Analysis and optimization of enantioselective extraction in a multi-product environment with a multistage equilibrium model

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Abstract

Based on a single stage model and experimental results for enantioselective extraction of amino acids and amino alcohols, simulations are carried out for a fractional extractor using a multistage equilibrium model. A higher pH, lower temperature, higher concentrations and a higher excess of extractant all result in higher purities in both product streams, but a higher wash stream is required to realise good yield and good purity. The improved purity can be explained from a higher operational selectivity in the single stage, from lower variation of the extraction factors along the extractor, or from a combination of these effects. Application of “reflux” results in higher product purities at a lower wash stream requirement, but a lower process capacity. It was shown that various combinations of process conditions result in the desired product specifications (99% yield and 98% enantiomeric excess for both extract and raffinate). This leads to optimization possibilities in a multi-product environment: the more stages available above the minimum number for a specific compound, the larger the process capacity for that compound. All systems for which a single stage selectivity of 1.5 was obtained can be separated in a multi-product extractor containing 50 stages, evenly distributed over the wash and strip section.

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1. Introduction

In the pharmaceutical and fine chemical industry, chirality and chiral compounds play an important role as intermediates and end products. To obtain optically pure substances, chiral separation is often the most cost-effective choice. The common chiral separation methods suffer from either a low versatility (crystallization-based methods) or they are unsuitable for commercial production scale (analytical separations). Fractional reactive extraction (FREX) is a promising alternative to existing methods, as it is both versatile and suitable for application at large scale. In this technique an enantioselective extractant is employed as separating agent (Fig. 1a) in the fractional extraction scheme (Fig. 1b). A versatile and highly enantioselective extractant should be employed. The wash stream in the fractional extraction scheme serves to wash the less strongly bonded enantiomer from the extract. Thus it is possible to recover each of the two enantiomers at the desired purity [1].

So far, (fractional) reactive extraction has been studied by a number of authors for chiral separation of amino acids [2–7] and occasionally for other enantiomer classes [8–12]; the focus has mostly been on synthesis of new chiral selectors, obtaining high selectivity in the single stage and on design of dedicated small-scale equipment. In literature, translation of lab-scale knowledge on FREX into industrial practice or into a general design method has been very scarce. In our previous papers, we have discussed a general method to identify versatile enantioselective extractants and we applied this method to develop an azophenolic crown ether as a versatile, i.e. multi-product, and highly selective extractant for various amines and amino alcohols [13]. The single-stage extraction equilibria including back-extraction were investi-
gated [14] as well as the kinetics of the complexation reactions [15].

As a next step towards industrial implementation of FREX, it is the aim of this paper to study which combinations of process and product parameters generate a specified yield and product purity in a multistage extractor. This will be studied for conditions that are ‘economical’ i.e. low inventory of solvent and extractant, high volumetric capacity, low dilution of product enantiomers, etc., and especially for a multi-product environment. To reach this goal, a multi-stage equilibrium model will be constructed based on the existing single stage description comprising the chemical and physical equilibria of the system. Simulations will be done to study the effect of process parameters. In order to understand the deviations from Kremser-like shortcut model predictions of this system, the role of the local operational selectivity and local extraction factors is discussed. Finally, the consequences for the design of a multi-product extractor will be discussed qualitatively.

2. Theory

2.1. Chemistry of the single extraction stage

In our previous work, an azophenolic crown ether was identified as a versatile enantioselective extractant for separation of several amino-alcohols and amines. From the set of target enantiomers, two substances were selected for the present modelling study: phenylethylamine and phenylglycinol. These compounds differ in complexation strength with the crown ether \( K_R \) and \( K_S \), in intrinsic selectivity \( (K_R/K_S) \) and in physical partitioning \( P \). The relevant parameters are presented in Table 1.

The influence of various process parameters on the operational selectivity and distribution ratios in a single stage was studied experimentally for this extractant and a predictive single stage equilibrium model was constructed and validated [14]. This model solves the main physical and chemical equilibria in the system simultaneously:

- Acid–base equilibrium of the amines/amo-no-alcohols in the aqueous phase.
- Physical partitioning of neutral amines/amo-no-alcohols between organic and aqueous phase.
- Enantioselective complexation of amine/amo-no-alcohols with the enantioselective extractant, the crown ether.

