Acetic acid	HAc	118.1	4.8		
Butyric acid	HBu	163	4.8		
m-Cresol		203	10.1		(see PhOH)
18-Crown-6		438			1.2
Cyclohexanol		160			1.14
Cyrene		116			
Dehypon G162		>350	16-18		
Diethylene glycol	DEG	245			
Dimethylsulfoxide	DMSO	190		105.34	2.54
Dipropylamine	DPA	110	11	(see TOA)	2
Dibutyl amine	DBA	159	11	(see TOA)	2.11
Dibutylether	DBE	142	≈ 17 (pK _b)	78.57	0.88
Diglyme		162		(see DBE)	(see DBE)
Ethylbenzene		136			-0.36
Ethylene glycol	EG	195			0.97
Ethyl levulinate	EtLev	204	25	(see MeOct)	(see MeMeBu)
Glycerol		290			
Hexadecane	HexD	286.8			
Methyl-2-methylbutyrate	MeMeBu	102.8	25	(see MeOct)	1.11 (ethyl-isovalerate)
Methyl levulinate	MeLev	193-195	25	(see MeOct)	(see MeMeBu)
Methyl octanoate	MeOct	194-195	25	75.55 (ethyl acetate)	(see MeMeBu)
Iso-octane		99.3			
1-octanol	1-Oct	196			1.04
Octyl octanoate	OctOct	306-307	25	(see MeOct)	(see MeMeBu)
Oleic acid	HOl	360	5		
Phenol	PhOH	181.7	9.98		-0.07
Propylene glycol	PG	187			(see EG)
Sulfolane		285		51.32	1.47
Trioctylamine	TOA	365-367	10	135.87 (triethylamine)	1.57
Tributylphosphate	TBP	289		84.75 (trimethylphosphate)	2.66
Tribenzylamine	TBzA	380-390			-1.5
Trioctylphosphine oxide	TOPO	310 (50 mmHg)		119.28 (triethylphosphine oxide)	3.59
Tridodecylamine	TDDA	>400	10	(see TOA)	(see TOA)
Valeric acid	HVal	185.4	4.8		
p-xylene		138			-0.29
5-methyl-2-hexanone	5-m-2-one	144		74.84	1.13 (heptane-4-one)

9.3.2.2 DEMA - DIPE

As neither DEMA nor DIPE is clearly most volatile, solvents were selected based on expected differences in interaction with both of the components.^{31,32} Because of the basic nature of DEMA, acids were selected (acetic acid (HAc), valeric acid (HVal) and oleic acid), but also bases were selected (dipropylamine (DPA), dibutylamine (DBA)). DPA and DBA were also chosen for their structural resemblance with DEMA and for structural resemblance with DIPE the solvent diethylene glycol dimethyl ether (diglyme) was chosen. Because of expected hydrogen bonding with both DEMA and DIPE and predicted deviations from Raoult's law,^{1,36} phenolics and alcohols were selected (phenol (PhOH), m-cresol, ethylene glycol (EG), diethylene glycol (DEG) and propylene glycol (PG)). Deviations from Raoult's law are also expected for the solvent iso-octane that was chosen.

9.3.2.3 2-BuO - 2-BuOH

Because of the hydrogen bond donating and accepting functional groups in the mixture of 2-BuO and 2-BuOH several solvents were chosen that can either accept a hydrogen bond (DMSO, diglyme, dibutyl ether (DBE), MeLev, 5-methyl-2-hexanone (5-m-2-one), cyrene), donate a hydrogen bond (glycol, 1-octanol, PG, glycerol) or both (butanoic acid (HBu)). P-xylene and ethylbenzene were chosen based on promising results in the separation of the alcohol-ketone mixture of methanol and acetone.^{20,31,32}

9.3.3 Solvent interaction simulation with MM

The interaction energy between the solvents and the high-boiling mixture component, i.e. HLev, DEMA and 2-BuOH, was calculated with the DFT- ω B97X-D-6-31G* level of calculation and CPCM solvation using a default dielectric constant for a polar solvent of 37. The solvents are sorted from most exothermic to most endothermic interaction in Table 4 (first columns for each case).

Table 4 Interaction energy calculated with Spartan Parallel'16 (DFT- ω B97X-D-6-31G* level of calculation and CPCM solvation in polar solvent) for interaction between the solvents of each of the cases with the high-boiling component (first column) and the interaction of the ensemble of 2 solvent molecules with a third mixture component relative to interaction with a third solvent molecule (2^{nd} and 3^{rd} column, see Figure 1).

HOct - HLev				DEMA - DIPE				2-BuO - 2-BuOH			
Solvent	Interaction with		Interaction with mixture component	Solvent	Interaction with		Interaction with mixture component	Solvent	Interaction with		Interaction with mixture component
	HLev	HOct			DEMA	DIPE			2-BuOH	2-BuO	
Dehypon G162	-68	23.6	15	HVal	-69	16	16	PG	-47	39	5.4
TOA	-62	-34	-29	PhOH	-59	8.4	-42	HBu	-46	18	13
TOPO	-61	-23	-22	PG	-58	-4.2	-14	EG	-45	29	-0.7
glycerol	-57	-21	-28	m-cresol	-58	-11	7.4	DMSO	-44	-3.8	-22
TBP	-52	-8.7	8.2	EG	-57	15	-25	MeLev	-41	12	-2.1
EtLev	-47	-5.4	-3.8	cyclohexanol	-51	2.3	-10	cyrene	-40	650	640
MeLev	-46	-28	-21	DEG	-50	68	91	5-m-2-one	-38	11	-5.7
OctOct	-42	11.2	-5.5	DBA	-30	-1.5	21	1-octanol	-37	-18	-7.1
18-Crown-6	-40	22	-37	DBE	-30	9.6	36	diglyme	-33	21	19
TBzA	-32	-9.3	12	diglyme	-28	21	27	ethyl-benzene	-32	5.6	6
MeMeBu	-27	-22	14	DPA	-24	3	10.2	DBE	-31	6.7	12
MeOct	-26	34	32	iso-octane	-20	4	-0.85	p-xylylene	-25	1	2.1
sulfolane	-26	-13	-16					TPA	-23	1.5	-5.9
HexD	-25	13	11					glycerol	-18	58	-1.3
								sulfolane	-13	0.2	-20

Based on prior work by Jongmans et al.,³⁰ too strong exothermic interactions should be avoided because of regeneration problems, and in general it is assumed that solvents with an intermediate interaction strength may increase α , without compromising the regeneration. The solvent interactions with the high-boiling component should be stronger than the interaction between the mixture components, i.e. -21 kJ/mol for the case of DEMA - DIPE, -31 kJ/mol for the case of 2-BuO - 2-BuOH and -38 kJ/mol for HOOct - HLev. Figure 3a shows a schematic representation of the regions of the calculated direct interaction energy with the high-boiling component where solvent effects on α are expected, assuming that an exothermic interaction energy of more than -60 kJ/mol is too strong. For moderately endothermic interaction energies a negative effect on α is expected as a result of repulsion of the low-boiling component, however no specific values for this region were predicted in this work.

Figure 3 Expected solvent effect based on direct interaction energy calculated with MM, with **a)** general representation of boundaries and region for positive effect (less exothermic than -60 kJ/mol and more exothermic than the interaction between the binary mixture components) and negative effect (no specific boundaries were defined in this work), and **b)** specific regions for expected positive solvent effects for the three cases studied.

Assuming a maximum (exothermic) interaction energy of -60 kJ/mol, the list of selected solvents based on the direct interaction energy with the low-boiling component calculated with MM includes for HOOct - HLev

18-Crown-6, OctOct, MeLev, EtLev, TBP and glycerol, for DEMA - DIPE cyclohexanol, m-cresol, EG, PG, DEG, DBA, DBE, DPA, diglyme and PhOH, and for 2-BuO - 2-BuOH DBE, ethylbenzene, diglyme, 1-octanol, 5-m-2one, cyrene, MeLev, DMSO, EG, HBU and PG. The boundaries for the solvent affinities that were considered for further studies are graphically displayed in Figure 3b. To further study the effect of solvent properties on the interaction energies using MM, also the interaction energy of two solvent molecules with a third molecule from the mixture was calculated and listed in Table 4.

Especially for calculations with multiple molecules and molecules with multiple interacting sites there are various options of optimizing the geometry and energy towards a local minimum. To minimize the chance of reporting local minima, duplo calculations for each three molecule ensemble were performed with different starting geometries and the standard deviations in the calculated energies were determined. The deviations were stronger for molecules with multiple interacting sites, e.g. glycerol and the larger esters and ethers. Including all solvents studied, on average the standard deviation in the differences of the duplo calculations equaled 13 kJ/mol. This indicates the importance of performing the geometry optimization with multiple initial geometries to avoid finding only local minima, especially in the case of multiple or larger molecules. The effect of the increased number or size of molecules could be addressed by applying molecular dynamics simulations with large groups of molecules. These simulations would induce strongly increased computational costs and are therefore not applied in this quick screening method based on MM. To avoid the risk of not selecting a suitable solvent, the guidelines for selecting solvents based on MM calculations should not be applied too strict and it is therefore suggested not to exclude solvents if the calculated values are not significantly out of the desired range.

The values obtained for the solvent cyrene in the case with 2-BuO - 2-BuOH are extremely high as a result of very strong (calculated) interaction energy of two cyrene molecules with a third molecule. Theoretically, a good solvent will attract a molecule of the high-boiling component over an additional solvent molecule, and thus show a negative relative interaction with the high-boiling component. Moreover, a smaller negative value for the interaction of the low-boiling component (compared to the high-boiling) relative to interaction with the solvent should be beneficial, indicating less affinity with the low-boiling component. However, since most interactions between the components take place in the liquid phase, this last assumption was not taken into account in the selection of solvents.

Considering the calculated values for interaction of the ensemble of two solvent molecules with a third solvent molecule (relative to a third solvent molecule), the solvent TBP could be excluded for the case with HOct - HLev based on calculated exothermic interactions of the solvent ensemble with the low-boiling component as a third molecule and endothermic interaction with the high-boiling component as a third molecule. Thus, the list of selected solvents for further studies by ITC and VLE includes for HOct - HLev: 18-Crown-6, OctOct, MeLev, EtLev and glycerol, for DEMA - DIPE: cyclohexanol, m-cresol, EG, PG and PhOH, and for 2-BuO - 2-BuOH: ethylbenzene, 1-octanol, 5-m-2one, MeLev, DMSO, EG and PG.

9.3.4 Solvent interaction measurements with ITC

For HOct - HLev, the heat of mixing measured with ITC for each of the solvents and mixture components is shown in Figure 4a for interaction with HOct and in Figure 4b for interaction with HLev. These curves are accumulative, i.e. each point represents the total amount of heat taken up or released by the sample as a results of all previous injections divided by the total number of moles in the sample. Theoretically, the curve that was measured by titrating HOct into solvent should exactly meet the curve obtained by titrating solvent into HOct. The measured curves typically meet each other but with small off-sets. These differences are a result of experimental errors, enhanced by the accumulative nature of the curve itself. The interaction with TOA and TBP is clearly exothermic and strong for both acids, which is explained by the basic character of these solvents. Also with Dehypon G162 a small exothermic interaction is observed, which is not so obvious. From the organization of the three molecule ensembles, a clear multiple interaction of the acid molecule with both the alcohol and the ether functionalities in the Dehypon G162 was observed. Most other solvents show a small endothermic heat of mixing for each of the acids. The heat of mixing of MeLev and EtLev with HOct are two exceptions to this, these show a more endothermic mixing enthalpy with HOct than the mixing enthalpy of HLev with HOct. The interaction is more endothermic because both MeLev and EtLev are esters and thus only hydrogen bond acceptors with weaker hydrogen bonds than the acid-acid dimers of HOct and HLev.