The main parameters in this model are the chemical properties of the system (complexation constants \( K_R \) and \( K_S \), physical partitioning ratio \( P \) and acid–base dissociation constant \( pK_A \)) and the process conditions (temperature, pH, concentrations of extractant \([C]\) and racemic mixture \([\text{rac}]\) and phase ratio \( \Phi \)). The enantiomer that complexes the most strongly with the crown ether has the largest distribution ratio and is recovered from the extract, whereas the raffinate will contain primarily the less strongly complexed enantiomer. The extent of extraction is characterised by the distribution ratios \( D_R \) and \( D_S \) for each enantiomer:

\[
D_R = \frac{[R]_{\text{org,allforms}}}{[R]_{\text{aq,allforms}}} = \frac{[R]_{\text{org}} + [RC]_{\text{org}}}{[R]_{\text{aq}} + [HR^+]_{\text{aq}}}
\]  

Table 1

<table>
<thead>
<tr>
<th>Phenylglycinol (PG)</th>
<th>Phenylethylamine (PEA)</th>
<th>Crown ether extractant</th>
</tr>
</thead>
</table>
| \( K_R = 12000 \text{ (m}^3/\text{kmol)} \) | \( K_R = 330 \text{ (m}^3/\text{kmol)} \) | |}
| \( K_S = 1200 \text{ (m}^3/\text{kmol)} \) | \( K_S = 900 \text{ (m}^3/\text{kmol)} \) | |}
| \( P = 0.1 (\text{–}) \) | \( P = 4 (\text{–}) \) | |}
| \( pK_A = 8.5 \) | \( pK_A = 9.4 \) | |}

Experimentally obtained partitioning ratios and complexation constants with crown ether in toluene at \( T = 25 \degree \text{C} \).
The distribution ratios are a complex function of all process parameters. A larger $D$ is caused by larger $K_R, K_S$, pH, $[C]$, $P$ and (usually) lower $T$. Especially the pH and $[C]$ influence the $D$s. The distribution ratios may range from $<<1$ to $>>1$.

- The selectivity is mainly determined by $[C]$ and $K_R$ and $K_S$. $\alpha_{op}$ ranges from 1 to $\alpha_{int}$. $\alpha_{int}$ can be approached closely if $K_R\cdot [C] >> 10$. The temperature influences the intrinsic selectivity (and the magnitude of $K_R$ and $K_S$); the other parameters such as enantiomer concentration and pH have a small influence on the operational selectivity.

2.2. From single stage to fractional extraction scheme

In fractional extraction equipment, additional degrees of freedom are the solvent-to-feed ratio ($S/F$), the wash flow (as $W/F$ or $W/S$), the number of stages and the location of the feed stage. To evaluate the extractor design, the important aspects are the purity and yield of the product enantiomers in their respective exit streams, the dilution of these product enantiomers and the inventory of solvent and (expensive) selector. Thus, it is necessary to study a flowsheet containing both the fractional extractor and the product recovery section (forward extraction and back-extraction).

As measure for optical purity of the raffinate and the extract, the enantiomeric excess (e.e.) is used [16]. The definition of e.e. depends on which enantiomer dominates; e.e. > 0 (Eq. (5)). Note that ‘$R$’ and ‘$S$’ encompass $R$ and $S$ in all forms (free, dissociated and complexed, so $R, HR^+, R^+, RC, RC^+$, etc.) in this equation.

\[
e.e. = \frac{[R] - [S]}{[R] + [S]} \quad \text{or} \quad e.e. = \frac{[S] - [R]}{[S] + [R]} \quad (5)
\]

The yield of the enantiomer $R$ in the extract is given in Eq. (6). Similarly, the yield of each enantiomer in each stream is defined.

\[
yield_{R, \text{EXTRACT}} = \frac{\text{total } R \text{ extract [mol]}}{\text{total } R \text{ feed [mol]}} \quad (6)
\]

The yields and e.e.s in extract and raffinate are coupled by the mass balance, with two degrees of freedom in steady-state operation. As a result, even if one of the two enantiomers is much less valuable than the other one, the optical purity of both enantiomers should be high in their appropriate exit streams, to ensure a good yield of the desired enantiomer.