Figure 4 Heat of mixing (accumulative, per mole of sample including titrant) of solvent for the HOct - HLev case at 20 °C with **a)** HOct over the full range of HOct mole fractions and **b)** HLev over the full range of HLev mole fractions.

Comparing the absolute values for the interaction energy between solvent and acid from ITC (Figure 4) with those from MM (Table 4), it is clear that the heat measured in ITC is significantly lower than the direct interaction energy calculated with MM. The direct interaction energy from MM only involves interactions between one solvent molecule and one solute molecule. When the relative interaction energy of a third solute molecule (relative to a third solvent molecule) from Table 4 is compared with the ITC results at low molar ratio, it is clear that the MM values are already more in the same range of values and thus also more realistic. These values do however not match exactly which may be explained by considering that in the MM calculations a very limited ensemble of only three molecules was calculated, whereas in ITC the net heat effect of all ongoing interactions and restructuring in the solvent upon titration of the acid is measured. Moreover, breaking of acid dimers in the titrant upon dilution through titration reduces the heat measured in the ITC measurements. In the MM calculations with three molecules, already some solvent-solvent interactions and geometric rearrangements are taken into account, resulting in more realistic energy values than MM calculations with only two molecules.

Considering regeneration problems with TBP and TOA (*vide infra*), a maximum cumulative exothermic heat effect of 4 to 5 kJ/mol mixture can be set as a guideline. Based on the ITC results in Figure 4 EtLev and MeLev, showing moderately endothermic heats of mixing (up to approximately 1.5 kJ/mol mixture), are selected for further study in VLE measurements and for the other solvents only a small or no effect on α is expected based on the small heats of mixing.

The disadvantage of these measurements of the heat of mixing is that solids (e.g. sulfolane, 18-Crown-6) cannot be taken into account as they cannot be titrated and will show a melting energy or enthalpy of dilution. To overcome this problem, it was attempted to perform a direct measurement of the heat of mixing of HOct and HLev in the presence of each of the solvents (Figure 5a), i.e. both titrant and sample are dissolved in the specific solvent. However, from Figure 5a it can be concluded that in this case the differences in the energy between the solvents are very small in terms of endothermic/exothermic heat of mixing. Therefore, based on this type of experiment, no solvent effects on the relative volatility can be predicted. A possible option for screening of these solvents would be adjusting the temperature of the ITC experiment.

a

b

Figure 5 a) Heat of mixing (accumulative, per mole of sample including titrant) of HLev and HOct at 20 °C in presence of solvent (≈ 50 vol% in both titrant and sample cell) and **b)** Heat of injection per mole of titrant for (symbols without vertical line) titration of HOct to solvent (not accumulative) at 20 °C and (symbols with vertical line) titration of solvent to HOct.

Although the accumulative nature of the heat of mixing curves does not allow for direct titration into solvents that are solid at room temperature, it is possible to measure the heat of mixing at lower solvent fractions without using the accumulated values. This was applied in another attempt to incorporate solvents that are solid at room temperature. The non-accumulative ‘heat of injection’ is shown in Figure 5b, in which each data point only represents the energy released by the last injection per mole of titrant (either the acid HOct (symbols without vertical line) or the solvent (symbols with vertical line)). Because of the non-accumulative nature of these curves, the lines starting at low and high HOct mole fraction are not expected to match around a mole fraction of 0.5. Qualitatively, the solvents in Figure 5b show the same order of the energy from exothermic to endothermic as in Figure 4a, but now it is possible to include TOPO and 18-Crown-6. TOPO has a strong exothermic heat of injection with HOct and the heat of injection with 18-Crown-6 is relatively small, thus both of these solvents are not selected for further study in VLE measurements.

For the case of DEMA - DIPE the heat of mixing with the solvents was also determined, see Figure 6a and b. After demonstrating the symmetric shape in the curves of Figure 4, it was not considered necessary to repeat this, and to limit labor intensity and use of chemicals, only the domain of high solvent fraction was measured for this system. Cyclohexanol and PG show the largest (endothermic) interaction in the range from -5 to +5 kJ/mol mixture where reversibility of the intermolecular interactions is expected upon titration with DIPE (Figure 6a). Therefore these two solvents were selected for study in VLE measurements. EG and DEG were not tested as results similar to those for PG are expected because of the strong similarity in molecular structure. HVal and m-cresol show a too strong interaction (≈ -10 kJ/mol) and the other solvents have only a small heat of mixing with DIPE, therefore these solvents are all excluded from the list of selected solvents for further study.

a

b

Figure 6 (a/b) ITC measurements of solvents for the DEMA - DIPE case at 20 °C, with the heat of mixing (accumulative, per mole of sample including titrant) for **a)** DIPE and **b)** DEMA.

Figure 6 (c/d) ITC measurements of solvents for the DEMA - DIPE case at 20 °C with the heat of injection (not accumulative, per mole of titrant) for **c)** DIPE and **d)** DEMA.

For the DEMA - DIPE case the non-accumulative ‘heat of injection’ is shown in Figure 6c and d, to be able to include PhOH in the screening. Also in this case, the qualitative results in terms of endothermic/exothermic energy relative to the ‘heat of injection’ with DEMA or DIPE and the order of solvents are equal to the results of Figure 6a and b. The ‘heat of injection’ of the solid PhOH with DIPE was strongly exothermic and therefore PhOH was not selected for further study.

For the case of 2-BuO - 2-BuOH (Figure 7) none of the applied solvents show a strongly exothermic interaction and also none of the solvents show a more endothermic interaction with 2-BuO than 2-BuOH. For most of the solvents, i.e. HBu, MeLev, cyrene, ethylbenzene, p-xylene, 5-m-2-one and diglyme, the interaction energy with 2-BuO is very low. Thus, none of these solvents was selected for further study. The list of solvents selected based on MM was reduced to 1-octanol, PG and EG based on the ITC measurements.

a

Figure 7 a) Heat of mixing (accumulative, per mole of sample including titrant) of solvents for the 2-BuO - 2-BuOH case at 20 °C with BuO.

Figure 7 b) Heat of mixing (accumulative, per mole of sample including titrant) of solvents for the 2-BuO - 2-BuOH case at 20 °C with 2-BuOH.

9.3.5 Pseudo-binary VLE data

For validation of the solvent selection procedure based on MM calculations and ITC measurements, the pseudo-binary VLE data were also measured for the solvents that were excluded based on ITC and MM. For the case of HOct - HLev VLE data were measured with the solvents at a solvent-to-feed ratio of 1 at high HOct concentration, considering the shape of the equilibrium line (Figure 2a). It appeared that TOA has too strong interactions, since the mixture was not fully stable in operation with the ebulliometer and a very strong complex was formed that dissociated very slow, because of which an increase in the acid concentrations was seen in the samples after a couple of days. Similar results were obtained for TDDA, where also other peaks showed up in the GC chromatogram, indicating reaction products. The mixture with TBP was also not stable in operation, a lot of undefined peaks appeared in the GC chromatogram. The system with glycerol was very unstable, and the possibility of the presence of two liquid phases could not be excluded. Although sulfolane was stable in operation, up to 20 wt% of sulfolane was detected in the condensed vapor phase samples, while the boiling point is 40 °C higher than the high-boiler HLev. Apparently there is solvent non-ideality and sulfolane cannot be applied as a solvent.

a

b

Figure 8 Pseudo-binary VLE data for levulinic acid and octanoic acid with several solvents at a volume based solvent-to-feed ratio of 1 at **a)** 200 mbar and **b)** 500 mbar. The error bars indicate the 1 % error in the liquid phase composition and 3 % error in the vapor phase composition that results from the GC analysis, see also section 9.2.5.

Pseudo-binary VLE data for the remaining solvents are shown in Figure 8. At both operating pressures (Figure 8) the application of the solvent MeLev results in an increase of the relative volatility of HOct over HLev. At a pressure of 500 mbar (Figure 8b), it can be seen that OctOct and MeOct have a negative influence on α , followed by smaller negative effects of hexadecane, MeMeBu, TBzA (showing some thermal instability indicated by a color change of the mixture), Dehypon G162 (also some thermal instability) and TOPO. There was no significant effect of EtLev and 18-Crown-6 on α . Only MeLev showed an improvement of α . At an operating pressure of 200 mbar (Figure 8a, Table 5 (left)), similar results were obtained. One of the exceptions is OctOct, which has a less strongly negative influence in this case. There is also a small positive effect on α visible when EtLev and 18-Crown-6 are applied as solvents, whereas MeMeBu and TOPO have almost no influence. For HexD and MeOct the addition of solvent resulted in HLev being the most volatile compound. In specific separations, depending on feed and product composition and the VLE data over the full range of compositions, these solvents inducing inverted relative volatility may also be applied.

Table 5 Relative volatility α for different solvents applied in the studied cases, from pseudo-binary VLE measurement with solvent (Data from Figure 8 for HOct - HLev, and for DEMA - DIPE and 2-BuO - 2-BuOH previously published in Sprakel et al..^{31,32}).

HOct - HLev		DEMA - DIPE			2-BuO - 2-BuOH	
$x_{\text{HOct}} \approx 0.9$, 200 mbar		$x_{\text{DEMA}} \approx 0.5$, 1000 mbar			$x_{\text{2BuO}} \approx 0.4$, 1000 mbar	
S/F = 1		S/F = 1		S/F = 3	S/F = 1	
No solvent	1.2	No solvent	1.05		No solvent	1.9
<u>Relative volatility DIPE over DEMA</u>						
TOA	Not stable	carboxylic acids	Too strong interaction		DMSO	2.9
TBP	Not stable	EG/DEG	Not fully miscible		EG	2.6
MeLev	2.5	m-cresol	unstable		PG	2.2
EtLev	1.5	PhOH (pos. unstable)	6.7	8.6	HBu	2.1
18-Crown-6	1.4	PG	1.8	2.8	1-octanol	1.8
TOPO	1.3	cyclohexanol	1.5	1.1	diglyme	1.6
MeMeBu	1.2	DPA	1	1	DBE	1.6
Dehypon G162	1	DBA	1	1.1	5-m-2-one	1.6
TBzA	0.88	DBE	1	1	ethylbenzene	1.4
OctOct	0.8	iso-octane	1	1	MeLev	1.3
HexD	0.62	Diglyme	0.9	0.8	p-xylene	1.2
MeOct	0.56				cyrene	1.1

For DEMA - DIPE the carboxylic acids had too strong interactions with the mixture components and m-cresol was not fully miscible with the mixture, see also Sprakel et al.^{31,32} EG was excluded in the VLE measurements because it was not fully miscible with the binary mixture. When diglyme was applied DEMA was the most volatile component as it was in the binary mixture, however for all other solvents DIPE was the most volatile component. The majority of the solvents (i.e. amines, ethers and alkanes) had almost no influence on the relative volatility (Table 5 (middle)). The alcohols cyclohexanol, PhOH and PG have the most positive effect on the relative volatility. For the solvent PhOH it should be mentioned that although equilibrium could be reached during the experiments, there was a significant color change of the sample mixture towards dark brown, indicating thermal instability. For the separation of 2-BuO - 2-BuOH the solvent glycerol showed limited miscibility with the mixture and no α could be measured, the other results are shown in Table 5 (right), see also Sprakel et al.^{31,32} DMSO, PG and EG result in the largest increase of relative volatility. The effect of EG is stronger than that of PG, probably a result of increased functional group density. In general, the less polar and less active solvents have a negative effect on the relative volatility for this case.

9.3.6 Interpretation of MM and ITC results with experimental VLE data

Solvents were selected based on MM calculations and with the ITC measurements the list of selected solvents was further reduced to just a few promising solvents of which VLE needed to be measured. For verification of the developed method, all solvents were used in the measurement of the pseudo-binary VLE data. For the case of HOct - HLev, based on MM and ITC EtLev and MeLev were selected as solvents and their positive effect on α was confirmed in the pseudo-binary VLE measurements (Table 5). For the DEMA - DIPE case, the positive effect was confirmed for cyclohexanol and PG, not for EG as it was not fully miscible in VLE experiments. For the case of 2-BuO - 2-BuOH, DMSO, PG and EG showed increased α in the pseudo-binary VLE measurements, which was not predicted for DMSO. This means that 1-octanol was wrongly selected and DMSO wrongly unselected based on ITC and MM. DMSO (as well as DBE) were excluded based on ITC measurements because of a similar heat of mixing as the low-boiling 2-BuO upon titration with the high-boiling 2-BuOH, apparently solvents should not be excluded based on this. For 1-octanol strong interactions were measured and calculated with both ITC and MM, although the effect on α is rather small which may be a result of the similar molecular structure of 1-octanol and 2-BuOH.

Based on the measured pseudo-binary VLE data for the three cases of binary mixtures and solvents studied with MM and ITC, several trends based on both techniques can be derived. In MM calculations, interactions between the solvent and the high-boiling component should be stronger than the interactions between the mixture components and weaker than an exothermic interaction energy of 60 kJ/mol. For the DEMA - DIPE case there was no significant relative volatility. The solvents that increase α showed exothermic interaction energies in the range of 50-60 kJ/mol with DEMA, indicating that for this difficult separation, stronger interaction with the components is required compared to the other studied cases. Moreover, the calculated value for the relative interaction of an ensemble of two solvent molecules with a third molecule of the high-boiling component (relative to a third solvent molecule) should preferably be exothermic. Nevertheless, a light endothermic effect could also work on the condition that there is a clear difference in the interaction with the low-boiling component. Especially for the cases with HOct - HLev and with DEMA - DIPE, this trend was clear. The trend of increasing direct interaction energy and relative exothermic interaction energy with the high-boiling component as a third molecule (Table 4) with increasing effect on α (Table 5 (right)) is the least clear for the 2-BuO - 2-BuOH case, possibly because of less specific interactions with these mixture components. The solvent selection would have been further improved for these cases with weaker intermolecular interactions, i.e. DEMA - DIPE and 2-BuO - 2-BuOH, by considering that a positive solvent effect on α is favored by a less exothermic interaction with the low-boiling component relative to interaction with a solvent molecule.

In subsequent ITC measurements, where lower absolute interaction energies are measured due to more complex ensembles of interaction, the interaction energy should be less exothermic than 5 kJ/mol of mixture in the measurement cell. Furthermore, a very low heat of mixing with the low-boiling component indicates minimum interaction between the solvent and low-boiling component, based on which a large effect on the relative volatility is unlikely. Moreover, when a larger endothermic heat of mixing with the low-boiling component is measured for the solvent compared to the heat of mixing of the mixture components, then more repulsive (less attractive) forces between the solvent and low-boiling component are expected and thus an increase of α . However, it was shown that solvents should not be excluded solely based on this last guideline.

9.3.7 Screening of solvent effects with Aspen Plus

As a comparison, a solvent screening with Aspen Plus software was performed for the case of HOct - HLev. The NRTL model was applied to model the VLE, in combination with UNIFAC since no binary interaction parameters are available in the database. The modeling was performed with the pseudo-binary system option with a solvent mole fraction of 0.5. This resulted in negative expectations for the effect on α for TOA, HexD, OctOct, MeMeBu and sulfolane. On the other hand, for MeLev, EtLev, MeOct and glycerol a positive effect on α was predicted. The prediction of the pseudo-binary VLE for the solvent TBP was not possible as UNIFAC experiences problems with the phosphate group.

When these predictions are compared with the determined values for α for the stable solvents (from Table 5 (left)), see Figure 9, the predicted values are far from the values measured in VLE experiments for MeOct and also not close to the values for the other solvents. Glycerol and TOA appeared unstable in the VLE measurements. Only for MeLev and EtLev the prediction of a positive effect on α is correct, although it is underpredicted.

Although MeLev and EtLev were successfully predicted as potential solvents, solvent screening based on Aspen Plus was not able to predict on the minimal or negative effect on α for the other solvents. Furthermore, screening of phosphate group containing solvents is not possible as UNIFAC experienced problems. These results on the separation of HOct and HLev lead to the conclusion that a solvent screening for a large group of solvents with Aspen Plus is not effective for this mixture that shows non-ideal VLE behavior.

Figure 9 Parity plot of pseudo-binary relative volatility α of HOct and HLev at 200 mbar predicted with Aspen Plus and NRTL based on UNIFAC versus α measured in VLE experiments with several solvents (mole fraction = 0.5).

9.4 Conclusion

An approach for solvent screening combining isothermal titration calorimetry (ITC) and molecular modeling (MM) was developed and validated based on three cases of mixtures of close-boiling compounds (octanoic acid (HOOct) and levulinic acid (HLev), diethylmethylamine (DEMA) and diisopropylether (DIPE), and 2-butanone (2-BuO) and 2-butanol (2-BuOH)).

It was shown that for systems where standard predictive methods (e.g. UNIFAC) are less reliable, initial predictions of solvent effects on the relative volatility can be done using MM, and measured using ITC. The interaction energy calculated with MM should be larger than the interaction energy of the two mixture molecules and less exothermic than -60 kJ/mol. Calculations of interactions based on ensembles of three molecules resulted in interaction energies that are more in the range of those measured in ITC. An exothermic (or a small endothermic interaction) of a two molecule solvent ensemble with the high-boiling component (relative to interaction with an additional solvent molecule) also indicated a positive effect on the relative volatility. For the cases with weaker intermolecular interactions a less exothermic interaction of the solvent with the low-boiling component than with the high-boiling component indicated a positive solvent effect. Heats of mixing can be determined experimentally in ITC, doing this for selected solvents can further narrow down the list of solvents to be measured in labor intensive VLE experiments. Using VLE, it was confirmed that the cumulative mixing energy as measured by ITC should not exceed +5 kJ/mol mixture or -5 kJ/mol mixture.

The developed and experimentally validated approach and guidelines for solvent effect prediction based on MM and ITC successfully predicted the solvent effects for each of the cases studied. No solvents with a positive effect on the relative volatility were missed in the predictions. Using this approach significantly reduces the time and material required for solvent screening because only for a limited number of solvents labor and material intensive VLE experiments are necessary. Additionally, MM allows for the design and development of new solvents for separation of close-boiling mixtures.

References

- (1) Doherty, M. F.; Knapp, J. P. *Kirk-Othmer Encyclopedia of Chemical Technology*, 2004.
- (2) Lei, Z.; Li, C.; Chen, B. *Sep Purif Rev* 2003, *32*, 121-213.
- (3) Wytze Meindersma, G.; Podt, A.; de Haan, A. B. *Fuel Process Technol* 2005, *87*, 59-70.
- (4) White, W. C. *Chem Biol Interact* 2007, *166*, 10-14.
- (5) Yeh, A.-I.; Berg, L.; Warren, K. J. *Chem Eng Commun* 1988, *68*, 69-79.
- (6) Laurence, C.; Graton, J.; Gal, J.-F. *J Chem Educ* 2011, *88*, 1651-1657.
- (7) Eckert, F.; Klamt, A. *AIChE J* 2002, *48*, 369-385.
- (8) Hu, Y.; Su, Y.; Jin, S.; Chien, I. L.; Shen, W. *Sep Purif Technol* 2019, *211*, 723-737.
- (9) Gutiérrez, J. P.; Meindersma, G. W.; de Haan, A. B. *Ind Eng Chem Res* 2012, *51*, 11518-11529.
- (10) Harper, P. M.; Gani, R. *Comput Chem Eng* 2000, *24*, 677-683.
- (11) Lek-utaiwan, P.; Suphanit, B.; Douglas, P. L.; Mongkolsiri, N. *Comput Chem Eng* 2011, *35*, 1088-1100.
- (12) Zhou, T.; Song, Z.; Zhang, X.; Gani, R.; Sundmacher, K. *Ind Eng Chem Res* 2019.
- (13) van Dyk, B.; Nieuwoudt, I. *Ind Eng Chem Res* 2000, *39*, 1423-1429.
- (14) Bastos, J. C.; Soares, M. E.; Medina, A. G. *Ind Eng Chem Proc Des Dev* 1985, *24*, 420-426.
- (15) Seader, J. D.; Henley, E. J.; Roper, D. K. *Separation process principles: chemical and biochemical operations*; 3rd ed. ed.; Wiley: Hoboken, N.J., 2011.
- (16) Kamlet, M. J.; Abboud, J. L. M.; Abraham, M. H.; Taft, R. W. *J Org Chem* 1983, *48*, 2877-2887.
- (17) Taft, R. W.; Abboud, J.-L. M.; Kamlet, M. J.; Abraham, M. H. *J Solution Chem* 1985, *14*, 153-186.
- (18) Kiss, A., *Distillation / Extractive Distillation*, Reference Module in Chemistry, Molecular Sciences and Chemical Engineering, 2013.
- (19) Gerbaud, V.; Rodriguez-Donis, I.; Hegely, L.; Lang, P.; Denes, F.; You, X. *Chem Eng Res Des* 2019, *141*, 229-271.
- (20) Kossack, S.; Kraemer, K.; Gani, R.; Marquardt, W. *Chem Eng Res Des* 2008, *86*, 781-792.
- (21) Falconer, R. J. *J Mol Recognit* 2016, *29*, 504-515.
- (22) Cuypers, R.; Murali, S.; Marcelis, A. T. M.; Sudhoelter, E. J. R.; Zuilhof, H. *ChemPhysChem* 2010, *11*, 3465-3473.
- (23) Cuypers, R.; Sudhoelter, E. J. R.; Zuilhof, H. *ChemPhysChem* 2010, *11*, 2230-2240.
- (24) Sprakel, L. M. J.; Schuur, B. *Ind Eng Chem Res* 2018, *57*, 12574-12582.