2.3. Role of extraction factor

From short-cut calculations based on the Kremser equation [17], it is clear that the operational selectivity in one stage mainly determines the required number of stages for a certain product purity: the larger the selectivity, the lower the stages requirement. The capacity of extraction (expressed as distribution ratio) influences the required solvent-to-feed ratio and wash-to-feed ratio, and thus the productivity. This effect is reflected in the extraction factors. In a fractional extractor, the extraction factors in the wash section are defined by (for enantiomer ‘$R$’ and ‘$S$’):

\[
E_R = \frac{D_R S}{W} \quad \text{and} \quad E_S = \frac{D_S S}{W} \quad (7)
\]

and in the strip section by:

\[
E_R = \frac{D_R S}{W + F} \quad \text{and} \quad E_S = \frac{D_S S}{W + F} \quad (8)
\]

According to literature on fractional extraction [17,18] a ‘symmetrical’ separation (=equal purity in extract and raffinate) is obtained with the fractional extraction scheme if:

\[
\frac{W}{S} = \sqrt{D_R D_S} \quad (9)
\]

This condition implies that the product of the extraction factors $E_R$ and $E_S$ is unity (in both sections), with one $E$ larger than unity and the other one smaller than unity, provided that the feed is entered in the middle of the extractor. The ratio $E_R/E_S$ equals the operational selectivity. Please note that this equation can only be used to describe a complete extractor if $E_R$ and $E_S$ are constant over the extractor, so if the distribution ratios are constant and if the phase ratio is the same in both sections of the extractor, (so if $W \gg F$). Under these circumstances, the optimal $W/S$ ratio can be determined directly from the values of $D_R$ and $D_S$, making the extractor design rather straightforward.

In several literature reports on chiral separation by fractional reactive extraction in a pilot set-up [19,20], it is attempted to measure the distribution ratios and then set the wash flow to its optimal value by applying Eq. (9). If the experimental conditions in these reports are considered, the conditions of ‘constant $D$s’ and ‘constant flow rate ratio in both sections’ seem to be fulfilled: a large excess of extractant is used (100–1000), so the variation of $D$ and selectivity from stage to stage is eliminated; and $W$ is large compared to $F$, so the phase ratio in both sections of the extractor is also more or less constant ($W \sim W + F$). So, the extraction factors are indeed constant here.

However, in an industrial extractor it is necessary to work at higher enantiomer concentrations and minimal excess of extractant (to increase the volumetric capacity, and to limit the inventory of expensive extractant), and to minimise $W$ and $S$ (to allow a larger throughput and/or a better volumetric capacity, and to limit the dilution of the product in the raffinate). In such a real extractor, the extraction factor is determined by the phase ratio in each section, and by the local distribution ratio on each stage; so the local $E$ (may) vary from section to section and from stage to stage. Under these conditions the optimal $W/S$ ratio and other process conditions cannot be found from Eq. (9), but should be
deduced from the multistage model as will be described in the next section.

3. Model construction and approach of simulations

A multistage equilibrium model is constructed. Each stage in the multistage model is described by the single stage equilibrium model. The exiting streams of each stage are assumed to be in equilibrium. The stages in the multistage model are connected countercurrently (Fig. 1b).

The process parameters that will be varied are the temperature, pH, flow ratios $S/F$ and $W/F$, number of stages and the concentrations of extractant and enantiomer. The concentrations of extractant and enantiomer are characterised by the ‘extractant excess’ (Eq. (10)) and the ‘concentration level’, which is the specific absolute concentration at a fixed extractant excess.

\[
\text{excess extractant} = \frac{S[C]_{\text{solvent}}}{F[C]_{\text{feed}}} \quad (10)
\]

Finding process conditions at which the e.e. is (for instance) 0.98 in each exit stream involves a lot of trial and error. To reduce the simulation time, the influence of process conditions is studied by doing simulations at a fixed number of stages of four (two in each section); the specification is ‘reach equal e.e. in each stream’. Because of the mass balance, this specification ensures the best yield at best purity with four stages. It is assumed that the process conditions which lead to higher e.e. with a fixed number of stages of four also lead to the lowest stages requirement for a fixed product purity, or at least that all trends observed with four stages hold at higher stage numbers as well. The validity of this assumption will be demonstrated in the results section.

Furthermore, it was seen during initial simulations that a single parameter change always results in a lower e.e. in one stream and a higher e.e. in the other stream if all other parameters are kept constant, so there is no unambiguous way to judge if the parameter change results in an improved or deteriorated separation. Therefore, after each process parameter change the wash flow (expressed as $W/S$ or $W/F$) is adapted to ‘shift’ the e.e.s in extract and raffinate to reach the point where the e.e. in the raffinate equals the e.e. in the extract. This operating point (new e.e. and new $W/S$) can be compared with the results for the old parameter setting. The approach is demonstrated in Fig. 2. It can be seen that at constant settings for the other parameters, a higher wash stream (higher $W/S$ ratio) results in a more pure extract stream, but in a less pure raffinate stream. The yield of the desired enantiomer in the extract stream decreases with increasing wash stream. There is only one operating point in which the e.e.s in both streams are equal, and at this point the yields are (necessarily) also equal.

After discussing the influence of process parameters on the performance of a 4-stages extractor and studying the concept of ‘reflux’, a number of ‘combinations of process parameters’ is presented which lead to an e.e. of 0.98 in extract and raffinate for separation of phenylethylamine (PEA). This set of ‘operating options’ will be used as basis for the discussion of an optimal extractor design in a multi-product environment.

The multistage model is implemented in gPROMS (PSE Ltd., London, UK). All equilibrium conditions and mass balances on all stages are solved simultaneously. This involves solving a large system of non-linear equations. The maximum number of stages that the model can solve is about 80; this number depends slightly on the chosen settings. The pH is assumed to be constant over the extractor and is given as an input value; although calculation of the electroneutrality balance (to identify the pH at equilibrium) is possible, the additional equilibrium condition would result in a larger set of equations for each stage, and therefore in a too severe restriction in the amount of stages that can be calculated. For application of this modelling approach in industrial design is recommended to check whether the assumption of constant pH is valid and to include the electroneutrality balance in the model if needed.

4. Results and discussion

4.1. Influence of process parameters

In this paragraph, the effect of various process parameters is presented. The process parameters of interest are resp. temperature (Fig. 3a) pH (Fig. 3b), extractant excess (either by $S/F$ or by extractant concentration [$C$]) (Fig. 4a) and concentration level (Fig. 4b). The results for $S/F$ and $[C]$ changes could be combined in the graph ‘extractant excess’ to show the similarities.

Figs. 3 and 4 are discussed simultaneously, because all trends can be explained by the same causes. It can be seen in Figs. 3 and 4 for both PG and PEA that an increase in extractant excess, an increase in pH, a decrease in temperature or a higher overall concentration level all result in an ‘equal e.e.’ point at a higher e.e. in both streams and at a higher $W/F$ ratio. By each of these changes, the extent of complexation between crown ether and both enantiomers increases: more ‘$RC$’ and ‘$SC$’ complexes are formed (see Fig. 1a). The yield in the extract increases, but the yield decreases. If now the wash stream is increased as well, more enantiomer is washed back from the extract, and equal yield and purity are obtained in extract and raffinate. The
overall result is a larger wash flow requirement to reach this equal e.e. point, and a better e.e. in both exit streams.

The increase in e.e. by each of the above process parameter changes can have two main causes.

The first explanation for the increase of e.e. at higher extent of complexation is an increase of operational selectivity in the single stage. This effect has been demonstrated experimentally for the single equilibrium stage [14]. The operational selectivity in each stage may be increased until it approaches the intrinsic selectivity. For PEA separation at 25°C, α_{int} is 2.7 under the circumstances given here. If the concentration level is raised from 0.01 to 0.04 M at a constant extractant excess of 2 (as in Fig. 4b), the single-stage operational selectivity increases from 1.95 to 2.54. This has a large effect on the e.e. that can be obtained in a four-stages contactor.

The second possible cause for an increase of e.e. with certain process parameter changes is the effect of these process parameters on the local extraction factors (Eqs. (7) and (8)) and their variations. The local Es and operational selectivities were calculated for the separation of PG as a function of pH (from Fig. 3b). It was seen that the operational selectivity α_{op} is rather constant along the extractor and that α_{op} is even slightly higher for pH 7.9 than for pH 9.1. Therefore, the increase in e.e. at higher pH cannot be explained by an operational selectivity effect. Instead, the...
local extraction factors are responsible (Fig. 5a). The variations for pH 7.9 are larger than for pH 9.1. If on a certain stage both extraction factors are larger (or both smaller) than one, that stage is counter-productive: one of the enantiomers is transported in the wrong direction. If an extraction factor is unity, that stage does not contribute to the purification of that enantiomer. In fact, on each stage for which the product of the extraction factors is not unity, the separation process is not optimal. As a result, the product purity is lowered with each variation in extraction factor and consequently a larger number of stages are required to obtain a certain product purity. It can be seen in Fig. 5b that this effect is more pronounced at pH 7.9.