- (25) Sprakel, L. M. J.; Schuur, B. *J Ind Eng Chem* 2018, *72*, 364-373.
- (26) Sprakel, L. M. J.; Schuur, B. *J Mol Liq* 2019, *accepted*.
- (27) Rodríguez de Rivera, M.; Socorro, F.; Matos, J. *Int J Mol Sci* 2009, *10*, 2911.
- (28) Cuypers, R.; Burghoff, B.; Marcelis, A. T. M.; Sudhölter, E. J. R.; de Haan, A. B.; Zuilhof, H. *J Phys Chem A* 2008, *112*, 11714-11723.
- (29) Krzyzaniak, A.; Schuur, B.; Sukumaran, M.; Zuilhof, H.; De Haan, A. B. *Chem Engineer Trans* 2011, *24*, 709-714.
- (30) Jongmans, M. T. G.; Londoño, A.; Mamilla, S. B.; Praght, H. J.; Aaldering, K. T. J.; Bargeman, G.; Nieuwhof, M. R.; Kate, A. t.; Verwer, P.; Kiss, A. A.; van Strien, C. J. G.; Schuur, B.; de Haan, A. B. *Sep Purif Technol* 2012, *98*, 206-215.
- (31) Sprakel, L. M. J.; Kamphuis, P.; Nikolova, A. L.; Keijsper, D. J.; Schuur, B. *Chem Eng Res Des* 2019, *144*, 123-134.
- (32) Sprakel, L. M. J.; Kamphuis, P.; Nikolova, A. L.; Schuur, B. *Chem Engineer Trans* 2018, *69*, 529-534.
- (33) Detlef Hoell; Thomas Mensing; Rafael Roggenbuck; Michael Sakuth; Egbert Sperlich; Thomas Urban; Wilhelm Neier; Strehlke, G. *Ullmann's Encyclopedia of Industrial Chemistry*, 2009.
- (34) Blahušiak, M.; Kiss, A. A.; Babic, K.; Kersten, S. R. A.; Bargeman, G.; Schuur, B. *Sep Purif Technol* 2018, *194*, 301-318.
- (35) Christian Laurence; Gal, J.-F. *Lewis Basicity and Affinity Scales*; John Wiley & Sons, Ltd, 2009.
- (36) Robbins, L. *Chem Eng Prog* 1980, *76*, 58-61.

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Conclusions & Outlook

10.1 Conclusions

The work in this thesis focused on affinity separations of close-boiling polar compounds and various related aspects, from both fundamental and practical perspectives. The applied mixtures include aqueous solutions of (carboxylic) acids, phenol and pyridines, as well as non-aqueous binary mixtures of acids, amines, alcohols, ketones and ethers. In the first part of the thesis solvent-solute interactions applicable to liquid-liquid extraction (LLX) processes were studied with isothermal titration calorimetry (ITC) and molecular modeling (MM) in combination with direct measurement of liquid-liquid equilibria (LLE). MM was applied using Wavefunction Spartan '16 software, as a tool that is readily available for process engineers and that can be used on a standard personal computer. In the second part of the thesis these methods were used for the study of interactions and solvent effects related to extractive distillation (XD) in combination with direct measurement of vapor-liquid equilibria (VLE).

The goal of the studies was to improve insight into and understanding of interactions, mechanisms and determining factors involved in extraction processes, as well as to develop predictive methods for solvent effect prediction and solvent selection to reduce the time, material and energy required for these procedures.

Studies on acid - tertiary amine interactions showed that the mechanism of complexation is best described by a sequential reaction model. Both proton transfer and hydrogen bonding interactions play a role in acid-base interactions, depending on the extractant, solute and diluent. Thermodynamic parameters obtained with ITC appeared to be concentration dependent. Thus ITC should always be applied at the concentrations applicable to the process. Enthalpy-entropy compensation was observed with ITC for small changes in extractant structure, showing the potential of optimizing the enthalpy of complexation and thereby the temperature dependency of the equilibrium for temperature-swing regeneration processes. Moreover, an optimum in the Gibbs free energy of complexation was observed.

Solvent effects regarding the mechanism can be predicted empirically, based on which, for example, the applicable affinity scale for solvent selection in LLX can also be chosen. Next to that, LLE can be calculated based on complexation constants determined with ITC. For solvents with too strong interaction with the solute, regeneration is problematic, although stronger

interactions (i.e. complex formation based on proton transfer) resulted in a larger effect of both a swing in temperature and diluent. Thus, solvents that result in moderate values of K_D for which regeneration is expected to be more feasible should be selected.

For prediction of solvent effects in XD, a method was developed based on fast theoretical MM followed by experimental ITC. As XD is performed at elevated temperature, thermal stability of the solvent is of importance. For XD interactions between the mixture and the solvent should thus also not be too strong and in general should be even weaker than interactions applied in LLX. This is because issues with chemical or thermal stability occurred for all XD related systems in which strongly interacting complexes were formed (e.g. with TOA, whereas this solvent was perfectly applicable in LLX processes). Solvents with a positive effect on the relative volatility were successfully predicted, thereby saving time, material and money, by strongly reducing the number of time-consuming solvent screening experiments required. Another advantage is that based on the obtained fundamental understanding of solvent effects and solvent selection, MM allows for the design and development of new solvents.

In conclusion, the specifications of a good solvent, e.g. the required strength of interaction, are always related to the interaction between the mixture components and to the similarity of the mixture components. For both MM and ITC, the optimal energy values obtained are related to the interaction of the binary mixture. The more similar the mixture components, the more difficult it is to separate them as they require a stronger interaction with the solvent, which may be problematic in terms of chemical stability.

10.2 Outlook

10.2.1 Roadmap for the Dutch Chemical Industry towards 2050

The VNCI roadmap for the Dutch Chemical Industry towards 2050, describes the chemical industry and the strengths, opportunities and focus points regarding the goals of the Paris agreement¹ in the year 2050. Amongst others, the goal is to reduce greenhouse gas emissions by 80-95 %.² The use of renewable energy strongly reduces the CO₂ emissions that would be present with fossil fuel power stations. This is mainly based on solar or wind energy, not biomass.³ The change from fossil fuels to other sources of energy will, however, become more and more expensive as it will require application in processes with higher costs for transmissions, distribution and storage.⁴ Side effects of attempts to reduce emissions by making use of more sustainable raw materials and processes may include more efficient production, increased efficiency, improved product quality and decreased energy usage.

The roadmap focusses on collaboration between different industrial sectors, the financial world, research, manufacturing and government, as investments are required.^{5,6} Process economics are important for a feasible sustainable process and therefore a full life cycle of the materials and processes in industry should be included in the assessment of sustainability.^{2,6-8} Although economy is not a bad driver for green processes, as lower costs almost always imply less energy, waste and material, for true sustainability more evaluations are required, e.g. regarding toxicity and CO₂ emissions.⁷ Unfortunately, the government policy mainly focuses on current emissions and should focus more on long-term implementation programs. The government can furthermore increase the (financial) incentive for improvements by regulating the price for CO₂ or other toxic materials, supporting collaboration, improving the (energy) infrastructure and increasing the company-level benefits of emission reduction measures.^{2,6} Other measures than the mainly applied financial measures include informative measures or working on barriers that hinder investments, e.g. uncertainties, low priority, high transaction costs.⁵

The required investments are still lagging because not all non-energy benefits are taken into account, e.g. increased efficiency, productivity, safety, positive image.^{5,9} Furthermore, during the economic recession around the year 2007 production at lower capacity reduced the efficiency. This has a significant effect on the overall energy use as the chemical industry accounts for about 20 %.⁹ The estimated capital investments required before 2030 are 5 billion euro and 25 billion euro up to 2050, of which about 50 % is for the use of alternative feedstock and 3.3 billion for chemical recycling. Energy and feedstock costs themselves are expected to increase as a result of the increasing use of biomass.²

10.2.2 Opportunities for fluid separation processes

To reach the targets and successfully implement green and sustainable processes, opportunities for (fluid) separation methods are related to chemical recycling, miniaturization of equipment, renewable energy based on biomass, application of bio-based feedstock, e.g. through fermentation, transesterification, waste-to-chemical conversion, improving the energy efficiency, process intensification and enabling of separations in general.^{2,5,6,8,10} In the roadmap presented by TNO on a “Sustainable Chemical Industry”¹⁰ there is a large focus on flexible use and application of biomass as a raw material in several refinery processes with flexible production.¹⁰ For the application of biomass as a raw material, affinity based (fluid) separation processes are required, since biomass contains many thermally sensitive components and has a strongly varying composition, for which the traditional distillation sequences in the petrochemical industry are unsuitable. Another field of interest for affinity separations is the storage of energy in the form of chemical energy instead of electrical energy, e.g. in the form of methanol.⁸ When methanol is produced by reduction of CO₂, this is a good example of reducing emission and producing fuels simultaneously.⁴ As the produced methanol and other alcohols can be converted to other chemicals, separation processes are required to obtain the final products.⁸

In industry and research, there is a trend of increasing complexity in solvents from the conventional organic solvents to mixed solvents, as well as ionic liquids (ILs), deep eutectic solvents (DES), natural DES, aqueous two-phase systems (ATPS), supercritical fluids and other multicomponent solvents or renewable solvents.⁷ There is a positive trend of increasing attention for green and sustainable solvents and for the regeneration step (e.g. switchable, responsive solvents).^{7,8,11} In addition to the environmental impact of the solvent itself and its production, the application in the process also determines the sustainability and requires assessment of the impact of solvents on the process, including solvent losses and solvent removal.⁷

Process intensification for existing processes is promising, as this is already applicable on the more short term.^{7,8} Biorefining is one of the four subjects that attracted most attention within research related to sustainable technologies in the recent years,⁸ in which fluid separations can be of essence although according to Beller et al. solvent-free approaches are to be favored. On the other hand, Clarke et al.⁷ suggest that one of the formerly announced “Principles of Green Chemistry”,¹² regarding avoiding application of solvents in general, may not be valid for sustainable solvents and applications.

Thus, on the short-term the efficiency of existing processes can be improved, for which extractive distillation, in particular, may be a good candidate. On the longer term there is opportunity for new functionalities and improved quality of materials, where affinity separations may enable separations or increase efficiency. Predictive methods for application performance such as those described in this thesis and improved insight and understanding can limit the risks, time span and costs associated with the application of new techniques.⁶ Although important in all industrial fields, a complete assessment of the process is key for affinity based separation in particular, since the price in the form of energy and other losses is paid in the regeneration step. Thus, all developments of solvents and fluid separation processes should aim for moderate interactions with the solvent to allow for regeneration; with a special focus on the shift in distribution in LLX processes and the solvent stability in XD processes.

References

- (1) United-Nations. Parties to the United Nations Framework Convention on Climate Change: <https://treaties.un.org>, 2015.
- (2) Stork, M.; de Beer, J.; Lintmeijer, N.; den Ouden, B. In *Roadmap for the Dutch Chemical Industry towards 2050*; VNCI, 2018.
- (3) UN Environment. Global Trends in Renewable Energy Investment 2017: Frankfurt School-UNEP Collaborating Centre, Bloomberg New Energy Finance: capacity4dev.eu, 2017.
- (4) Chu, S.; Cui, Y.; Liu, N. *Nat Mater* 2016, *16*, 16.
- (5) Schlomann, B.; Reuter, M.; Tariq, S.; Wohlfarth, K. Energy Efficiency Trends and Policies In Industry; An analysis based on the ODYSSEE and MURE Databases, Intelligent Energy Europe Programme of the European Union; Fraunhofer ISI (Germany)2015.
- (6) Marion, P.; Bernela, B.; Piccirilli, A.; Estrine, B.; Patouillard, N.; Guilbot, J.; Jérôme, F. *Green Chem* 2017, *19*, 4973-4989.
- (7) Clarke, C. J.; Tu, W.-C.; Levers, O.; Bröhl, A.; Hallett, J. P. *Chem Rev* 2018, *118*, 747-800.
- (8) Beller, M.; Centi, G.; Sun, L. *ChemSusChem* 2017, *10*, 6-13.
- (9) Rasmussen, J. In *Industrial Efficiency 2014*; European Council For an Energy Efficient Economy, 2014.
- (10) TNO. Sustainable Chemical Industry: new materials, bio-aromatics, electrification. In *TNO Roadmaps*, 2018.
- (11) Pena-Pereira, F.; Tobiszewski, M. *The Application of Green Solvents in Separation Processes*; Pena-Pereira, F.; Tobiszewski, M., Eds.; Elsevier, 2017, pp 3-16.
- (12) Anastas, P. T.; Warner, J. C. *Green chemistry : theory and practice*; Oxford University Press: Oxford, England, 1998.