The large variation in $E_s$ for pH 7.9 is mainly caused by the very small wash flow found at the ‘equal e.e.’ point. As a result, the phase ratio in the wash section (=S/W) is very different from the phase ratio in the strip section (=S/(W+F)). This effect is less pronounced at pH 9.1 (W/F = 2.86). There is also a variation in distribution ratio from stage to stage because of the variation in local concentrations (at both pH values), which adds to the variation in $E_s$. Variation of $E$ can be caused either by a variation of distribution ratios from stage to stage, or by flow rate ratio variation (i.e. $W \neq W+F$), or by a combination of both effects.

Summarising, it can be concluded from the above that the lowest amount of stages is required:

- if the operational selectivity is close to the intrinsic selectivity,
- if there is no variation in extraction factors along the extractor.

This situation is approached most closely if the excess of extractant is set high, to ensure high operational selectivity and low variation in $E_s$ from stage to stage, and if conditions are chosen that yield high distribution ratios (for both enantiomers), to ensure a high W/F at the operating point and consequently low variations of $E$ between wash and strip section. High distribution ratios can be obtained by choosing a high pH, low $T$ and high extractant excess. On the other hand, operating an extractor at high extractant concentration and high S/F and W/F restricts the process capacity and requires a large inventory of extractant: there is a trade-off here. The issue of designing an ‘optimal’ extractor will be discussed further in the last paragraph.

4.2. Influence of number of stages

An underlying assumption in all of the above is that the process parameter change that causes a higher e.e. in the four-stage extractor will also lead to less stages for a certain product specification. To justify this assumption, it was studied for PEA which combinations of process conditions and number of stages yield a product purity of 0.98 e.e. in each exit stream. The influence of pH and concentration level on the W/F ratio and required number of stages are presented in Fig. 6a and b. A larger list of combinations of process conditions that lead to the same purity result is given in the design paragraph in Table 2.

It can be seen that the trend observed in Figs. 3b and 4a for PEA separation in four stages is directly reflected in

![Fig. 6. PEA separation; e.e. = 0.98 in both extract and raffinate, S/F = 2, [rac-PEA] = 0.02 M, 25 °C. (a) Influence of pH on W/F ratio and stage requirement N, [C] = 0.02 M. (b) Influence of extractant excess (via increasing [C], [rac-PEA] = 0.02 M), pH 8.6.](image)

<table>
<thead>
<tr>
<th>$T$ (°C)</th>
<th>S/F</th>
<th>W/F</th>
<th>[C] in S</th>
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</tbody>
</table>

$N$ is total number of stages, evenly distributed over the two sections.
Fig. 6a and b: lower pH or lower extractant excess results in a lower e.e. in four stages and also in a larger stage requirement to reach e.e. = 0.98. Likewise, the effects of the other process parameter changes as given in the previous paragraph are reflected in Table 2. It is concluded that all the effects of process parameter changes predicted for the four-stage extractor can be translated directly to predict the effect on the stages requirement for a given purity specification.

4.3. Minimal excess of extractant

It was observed in the simulations that if there is no excess of extractant over the enantiomers, a full separation can never be obtained in the fractional extractor although a substantial enantiomeric excess may be found in 2 + 2 stages. Under these circumstances, the extractant will eventually become fully loaded, and adding more stages will not increase the product purity any further. Therefore, the extractant always has to be present in some excess. The minimal excess is around 1.5 for the conditions studied in this paper, but depends on the strength of the interaction and should be studied for each compound separately.

4.4. Reflux

The behaviour of an extractor was studied in more detail by using concentration profiles. The concentration profiles for the reactive extraction of PG are given in Fig. 7. The ammonium ions $HR$ and $HS$ were left out for clarity, $[C]$ is negligible in the aqueous phase and neutral $[R]$ and $[S]$ are negligible in the organic phase.

It was observed that the concentration profile is unfavourable in almost all cases. It can be seen in Fig. 7b that the concentration of complexes $RC$ and $SC$ decreases towards the extract exit ($N=1$): a considerable fraction of both complexes decomplex and the free enantiomers are washed back from the organic phase to the aqueous phase, including the more strongly complexed enantiomer that should remain in the extract (here: $R$).