Summary

There is a continuous incentive to improve industrial processes, not only from an economic and energy point of view, but also from the increasingly important perspective of green chemistry and bio-based production. The demand for the production of chemicals based on renewable feedstock and the design for energy efficiency is therefore increasing. For diluted aqueous streams ordinary distillation would require evaporation of large amounts of water and is therefore energy intensive. Also for mixtures of components with a low relative volatility ordinary distillation is energy intensive and in the case of azeotropes this separation process may even be impossible. Furthermore, some components that are applied in industry may even decompose at elevated temperatures. In these cases, affinity separations such as liquid-liquid extraction (LLX), extractive distillation (XD) and adsorption based processes are promising alternatives, as they improve or enable the separation by adding an affinity agent.

In affinity based separation processes there is a second column, next to the initial separation column, in which the regeneration of the affinity agent takes place. This is an important step for the overall feasibility of the process. In the case of LLX and XD the solvent is (or contains) the affinity agent and is regenerated in this second column, after which the solvent is recycled to the first column. Generally there is a trade-off between the LLX or XD step and the regeneration step in terms of the required energy input and other costs.

This thesis focuses on two main subjects. The first subject is liquid-liquid extraction of polar components such as acids from dilute aqueous streams and the second main subject is the separation of close-boiling mixtures of polar components by extractive distillation. LLX is already applied in industry for separation of carboxylic acids, which are polar components that are often present in highly diluted aqueous streams. Carboxylic acids are building blocks in the production of many bio-based plastics and other chemicals in the pharmaceutical, food and chemical industry. As a consequence there is a strong desire to produce these acids through fermentation, after which they are present in (dilute) aqueous streams and separation processes are required. Also in other diluted industrial (waste) streams a variety of valuable polar components or contaminants is present for which separation processes are required. Non-aqueous streams of polar components are studied for the second main subject of this thesis. Also for these components industrial application of affinity based separation can be of interest. For example in the case of very low relative volatility or azeotrope formation, XD is a promising technique instead of ordinary distillation.

Both LLX and XD are solvent based processes. There is a widespread interest in solvent selection criteria and methods. Initial selection can be based either on practical considerations, one of the several solvent scales that have been developed, empirical data and predictions or calculations based on activity coefficients. However, prediction of solvent effects on the relative volatility or acid distribution is a challenging task, especially for the (close-boiling) polar mixtures that are central to this thesis and in which specific and strong interactions, azeotropes and non-ideality are all common. Moreover, the feasibility of the regeneration should always be taken into account, for which more research and data may be required than only the solvent effects in the initial separation step.

Ideally, solvent selection should be simple, time-efficient and include considerations on the regeneration. The development of such a procedure requires fundamental understanding of the mechanisms and phenomena involved in LLX and XD. The use of isothermal titration calorimetry (ITC), and molecular modeling (MM) to characterize mechanisms, interactions and the effect of extractant and solvent composition on liquid-liquid equilibria (LLE) and vapor-liquid equilibria (VLE) were studied in this thesis. The thesis consists of two parts that each deal with affinity separations of close-boiling polar compounds. In the first part (Chapters 4-7) the focus is on LLX of acids and other polar compounds from aqueous solutions, while the second part (Chapters 8-9) focuses on extractive distillation processes of non-aqueous polar mixtures. The methods applied (ITC and MM) are introduced in the Chapters 2 and 3.

The study on the use of ITC to analyze acid-base interactions relevant for LLX is described in Chapter 2. The concentrations applied in LLX are up to a factor thousand higher than those applied in the biotechnology field where ITC is commonly applied. As complexation constants appeared to be extractant concentration dependent, a thorough analysis of the accuracy of ITC applied in the molar concentration domain applicable to LLX, is presented. Standard deviations were determined for the calculated thermodynamic parameters. Two different reaction models, based on either a single reaction or sequential reactions were compared for their applicability in acid-base interactions in LLX. The sequential reaction model is most suitable to fit ITC-results for acid-base titration in the system of acetic acid and trioctylamine (TOA) in toluene. Fitting of the sequential reaction model was found to be sensitive to the initial values as local minima do occur as a result of the number of parameters, indicating the importance of good initial guess values. Chapter 3 describes the method and calculation options of molecular modeling with Spartan'16 Parallel software. Furthermore, it

includes a validation of the calculation levels applied and the assumptions related to molecular geometry and the incorporation of water molecules in the molecular modeling calculations.

Chapter 4 is the first chapter in the part of this thesis focusing on LLX and reviews solvent developments for LLX of carboxylic acids for three main categories of solvents, i.e. nitrogen-based extractants, phosphorous based extractants and ionic liquids. The mechanism of extraction is influenced by multiple variables, including extractant type, solvent composition and specific interactions with the diluent. Combining both active and inactive diluents was shown to be a promising approach. No single parameter can describe all solvent effects on the LLE. Based on a comparison of different regeneration strategies for a typical LLX process, a diluent-swing based process appeared to be the most feasible. For a viable process, focusing on the change in acid distribution that can be achieved between the extraction and regeneration step is more important than the absolute distribution ratio itself. For temperature-swing regeneration processes this change can be related to the enthalpy of complex formation between acid and extractant. Therefore a study on the effect of extractant structure and composition on the enthalpy of complexation (Chapter 6) can strongly contribute to design of solvents.

Chapter 5 and 6 each focus on the understanding of mechanisms involved in LLX and study implications thereof on the molecular structure of good extractants. For these studies ITC was applied - supported by MM - on various acid-base interactions directly related to LLX. Chapter 5 focuses on the role of the diluent in the extraction mechanism for complexation of acetic acid and phenol with extractants TOA, trioctylphosphine oxide (TOPO) and tributylphosphate (TBP) in various diluents. With the help of ITC it was shown that increasing the temperature decreases all complexation constants and - supported by MM - that the diluent affects the mechanism of complexation, e.g. in the case of protic diluents there is competition between the acid and diluent, whereas inactive diluents resulted in more overloading of the amine. The method of ITC was validated with LLE experiments and the equilibrium model based on ITC data can also be used to directly predict LLE. The differences between phenol and acetic acid that were observed in the LLE experiments, and expected on the basis of ITC and MM, could be described using the BF_3 -affinity scale for acetic acid and the hydrogen bond basicity pK_{BHX} scale for phenol.

The effect of molecular structure of the extractant on the enthalpy of complexation and thereby the temperature sensitivity of the complexation reaction is the focus point of Chapter 6. ITC and MM were applied to two cases, i.e. interaction of 4-cyanopyridine with (substituted) phenols and interaction of acetic acid with tertiary amines. A form of Entropy-Enthalpy-Compensation (EEC) was shown for extractants with varying side groups, which means that (small) changes in molecular structure hardly affect the complexation constant, but affect both the enthalpy and entropy of complexation. As a consequence, through optimizing the enthalpy of complexation, the temperature dependency of the equilibrium can be increased. The enthalpy of complexation itself appeared to increase with temperature, an effect that was stronger for tertiary amines with longer carbon chains compared to aminopyridines. For a typical system in LLX there is an optimum in Gibbs energy of complexation for every value of the enthalpy of complexation. Chapter 5 and 6 show that combination of ITC with MM is a strong approach to study the thermodynamics of interactions in LLX processes, by improving the understanding of the interaction mechanism and the effect of extractant structure thereon.

Swing processes for solvent regeneration in LLX processes of succinic acid based on temperature and diluent-swing were compared in the study described in Chapter 7. Diluent-swing can be performed by either adding an anti-solvent or evaporating a part of the (active) diluent. Solvents composed of trioctylamine (TOA) in methyl isobutyl ketone (MIBK) showed the largest swing in acid distribution. The application of a gaseous anti-solvent has a high potential as regeneration can be performed by reducing the pressure, although extra compressors and pumps are required. With the gaseous ethane a swing in acid distribution was obtained similar to the swing with the liquid pentane. An evaluation on required investments and energy input performed using Aspen Plus showed that the ethane-based process is the most profitable process as the energy required is only 21% (13 MW/kg pure acid product) of what would be required for evaporation of water with a four-stage evaporator. The return of the increased capital investments required for this process requires 110 days of production. Combining both diluent-swing and temperature-swing was also beneficial as it results in higher product concentrations.

In XD of close-boiling polar compounds, strong interactions or azeotropes are common and prediction of VLE data is thus not always straightforward. Chapter 8 describes the study with the aim to find heuristics for a first selection of solvents for XD, based on three different mixtures of close-boiling polar compounds, i.e. a mixture of diethylmethylaniline and diisopropylether,

a mixture of valeric acid and its isomer 2-methylbutyric acid, and a mixture of 2-butanol and 2-butanone. Solvent effects were measured for solvents selected based on e.g. acidity, structural similarity, steric hindrance, polarity and hydrogen bonding affinity. For mixtures of very similar components in terms of acidity, boiling point and structure, stronger interaction with the solvent is required, although this is limited by the chemical stability. Therefore, solvents can be initially selected based on ITC or MM. This was further implemented in Chapter 9 in which a procedure was developed for solvent screening, combining MM and ITC to predict solvent effects on the relative volatility. The interaction energies of the mixture components and solvents were calculated with MM and the heat of mixing was measured with ITC and related to the solvent effect on the relative volatility. Guidelines for desired values of these energies and heats were defined and experimentally validated based on three cases; a) a mixture of octanoic and levulinic acid, b) the amine-ether mixture of Chapter 8, and c) the alcohol-ketone mixture of Chapter 8. With this solvent selection procedure the number of solvents, for which extensive experimental screening on the basis of VLE measurements is required, is strongly reduced.

Chapter 10 concludes this thesis by evaluating and comparing the results obtained for both LLX and XD systems. Moderate interactions are favored for both processes to allow for successful solvent regeneration and to avoid chemical or thermal instability. For LLX processes, affinity agents that form stronger interacting complexes with the mixture components based on proton transfer were successfully applied, whereas this type of interaction appeared too strong for XD processes where only interactions up to the strength of hydrogen bonding could successfully be applied. In an outlook regarding the international climate goals for 2050 opportunities for affinity fluid separations are discussed and directions for further research and applications are given.

Samenvatting

Binnen de industrie is er altijd een drijfveer geweest om processen te verbeteren en dit zal ook altijd zo blijven, niet alleen vanuit een economisch of energiebesparend perspectief, maar ook vanuit het steeds belangrijker wordende perspectief van de zogeheten green chemistry, oftewel groene chemie, en productie op basis van al dan niet gerecyclede biologische grondstoffen. Hierdoor is er een groeiende vraag naar chemicaliën die geproduceerd worden op basis van gerecyclede grondstoffen en het verbeteren van processen in termen van efficiëntie. Voor processtromen die veel water bevatten vereist traditionele destillatie de verdamping van grote hoeveelheden water, zodoende is dit een energie-intensief proces. Ook voor het scheiden van mengsels met een lage relatieve vluchtigheid is traditionele destillatie energie-intensief en in het geval van azeotropen kan dit proces zelfs onmogelijk zijn. Daarnaast zijn er ook componenten die ontleden bij de verhoogde temperaturen die bij destillatie worden toegepast. In al deze gevallen zijn affiniteitsscheidingen zoals vloeistof-vloeistof extractie (LLX), extractieve destillatie (XD) en op adsorptie gebaseerde processen veelbelovende alternatieven. Bij deze processen wordt de scheiding namelijk verbeterd of zelfs mogelijk gemaakt door het toevoegen van een affiniteitsagent.

Bij scheidingsprocessen die op affiniteit gebaseerd zijn is er, naast de scheidingskolom, een tweede kolom nodig waarin de affiniteitsagent wordt geregenereerd en daarna gerecycled. Voor de totale haalbaarheid en efficiëntie van het proces is dit een belangrijke stap. Bij LLX en XD is (of bevat) het oplosmiddel de affiniteitsagent. Het oplosmiddel wordt dus geregenereerd in de tweede kolom, waarna het kan worden gerecycled naar de eerste kolom. In de meeste gevallen is er een compromis tussen de eerste scheidingsstap en de regeneratiestap in termen van de benodigde energie en andere kosten. In deze thesis ligt de focus op twee hoofdonderwerpen. Het eerste onderwerp is vloeistof-vloeistof extractie van polaire componenten, zoals zuren, vanuit waterige oplossingen van lage concentratie. Het tweede hoofdonderwerp is de scheiding van mengsels van polaire componenten met een klein verschil in kookpunt door middel van extractieve destillatie. LLX wordt in de industrie al toegepast voor scheidingen van carbonzuren, dit zijn polaire componenten die vaak in sterk verdunde processtromen voorkomen. Voor de productie van veel plastics en andere chemicaliën die op biologische grondstoffen gebaseerd zijn, zijn carbonzuren de grondstoffen die gebruikt worden in de farmaceutische, voedings- en chemische industrie. Een gevolg hiervan is dat er een grote vraag is naar de productie van deze zuren door middel van fermentatie, waarna ze in verdunde waterige stromen aanwezig zijn en scheidingsprocessen noodzakelijk zijn. Ook in andere verdunde processen en afvalstromen bevindt zich een grote verscheidenheid aan waardevolle

componenten of verontreinigingen, waarvoor scheidingsprocessen noodzakelijk zijn. Voor het tweede hoofdonderwerp van deze thesis worden niet-waterige oplossingen van polaire componenten bestudeerd. Ook voor deze componenten kan industriële toepassing van affiniteitsscheidingen interessant zijn. In plaats van traditionele destillatie, is extractieve destillatie bijvoorbeeld een veelbelovende techniek als er sprake is van een erg lage relatieve vluchtigheid of de aanwezigheid van azeotropen.

Zowel LLX als XD zijn processen op basis van een oplosmiddel. Er is vanuit de industrie een algemene grote interesse in criteria en methoden voor de keuze van een oplosmiddel. De eerste selectie kan gebaseerd worden op praktische overwegingen, op verschillende schalen die ontwikkeld zijn voor het vergelijken van oplosmiddelen, op empirische gegevens en op basis van voorspellingen of berekeningen op basis van activiteitscoëfficiënten. De voorspelling van de effecten van oplosmiddelen op de relatieve vluchtigheid of een vloeistof-vloeistof evenwicht is echter een uitdagende taak, zeker in het geval van de polaire mengsels (met een klein verschil in kookpunt) die in deze thesis centraal staan. Voor deze mengsels zijn specifieke interacties, azeotropen en niet-idealiteit gebruikelijke fenomenen die de voorspellingen compliceren. Daarnaast is het op basis van de effecten van een oplosmiddel in de initiële scheidingsstap niet altijd direct mogelijk om de haalbaarheid van de regeneratie van het oplosmiddel te bepalen. Daarvoor kan meer onderzoek en data nodig zijn.

In het ideale geval is de selectie van oplosmiddelen eenvoudig, tijdsefficiënt en worden overwegingen met betrekking tot de regeneratie meegenomen. Het ontwikkelen van een procedure hiervoor vereist een fundamenteel begrip van de mechanismen en fenomenen die betrokken zijn bij LLX en XD. In deze thesis zijn het gebruik van isotherme titratie calorimetrie (ITC) en moleculair modelleren (MM) bestudeerd, voor het karakteriseren van mechanismen, interacties en de effecten van oplosmiddelen en de samenstelling daarvan op vloeistof-vloeistof evenwichten (LLE) en gas-vloeistof evenwichten (VLE). De thesis bestaat uit twee delen die beide betrekking hebben op affiniteitsscheidingen van pare stoffen met een klein verschil in kookpunt. In het eerste deel (Hoofdstuk 4-7) ligt de focus op LLX van zuren en andere polaire componenten uit waterige oplossingen, terwijl in het tweede deel (Hoofdstuk 8-9) processen met extractieve destillatie centraal staan voor het scheiden van niet-waterige polaire mengsels. In de Hoofdstukken 2 en 3 worden de methoden die gebruikt worden (ITC en MM) geïntroduceerd.

Het gebruik van ITC om zuur-base interacties die relevant zijn voor LLX te analyseren is beschreven in Hoofdstuk 2. De concentraties die in LLX processen gebruikt worden zijn tot wel een factor duizend groter dan de concentraties die gebruikt worden binnen de biotechnologie waar ITC veelal wordt toegepast. Het is gebleken dat complexatie-constanten afhankelijk zijn van de concentratie van het oplosmiddel. Daarom is er een uitgebreide analyse gedaan van de nauwkeurigheid van ITC voor het molaire concentratiedomein dat van toepassing is op LLX. Standaard deviaties zijn bepaald voor de gemeten en berekende thermodynamische parameters. Twee verschillende reactiemodellen, gebaseerd op ofwel een enkele reactie of een reeks opeenvolgende reacties, zijn vergeleken op basis van de toepassing in zuur-base interacties voor LLX. Het model op basis van een reeks opeenvolgende reacties is het meest geschikt om de ITC resultaten te fitten voor zuur-base titratie in het systeem van azijnzuur en trioctylamine (TOA) in toluen. Het fitten van dit model bleek gevoelig voor de initiële waarden die gebruikt worden, aangezien lokale minima gevonden kunnen worden als gevolg van het aantal gefitte parameters. Dit benadrukt het belang van goede initiële waarden. Hoofdstuk 3 beschrijft de methode en de opties voor berekeningen op basis van moleculair modelleren met Spartan'16 Parallel software. Daarnaast bevat dit hoofdstuk de validatie voor de gebruikte methoden en vergelijkingen bij het modelleren. Ook worden de aannames beschreven met betrekking tot de moleculaire geometrie en het al dan niet gebruiken van watermoleculen in de berekeningen.

Hoofdstuk 4 is het eerste hoofdstuk in het deel van deze thesis dat focust op LLX en biedt een overzicht van de ontwikkelingen op het gebied van oplosmiddelen voor LLX van carbonzuren voor drie categorieën oplosmiddelen, te weten de oplosmiddelen op basis van stikstof, oplosmiddelen op basis van fosfor en ionische vloeistoffen (IL). Het extractiemechanisme wordt door meerdere factoren beïnvloed, waaronder het type oplosmiddel, de samenstelling van het oplosmiddel en specifieke interacties met een eventueel verdunningsmiddel in het oplosmiddel. Het is aangetoond dat het combineren van zowel actieve als inactieve verdunningsmiddelen in het oplosmiddel een veelbelovende aanpak is. Er is geen parameter die, zonder toevoeging van andere parameters en factoren, alle effecten van oplosmiddelen op LLE kan beschrijven. Op basis van een vergelijking van verschillende regeneratiemethoden voor een typisch LLX proces, is gebleken dat een proces op basis van een verandering, oftewel swing, in verdunningsmiddel het meeste potentie heeft. Voor een rendabel proces is het belangrijker te focussen op de verandering in de zuurverdeling bij het LLE die behaald kan worden tussen de extractie- en regeneratiestap, dan op de absolute zuurverdeling die behaald kan worden. Voor regeneratieprocessen op basis van een swing in temperatuur kan deze

afname van de zuurverdeling worden gerelateerd aan de enthalpie van de complexvorming tussen het zuur en het oplosmiddel. Om deze reden kan een studie naar het effect van de molecuulstructuur en de samenstelling van het oplosmiddel op de complexatie-enthalpie (Hoofdstuk 6) sterk bijdragen aan de ontwikkeling van nieuwe oplosmiddelen.

Hoofdstuk 5 en 6 focussen beide op het begrip van de mechanismen die betrokken zijn bij LLX en bestuderen de gevolgen daarvan voor de molecuulstructuur van geschikte oplosmiddelen. Voor deze studies is ITC toegepast – ondersteund door MM – voor het analyseren van verschillende zuur-base interacties die direct gerelateerd zijn aan LLX. Hoofdstuk 5 draait om de rol van het verdunningsmiddel in het extractiemechanisme voor de complexatie van azijnzuur en phenol met de oplosmiddelen TOA, trioctylphosphine oxide (TOPO) en tributylphosfaat (TBP) in verschillende verdunningsmiddelen. Door middel van ITC is aangetoond dat het verhogen van de temperatuur alle complexatie-constanten verlaagt en – ondersteund door MM – dat het verdunningsmiddel het mechanisme van de complexatie beïnvloedt, bijv. in het geval van protische verdunningsmiddelen is er competitie tussen het zuur en het verdunningsmiddel, terwijl inactieve verdunningsmiddelen zorgen voor het overladen van amine. De methode op basis van ITC is gevalideerd door middel van LLE experimenten en er is aangetoond dat een evenwichtsmodel op basis van ITC data gebruikt kan worden om LLE direct te voorspellen. De verschillen tussen phenol en azijnzuur die aan het licht kwamen in LLE experimenten en ook verwacht waren op basis van ITC en MM, konden worden beschreven door middel van de BF_3 -affiniteitsschaal voor azijnzuur en de waterstofbrug basiciteit pK_{BHX} - schaal voor phenol.

Het effect van de molecuulstructuur van het oplosmiddel op de complexatie-enthalpie en daarmee op de temperatuursgevoeligheid van de complexatiereactie is waar het in Hoofdstuk 6 om draait. ITC en MM zijn hiervoor toegepast op twee cases, namelijk de interactie van 4-cyanopyridine met (gesubstitueerde) fenolen en interactie van azijnzuur met tertiaire amines. Er is een vorm van Entropie-Enthalpie-Compensatie (EEC) aangetoond voor oplosmiddelen met variaties in zijgroepen. Dat betekent dat (kleine) veranderingen in de molecuulstructuur de complexatie-constante nauwelijks beïnvloeden, terwijl er wel een effect is op de enthalpie en entropie van de complexatie. Een gevolg hiervan is dat de temperatuursafhankelijkheid van het evenwicht kan worden vergroot door de complexatie-enthalpie te maximaliseren. De complexatie-enthalpie zelf bleek toe te nemen bij verhoogde temperatuur en dit effect was sterker voor de tertiaire amines met lange koolstofketens in vergelijking met de aminopyridines. Voor een

typisch systeem in LLX processen is er een optimale Gibbs complexatie-energie voor elke waarde van de complexatie-enthalpie. Hoofdstuk 5 en 6 laten zien dat het combineren van ITC en MM een sterke aanpak is voor het bestuderen van de thermodynamica van interacties in LLX processen, door het begrip te vergroten van het interactie-mechanisme zelf en de effecten die de structuren van de oplosmiddelen daarop hebben.