The entrance of the clean wash stream gives a large driving force for mass transfer towards the aqueous phase, for both enantiomers. This is very inefficient. Introduction of the more strongly bound enantiomer in the wash stream will (partially) prevent the large concentration drop of this enantiomer in the extract, by reducing the driving force for mass transfer for that enantiomer. This mode of operation is called ‘reflux’. Reflux is a standard part of a distillation design, but in extraction it is not encountered very often.

In the FREX operation for chiral separation, the strongest bonded enantiomer is obtained enantiomerically pure in the product stream that exits the back-extraction unit as raffinate 2 (see Fig. 9 in the next paragraph), so reflux can be implemented by recycling a small portion of raffinate 2 into the wash stream. The effect of the presence of enantiomer $R$ in the wash stream is that a lower amount of $R$ is washed back from the loaded extract, compared to a clean wash stream. There is no influence on the back-washing of $S$. As a result, the optical purity in the extract increases. Secondly, the required wash stream flow rate to reach
Fig. 9. Conceptual flow sheet comprising fractional extraction and back-extraction unit with recycle of solvent stream. Assumption: $R$ is preferentially extracted ($K_R > K_S$).

The extent of back-extraction in the back-extraction unit is determined by the distribution ratios, $W_2/S$ ratio and the number of stages. To ensure an efficient back-extraction, the back-extraction unit should be run under process conditions that yield low distribution ratios for both enantiomers: the extraction factor (Eq. (7)) has to be as low as possible, but in any case lower than 1. In our previous work [14] it was demonstrated experimentally that (partial) back-extraction in a single stage can be carried out by temperature increase (for components with low physical partitioning such as PG) or by pH decrease (for all components). Therefore, simulations of back-extraction by pH decrease were done for PEA and PG, and by temperature increase for PG only. The specification was set to a recovery of 99.5% (sum of enantiomers) from the loaded solvent stream into raffinate 2.

The results for back-extraction of PEA and PG by pH shift are presented in Fig. 10a and b for two and three equilibrium stages. It can be seen that with a higher number of stages, a higher extraction factor (but still $E < 1$) can be allowed. It is also clear that back-extraction of PEA can be effected at a slightly higher pH than for PG. This is caused by the lower $pK_A$ value for PG and by the stronger complexation between PG enantiomers and the extractant. The $W_2/F$ ratio decreases with decreasing pH and increasing number of stages. $W_2/F$ determines the dilution of the product in raffinate 2 compared to its concentration in the original feed: if $W_2/F < 1$, the product in raffinate 2 is concentrated compared to the feed concentration. This is remarkable: most ‘liquid-phase’ chiral separation methods give diluted product streams.

In our previous work it was demonstrated experimentally [14] that the pH shift required for back-extraction in this system (pH from about 9 to about 6) can be carried out conveniently with low-pressure CO$_2$. In a real process, CO$_2$ may be removed from raffinate 2 by stripping with nitrogen. In this way, product recovery can be carried out by a pH shift without producing salts.

Back-extraction of PG by temperature increase is possible, but a considerable $W_2/F$ and number of stages are required with temperature shift compared to pH shift. With higher temperature, the contribution of the complexation reaction is eliminated, but the extent of physical extraction increases. For PEA or any other component in which the physical extraction (partitioning ratio $P$) is substantial, back-extraction by temperature shift is technically
possible, but only with a large number of stages and a large W2/F ratio, which is very inefficient.

5. Design considerations in a multi-product environment

Conventionally, an extractor is designed to separate a specific compound in the most economical way. However, the real strength of the developed versatile extraction system is the possibility to use it for various enantiomer separations in a multi-product environment. In this paragraph the design of multi-product equipment is discussed.

The versatile crown ether extractant is able to separate a number of amines and amino-alcohol enantiomers with a high enantioselectivity (>1.5, varying from component to component) and reasonable extraction power (good distribution ratios at low excess). The availability of this unique separating agent is the primary basis for multi-product extraction.

The theoretical minimum selectivity and number of stages to reach a certain separation is given by the Kremser equation. Furthermore, it has been shown that each variation of the extraction factors over the extractor results in a higher stages requirement. In other words, if we have sufficient stages available in a given extractor (if the selectivity is larger than the minimum value), conditions can be allowed that result in (more) variation in Es over the column. These are generally conditions that will increase the capacity or lower the cost: lower S/F and W/F and/or lower extractant concentration. So, a multi-product extractor should be built with a number of stages that is higher than the minimum number for each component of (future) interest. Any ‘excess’ stages for a certain component open possibilities to increase the capacity or lower the cost in that specific separation. The multistage model can be used to optimize each case.