In de studie die beschreven is in Hoofdstuk 7 worden swingprocessen voor het regenereren van oplosmiddelen in LLX processen van barnsteenzuur vergeleken. Deze processen zijn gebaseerd op een swing in temperatuur of in verdunningsmiddel. Een swing in verdunningsmiddel kan uitgevoerd worden door ofwel een anti-oplosmiddel toe te voegen, ofwel een deel van het (actieve) verdunningsmiddel te verdampen. Oplosmiddelen die bestaan uit trioctylamine (TOA) in methyl isobutylketon (MIBK) lieten de grootste verandering in zuurverdeling zien. Het toepassen van een gas als anti-oplosmiddel heeft grote potentie aangezien het regenereren in dit geval uitgevoerd kan worden door de druk te verlagen. Wel zijn er in dit proces extra compressoren en pompen noodzakelijk. Met het gas ethaan kon een verandering in zuurverdeling behaald worden die vergelijkbaar is met het gebruiken van de vloeistof pentaan als anti-oplosmiddel. Met Aspen Plus is een evaluatie van de benodigde investeringen en energie-input uitgevoerd, waarin werd getoond dat het proces op basis van ethaan het meest rendabel is omdat de benodigde energie voor dit proces slechts 21% (13 MW/kg puur zuur product) is van wat benodigd zou zijn voor het verdampen van water in een vier-traps verdamper. Voor het terugverdienen van de verhoogde kapitaalinvesteringen voor dit proces zijn 110 dagen productie benodigd. Het bleek ook gunstig zowel een swing in verdunningsmiddel als temperatuur toe te passen, aangezien hierdoor hogere product-concentraties behaald kunnen worden.

Bij XD van polaire componenten met een klein verschil in kookpunt zijn sterke interacties of azeotropen veelvoorkomende aspecten en is het voorspellen van VLE data daardoor niet altijd eenvoudig. In Hoofdstuk 8 wordt de studie beschreven naar een methode en vuistregels voor het maken van een eerste selectie van oplosmiddelen voor XD. Deze studie is uitgevoerd op basis van drie verschillende mengsels van polaire componenten met een klein verschil in kookpunt, namelijk een mengsel van diethylmethyleenamine en diisopropylether, een mengsel van pentaanzuur en het isomeer 2-methylbutaanzuur, en een mengsel van 2-butanol en 2-butanon. De effecten van oplosmiddelen zijn gemeten voor oplosmiddelen die geselecteerd zijn op basis van bijv. zuurgraad, vergelijkbaarheid van structuur, sterische hinder, polariteit en affiniteit voor het vormen van waterstofbruggen.

Sterkere interacties met het oplosmiddel zijn nodig voor mengsels van erg vergelijkbare componenten in termen van zuurgraad, kookpunt en structuur. De sterkere interacties zijn echter gelimiteerd door de chemische stabiliteit en daarom kunnen oplosmiddelen eerst geselecteerd worden op basis van ITC of MM. Dit is verder geïmplementeerd in Hoofdstuk 9, waarin een procedure is ontwikkeld voor de initiële selectie van oplosmiddelen. Voor deze procedure worden MM en ITC gecombineerd voor het voorspellen van de effecten van oplosmiddelen op de relatieve vluchtigheid van een mengsel. De interactie-energieën van de componenten van het mengsel en de oplosmiddelen zijn berekend met MM en met ITC is de mengwarmte gemeten en gerelateerd aan de effecten van de oplosmiddelen op de relatieve vluchtigheid. Er zijn richtlijnen gedefinieerd voor gewenste waarden van deze energieën en gemeten warmte, welke gevalideerd zijn op basis van drie experimentele cases. Deze cases zijn a) een mengsel van octaanzuur en levulinezuur, b) het amine-ether mengsel van Hoofdstuk 8, en c) het alcohol-keton mengsel van Hoofdstuk 8. Met deze procedure voor het selecteren van oplosmiddelen wordt het aantal oplosmiddelen waarvoor extensieve experimentele VLE metingen nodig zijn sterk gereduceerd.

Hoofdstuk 10 is het afsluitende hoofdstuk van deze thesis, waarin de resultaten voor systemen op basis van zowel LLX als XD geëvalueerd en vergeleken worden. Gematigd sterke interacties zijn gunstig voor beide typen processen wanneer gekeken wordt naar de regeneratie van de oplosmiddelen en het vermijden van chemische en thermische instabiliteit. Affiniteitsagenten die complexen vormen op basis van sterkere interacties met de componenten van de mengsels, bijvoorbeeld op basis van protonen-overdracht, zijn succesvol toegepast voor LLX processen. Daartegenover staat dat dit type interactie te sterk is gebleken voor XD processen, waarbij alleen interacties met een maximale sterkte van waterstofbrugvorming succesvol konden worden toegepast. Als laatste worden de kansen en potentiële toepassingen van vloeistofscheidingen op basis van affiniteit bediscussieerd in een vooruitblik met betrekking tot de internationale klimaatdoelen voor 2050, waarbij ook suggesties voor verder onderzoek en verdere implementatie zijn gegeven.

Abbreviations

2MBA	2-methylbutyric acid
2MDDAP	2-methyl-didodecylamine
2-BuO	2-butanone
2-BuOH	2-butanol
3G	three primitive Gaussian type orbitals
2-BrPhOH	2-bromophenol
3-BrPhOH	3-bromophenol
5-m-2-one	5-methyl-2-hexanone
Alamine 336	mixture of tertiary amines with C ₈ -C ₁₀ carbon chains
Aliquat 336	<i>N</i> -methyl- <i>N,N,N</i> -trioctylammonium chloride, a quaternary ammonium salt
ATPS	aqueous two phase system
BF ₃ -affinity	BF ₃ -affinity scale for extractant strength based on enthalpy of complexation with BF ₃ (kJ/mol)
BP	boiling point
CCl ₄	carbon tetrachloride
Cit	citric acid
CAMD	computer aided molecular design
CF	concentration factor
C-PCM	conductor like polarizable continuum model
COSMO-RS	conductor like screening model for real solvents
Cyanex 923	commercial mixture of four trialkylphosphine oxides based on C ₆ and C ₈ carbon chains
DBA	dibutylamine
DBE	dibutylether
DCM	dichloromethane
DDAP	<i>N,N</i> -didodecyl-4-amine pyridine
DEG	diethylene glycol
DEGDBE	diethylene glycol dibutylether
DEMA	diethylmethyl amine
DES	deep eutectic solvent
DFT	density functional theory
Diglyme	diethylene glycol dimethyl ether
DIPE	diisopropyl ether
DLS	dynamic light scattering
DMSO	dimethylsulfoxide
DOAP	dioctylamine pyridine

DPMDAP	diphenyl (mono)-dodecylamine pyridine
DPPA	diphenyl amine pyridine
DPA	dipropylamine
EEC	enthalpy-entropy compensation
EG	ethylene glycol
EtLev	ethyl levulinate
EU	European Union
F	feed
FDCA	2,5-furandicarboxylic acid
FID	flame ionization detector
FTIR	fourier-transform infrared
GC, GC-MS	gas chromatography (Mass - Spectrometry)
HAc	acetic acid
HBu	butyric acid
HexD	hexadecane
HF	Hartree-Fock
HLa	lactic acid
HLev	levulinic acid
HOct	octanoic acid
HSuc	succinic acid
HVal	valeric acid
IL	ionic liquid
IL-101	trihexyl tetradecyl phosphonium chloride, [P _{666,14}][Cl]
IL-104	trihexyl(tetradecyl)phosphonium di-2,4,4-trimethylpentyl phosphinate [P _{666,14}][Phos]
IR	infrared
isoHVal	isovaleric acid
ITC	isothermal titration calorimetry
LLE	liquid-liquid equilibrium
LLX	liquid-liquid extraction
LSER	linear solvation energy relationship
MeLev	methyl levulinate
MeMeBu	methyl-2-methyl-butyrate
MeOct	methyl octanoate
MIBK	methyl isobutyl ketone
MM	molecular modeling

MMFF	Merck molecular force field
MOAP	(mono)-octyl amine pyridine
MP	Møller-Plesset
NMR	nuclear magnetic resonance
nonyl-PhOH	4-nonylphenol
NRTL	non-random two liquid model
OctOct	octyl octanoate
PG	propylene glycol
PhOH	phenol
Proton Sponge ®	1,8-bis(dimethylamino)naphthalene
PEF	polyethylene furanoate
PET	polyethylene terephthalate
PhOH	phenol
Phos	phosphinate (di-2,4,4-trimethylpentyl phosphinate)
P _{666,14}	trihexyl(tetradecyl)phosphonium
pK _{BHX}	hydrogen bond basicity scale for based on the equilibrium complexation constant of complexation with 4-fluorophenol (-)
RID	refractive index detector
RSH - GGA	range separated hybrid generalized gradient approximation
S	solvent
SAXS	small-angle x-ray scattering
STO	slater type orbitals
TBA	tributylamine
TBP	tributylphosphate
TBPO	tributylphosphine oxide
TBzA	tribenzylamine
TDDA	tridodecylamine
TEA	triethylamine
THA	trihexylamine
TMA	trimethylamine
TMS	trimethylsilane
TNO	Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek (Netherlands Organisation for applied scientific research)

TOA or Alamine 336	trioctylamine
TOPO	trioctylphosphine oxide
TPA	tripropylamine
UNIFAC	universal (quasi-chemical) functional-group activity coefficients
VLE	vapor-liquid equilibrium
VNCI	Koninklijke Vereniging van de Nederlandse Chemische Industrie (Royal Association of the Dutch Chemical Industry)
XD	extractive distillation

Nomenclature/Symbols

Symbol	explanation	Unit
α	Kamlet-Taft hydrogen bond donor parameter	(-)
α	relative volatility	(-)
a, b and s	LSER fit parameters	(-)
AN	acceptor number	(-)
A, HA	acid	(-)
A^-	deprotonated anion of acid	(-)
A, B	feed components	(-)
A, B	titrant molecule and sample molecule in ITC-experiment	(-)
A_{tot}	acid including all forms (e.g. dissociated and complexed)	(-)
$[A]$	concentration of A in aqueous phase	(M)
$\overline{A}$	acid in organic phase	(-)
$[\overline{A}]$	concentration of A in organic phase	(M)
$[A]_{\text{syr}}$	concentration of titrant A in syringe (ITC-experiment)	(M)
$[A]_{\text{tot, final}}$	final concentration of titrant A in cell (ITC-experiment)	(M)
A_{ij}, B_{ij}, C_{ij}	parameters of NRTL model	-
$([A]_{\text{tot}}/[B]_{\text{tot}})_{\text{final}}$	final ratio of $[A]_{\text{tot}}$ and $[B]_{\text{tot}}$ after ITC experiment	(-)
$A_n B_m$	(n,m)-acid-base complex	(-)
B	base	(-)
β	Kamlet-Taft hydrogen bond acceptor parameter	(-)
$[B]_0$	initial concentration of sample component in cell (ITC-experiment)	(M)
$[B]_{\text{tot, final}}$	final concentration of sample component in cell (ITC-experiment)	(M)
c, e, s, a, b and v	Abraham's solvent coefficients	(-)
$c_{\text{a,org}}, c_{\text{org}}$	concentration (of a) in solvent phase	(M)
$c_{\text{a,aq}}, c_{\text{aq}}$	concentration (of a) in raffinate phase	(M)
c_0	initial concentration	(M)
c	Wisemen c-value	(-)
δ	Hildebrand's solubility parameter	(MPa ^{1/2})