As illustration, a number of operating points are presented in Table 2 for PEA separation assuming a varying number of stages. Note that the lower S/F and W/F, the larger the possible throughput, and the lower [C]*S, the lower the inventory of expensive extractant. This list contains a variety of options, some of them more practical than others. It can be extended almost infinitely.

According to the Kremser equation, \( N_{\text{min}} \) is about 18 stages at 25°C and about 15 stages at 5°C for separation of PEA. It can be seen in Table 2 that most options require between 10 and 60% more stages than this minimum number. This range of 10%–60% more stages than the number given by the Kremser equation as ‘minimal’ may be used as a guideline. If a multi-purpose extractor with 50 stages is built, all systems with \( \alpha_{\text{op}} > 1.5 \) can be successfully separated, and with 30 stages, all systems with \( \alpha_{\text{op}} > 2.0 \) can be successfully separated.

If reflux is implemented, the required amount of stages can be decreased by 10–20%. The ‘cost’ of reflux is a large loss in capacity, because a substantial fraction of one of the product enantiomers has to be refluxed. Therefore, reflux is probably only interesting for a separation in which the purity specification cannot be met without reflux, and only a reduction of \( \sim 10\% \) of the stages requirement seems to be feasible. This means that the number predicted by the Kremser model can be considered as a realistic \( N_{\text{min}} \).

6. Conclusions

The availability of the versatile crown ether extractant in combination with the multistage model results in a unique separation tool in a multi-product environment. The influence of changes in process parameters (pH, T, concentrations) can be predicted with the multistage equilibrium model for reactive extraction of phenylglycinol and phenylethylamine. The purity and yield can be improved by each measure that results in a higher extent of complexation; a higher wash flow rate is required then to obtain a good yield and purity in both product streams. Implementation of reflux results in somewhat higher product purities (or less stages) at a slightly smaller W/F ratio, but a significant loss in capacity. Recovery of product and extractant by backextraction should be carried out by pH shift, preferably with CO2 to prevent salt formation.

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Appendix A. Nomenclature

\[
\begin{align*}
[C] & \quad \text{concentration of extractant (kmol/m}^3) \\
D_R & \quad \text{distribution ratio of } R\text{-enantiomer } (\text{–}) \text{ (Eq. (1))} \\
D_S & \quad \text{distribution ratio of } S\text{-enantiomer } (\text{–}) \text{ (Eq. (2))} \\
E_R & \quad \text{extraction factors for enantiomer ‘} R’ \text{‘ (–) \text{ (Eq. (7))} \\
E_S & \quad \text{extraction factors for enantiomer ‘} S’ \text{ (–) \text{ (Eq. (7))} \\
F & \quad \text{feed flow rate (m}^3/\text{s}) \\
e.e. & \quad \text{enantiomeric excess } (\text{–}) \text{ (see Eq. (4))} \\
K_A & \quad \text{acid-base dissociation constant} \\
K_R & \quad \text{complexation strength of } R\text{-enantiomer with crown ether (m}^3/\text{kmol}) \\
K_S & \quad \text{complexation strength of } S\text{-enantiomer with crown ether (m}^3/\text{kmol}) \\
N & \quad \text{number of equilibrium stages } (\text{–}) \\
N_{\text{min}} & \quad \text{minimum number of extraction stages according to Kremser equation} \\
P & \quad \text{physical partitioning ratio } (\text{–}) \\
\text{PEA} & \quad \text{phenylethylamine} \\
\text{PG} & \quad \text{phenylglycinol} \\
[rac] & \quad \text{concentration of racemic mixture (kmol/m}^3) \\
S & \quad \text{solvent flow rate (m}^3/\text{s}) \\
T & \quad \text{temperature (°C)} \\
W & \quad \text{wash flow rate (m}^3/\text{s}) \\
W_2 & \quad \text{wash flow rate in backextraction (m}^3/\text{s}) \\
\alpha_{\text{int}} & \quad \text{intrinsic selectivity } (=K_R/K_S) \text{ (Eq. (4))}
\end{align*}
\]

Greek symbols

\[
\alpha_{\text{int}} \quad \text{intrinsic selectivity } (=K_R/K_S) \text{ (Eq. (4))}
\]
α_{op} \quad \text{operational selectivity (}=D_R/D_S\text{) (Eq. (3))}

Φ \quad \text{phase ratio of solvent to feed (single stage)}

References