DN	donor number	(kJ/mol)
δ_p	Hansen parameter	(MPa ^{1/2})
DP and DP*	Schmidt's parameters	(-)
ϵ	dielectric constant	(-)
E	flow of extract-phase in back-extraction	(L/s)
E	extraction factor, defined as $E = K_D^* S'/F'$	(-)
E, S, A, B and V	Abraham's solute parameters	(-)
$E_{\text{product}}/$ $E_{\text{evaporation}}$	energy required for the process expressed as fraction of energy for evaporation	(-)
$E_T(30)$	Dimroth-Reichardt parameter	(kJ/mol) or (kcal/mol)
F	feed flow	(L/s)
$\Delta G, \Delta G_{n,m}$	Gibbs energy change of a reaction, of (n,m)-complexation	(kJ/mol)
$\Delta H, \Delta H_{n,m}$	enthalpy change of a reaction, of (n,m)-complexation	(kJ/mol)
H^+	proton	(-)
HA	acid	(-)
[HA]	concentration of acid	(M)
$[\overline{HA}]$	concentration of acid in organic phase	(M)
$(HA)_n B_m$	(n,m)-acid-base complex	(-)
K_a	acid-dissociation constant	(-)
pK_a	acidity	(-)
$pK_{a,n}$	pK_a of n-th acid group	(-)
$K_{a,BS}$	biphasic equilibrium constant of relative basicity of extractant with respect to solute	(-)
$pK_{a,BS}$	relative basicity of extractant with respect to solute	(-)
pK_b	basicity	(-)
pK_{BHX}	hydrogen bond basicity	(-)
K	equilibrium constant	(-)
K^0	equilibrium constant of reference (diluent)	(-)
K_c, K_E	complexation constant	(M ^{-(n+m-1)})
$K_{D,a}, K_D$	distribution coefficient of a	(M/M), (-)
K'_D	distribution coefficient in backward extraction step	(-)

K_D/K'_D	ratio of distribution coefficients in forward and back-extraction	(-)
K_m	physical extraction constant	(-)
$K_{n,m}$	(n,m)-complexation constant	(M ^{-(n+m-1)})
μ	dipole moment	(D)
m	number of basis in acid-base complex	(-)
n	number of acids in acid-base complex, or, in case of sequential binding, number of sequentially binding acids to a (1,1)-complex	(-)
n_{base}	moles of sample molecule (base) in ITC-experiment	(mol)
n_{inj}	number of injections in ITC-experiment	(-)
(n,m)-complex	complex with n acid molecules and m base molecules	(-)
P_i^{sat}	saturated vapor pressure of a component	(Pa)
$\log P$	solvent-water partitioning	(-)
$\log P_{O/W}$	octanol-water partitioning	(-)
π^*	Kamlet-Taft polarizability parameter	(-)
Q	heat of mixing	(kJ/mol)
Q_{tot}	total heat released (in ITC-experiment)	(kJ/mol)
Q_{inj}	heat of injection	(kJ/mol)
R	gas constant, 8.314	(J/mol/K)
R_m	final ratio of concentrations of titrant and sample components after ITC-experiment	(-)
R_3N	tertiary amine with R representing the alkyl groups	(-)
ρ	density	(g/mL)
S, S_a	selectivity of extractant towards a	(-)
S	solvent flow	(L/s)
S	solvent	(-)
S_s	concentration of solute in organic solvent	(M)
S_w	concentration of solute in water	(M)
$\Delta S, \Delta S_{n,m}$	entropy change of reaction, of (n,m)-complexation	(J/mol/K)
$S/F, S/F\text{-ratio}$	solvent-to-feed ratio	(-)
$(S/F)_{min}$	minimum solvent-to-feed ratio	(-)
σ	standard deviation	(-)

TOAHA (TOA•HA)	complex of TOA and acid	(-)
T	temperature	(°C)
T _b , T _{boil}	boiling point	(°C)
T _m	melting point	(°C)
V _{init}	initial volume (ITC-experiment)	(mL)
V _{inj}	injection volume (ITC-experiment)	(μL)
V _{tot}	total sample volume (ITC-experiment)	(mL)
W	flow of wash-phase in back-extraction	(L/s)
(W/E) _{min}	minimum wash over extract ratio	(-)
X _{in}	acid fraction in feed of forward extraction step	(-)
X _{out}	acid fraction in raffinate	(-)
x	intermolecular distance	(Å, Ångström)
x _i	liquid phase mole fraction of i	(-)
y _i	vapor phase mole fraction of i	(-)
y _{in}	initial concentration of acid in extract	(M)
y _{out}	remaining concentration of acid in extract after back-extraction	(M)
Y _{out,max}	maximum concentration of acid in extract, based on K _D	(-)
Y _{in}	initial acid fraction in solvent phase	(-)
Y	property that is specific to compound and proportional to Gibbs energy	(-)
Y ⁰	property in hypothetical solvent with zero values for α , β and π^*	(-)
Z	extractant loading	(-)
Z-parameter	Kosower's Z-parameter	(kJ/mol)

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About the author

Lisette Sprakel was born on the 12th of March 1990 in Apeldoorn, The Netherlands. After growing up in Vaassen and Hengelo where she graduated from high school S.G. De Grundel in 2008, she moved to Enschede for her studies in Chemical Process Engineering at the University of Twente. She was active in many committees during the course of her studies and was also a board member of the study association for Chemical Engineering C.T.S.G. Alembic in the function of educational affairs officer. The research of her bachelor's assignment "The effect of light on the photocatalytic activity", was conducted in the Photocatalytic Synthesis Group of prof. dr. Guido Mul. During the course of her master's studies at the same university she participated in the study tour to Dubai and Vietnam and spent four months at AkzoNobel in Frankfurt-am-Main (Germany) for her internship. In 2014 she finalized her Master's by graduating on the subject of "Non-Newtonian flow on bubble mattresses" in the group of prof. dr. ir. Rob Lammertink. From 2015 she was working as a PhD-student on "Affinity Separations" in the Sustainable Process Technology Group of prof. dr. Sascha Kersten under supervision dr. ir. Boelo Schuur. The project is part of the ISPT cluster "Energy Efficient Bulk Liquid Separation". The aim of the project is the development of liquid-liquid extractions and extractive distillations as alternatives for traditional distillations. A part of the results of this work are presented in this thesis. In her free time Lisette is an enthusiastic musician, she played and plays the saxophone in various ensembles and orchestras. Next to that, she loves to put her energy into different kinds of sports, from running (preferably in a different city or country every weekend), cycling, swimming and walking to kickboxing.

Publication list

Peer-reviewed journals

L.M.J. Sprakel, B. Schuur, Solvent developments for liquid-liquid extraction of carboxylic acids in perspective, *Separation & Purification Technology*, 2019, 211, 935-957

L.M.J. Sprakel, B. Schuur, Improving understanding of solvent effects on intermolecular interactions in reactive liquid-liquid extraction with isothermal titration calorimetry and Molecular Modeling, *Journal of Industrial Engineering Chemistry*, 2019, 72, 364-373

L.M.J. Sprakel, B. Schuur, Molecular design and engineering for affinity separation processes using isothermal titration calorimetry (ITC) and molecular modeling (MM), *Journal of Molecular Liquids*, 2019, 283, 312-324

L.M.J. Sprakel, B. Schuur, Thermal activity in affinity separation techniques such as liquid-liquid extraction analyzed by isothermal titration calorimetry (ITC) and accuracy analysis of the technique in the molar concentration domain, *Industrial Engineering Chemistry and Research*, 2018, 57, 12574-12582

L.M.J. Sprakel, P. Kamphuis, A.L. Nikolova, B. Schuur, Development of extractive distillation processes for close-boiling systems, *Chemical Engineering Transactions*, 2018, 69, 529-534

L.M.J. Sprakel, P. Kamphuis, A.L. Nikolova, D.J. Keijsper, B. Schuur, Solvent selection for extractive distillation processes to separate close-boiling polar systems, *Chemical Engineering Research and Design*, 2019, 144, 123-134

L.M.J. Sprakel, A.F.M. Holtkamp, R. Bassa, B. Schuur, Swing processes for solvent regeneration in liquid-liquid extraction of succinic acid, *submitted to a peer-reviewed journal*

L.M.J. Sprakel, D.J. Keijsper, A.L. Nikolova, B. Schuur, Predicting solvent effects on relative volatility behavior in extractive distillation using isothermal titration calorimetry (ITC) and molecular modeling (MM), *submitted to a peer-reviewed journal*

B. Schuur*, T. Brouwer, D. Smink, **L.M.J. Sprakel**, Green solvents for sustainable separation processes, *Current Opinion in Green and Sustainable Chemistry*, 2019, 18, 57-65

E. Reyhanitash, E. Fufachev, K. D. van Munster, M.B.M. van Beek, **L.M.J. Sprakel**, C.N. Edeliijn, B.M. Weckhuysen, S.R.A. Kersten, P. Bruijninx, B. Schuur, Recovery and conversion of acetic acid from a phosphonium phosphinate ionic liquid to enable valorization of fermented wastewater, *accepted for publication in Green Chemistry*, 2019

Conference contributions

L.M.J. Sprakel, B. Schuur, Solvent design for liquid-liquid extraction of acids studied by ITC and molecular modelling, *Chains 2018*, Eindhoven, The Netherlands

L.M.J. Sprakel, B. Schuur, Extractive distillation processes for close-boiling systems, *11th International Conference on Distillation & Absorption 2018*, Florence, Italy

L.M.J. Sprakel, B. Schuur, Solvent design for separation processes of acids using ITC and molecular modeling, *The Netherlands Process Technology Symposium 2018*, Enschede, The Netherlands

L.M.J. Sprakel, B. Schuur Solvent design for liquid-liquid extraction of acids studied by isothermal titration calorimetry (ITC) and molecular modelling, *Jahrestreffen der ProcessNet Fachgruppen Extraktion und Rohstoffe* (2018), Frankfurt-am-Main, Germany

L.M.J. Sprakel, B. Schuur, Affinity based liquid-liquid extraction of carboxylic acids analyzed by isothermal titration calorimetry, *Fachausschuss Extraktion 2017*, Cologne, Germany

L.M.J. Sprakel, S.R.A. Kersten, B. Schuur, Thermodynamics of liquid-liquid extraction of acids studied with ITC, *4rd International Conference on Methods and Materials for Separation Processes "Separation Science - Theory and Practice 2016"*, Brunow, Poland

Other publications

T.J. Hilbers, **L.M.J. Sprakel**, L.B.J. van den Enk, B. Zaalberg, H. van den Berg, A.G.J. van der Ham, Green diesel from hydrotreated vegetable oil process design study. *Chem. Eng. Technol.*, 2015, 38: 651-657.

A.S. Haase, J.A. Wood, **L.M.J. Sprakel**, and R.G.H. Lammertink, Inelastic non-Newtonian flow over heterogeneously slippery surfaces. *Phys. Rev. E.*, 2017. 95: 023105.