The uranyl unit as electrophilic catalyst of acyl transfer reactions

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Abstract

The kinetics of the base induced alcoholysis of a series of metallomacrocycles in which the salophen-uranyl unit is connected by polymethylene bridges of variable length to a pyrogallol monoacetate unit have been investigated in the $\text{MeO}^-/\text{Me}_4\text{N}^+/\text{MeOH}$ and $\text{EtO}^-/\text{Me}_4\text{N}^+/\text{EtOH}$ base-solvent systems. Analysis of rate data collected over a wide range of base concentrations, coupled with equilibrium measurements for complex formation between the alkoxide ion and the uranyl centre, showed that the ester cleavage processes are the results of two competing pathways involving alkoxide ion attack on uncomplexed and alkoxide-complexed substrates. Rate data related to the former pathway show that the proximal uranyl centre activates the ester carbonyl towards nucleophilic addition, thus behaving as an immobilized Lewis acid catalyst. The size of the acceleration critically depends on both solvent nature and distance of the ester function from the metal electrophile.

Keywords: Kinetics and mechanisms; Acyl transfer reactions; Uranyl complexes; Salophen complexes; Metallomacrocycles

1. Introduction

The salophen ligand is known to form a kinetically stable complex (1) with the uranyl cation UO_2^{2+} , which is neutral as a result of deprotonation of the two phenolic hydroxyls upon complexation [1]. The complexed uranyl cation has a well-known preference for pentagonal bipyramidal coordination, with the two oxygens in apical position.

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After accommodation of the four atoms of the salophen ligand, a fifth equatorial coordination site is still available for binding to an additional donor. Thus 1 can be viewed as an immobilized neutral Lewis acid, which can be easily

incorporated into more elaborate structures for use in complexation studies. On this basis, metallomacrocycles and clefts have been developed, which proved to be excellent receptors for anions [2] and neutral molecules [3]. In these host-guest complexes, coordination of a donor group of the guest (e.g. the carbonyl group of urea [4]) to the uranyl centre provides a major driving force to complexation.

In order to exploit further the hard Lewis acid character of the salophen complex, and with the idea of testing this unit for its possible use in the construction of metalloenzyme models, we decided to investigate its role as electrophilic catalyst in nucleophilic additions to the carbonyl group of acid derivatives (acyl transfer reactions).

As a first approach to this goal we have synthesized the metallomacrocycles 2, $n = 2-4$ in which a pyrogallol monoacetate moiety is covalently linked to the salophen unit by means of polymethylene bridges of variable length. Clearly the required proximity between electrophile and ester function is enforced in 2 by covalent bonding, rather than by weak, reversible interactions. A similar expedient was adopted in a series of investigations in which the role of alkali [5] and alkaline-earth [5,6]

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metal ions as electrophilic catalysts of ester cleavage was assessed. The kinetics of the base-induced alcoholysis of the synthesized compounds **2** (Eq. (1)) have been thoroughly investigated at 25°C in the MeO[−]Me₄N⁺/MeOH and EtO[−]Me₄N⁺/EtOH base-solvent systems. For comparison purposes the corresponding reactions (Eq. (2)) of the simple compound **4** were kinetically investigated under the same conditions.

2. Experimental

2.1. Instruments and general methods

Melting points are uncorrected. ¹H and ¹³C NMR spectra were recorded in CDCl₃ or DMSO-*d*₆ with either a Bruker AC 250 or AC 300 spectrometer, using Me₄Si as internal standard (*J* values in Hz). Mass spectra were obtained either with a Finnigan MAT 90 spectrometer (EI-MS and FAB-MS, positive mode) or with a Fisons Instruments VG-Platform Benchtop LC-MS (positive ion electrospray mass spectra, ESP⁺). Spectrophotometric measurements were carried out either on a Cary 219 or HP 8452 diode array spectrometer. HPLC analyses were carried out on a Hewlett Packard 1050 liquid chromatograph fitted with a UV-VIS detector operating at 230 nm. IR spectra were obtained from KBr pellets and recorded on a Biorad Digilab FTS 60 instrument. Elemental analyses were carried out on a Carlo Erba Strumentazione Elemental Analyser. Non-linear least-squares calculations were carried out using the programme SigmaPlot for Windows, 1.02 (Jandel Scientific).

2.2. Materials

Care was taken when handling uranyl containing com-

pounds because of their toxicity and radioactivity [7]. 2,6-Diethoxyphenol (**5**) [8] [¹H NMR (300 MHz, CDCl₃) δ 6.75 (dd, *J* = 8.9, *J* = 7.7, 1H, Ar H-4), 6.56 (d, *J* = 8.2, 2H, Ar H-3, H-5), 5.57 (s, 1H, OH), 4.11 (q, *J* = 7.0, 4H, CH₂), 1.44 (t, *J* = 7.0, 6H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 147.0 (Ar C-2, C-6), 135.9 (Ar C-1), 119.4 (Ar C-4), 106.6 (Ar C-3, C-5), 65.2 (CH₂), 15.2 (CH₃)] and 2-allyloxy-3-hydroxybenzaldehyde (**9**) [4] were prepared as reported in the cited literature. THF was distilled from sodium benzophenone ketyl before use. Acetonitrile was stored over 4 Å molecular sieves. Dry methanol [9] and dry ethanol [10] and stock solutions of tetramethylammonium methoxide in methanol [9] and tetramethylammonium ethoxide in ethanol [10] were prepared and handled as reported in the cited literature. 2,6-Dimethylanisole (Aldrich) was distilled under reduced pressure before use. Diisopropylethylamine (Aldrich) was fractionally distilled over tosyl chloride and subsequently over sodium. Other chemicals were used as received. Diisopropylethylammonium perchlorate was prepared according to a literature procedure [11].

Warning! Care was taken when handling diisopropylethylammonium perchlorate because it is potentially explosive [12]. No accident however occurred in the course of the present work.

2.2.1. Synthesis of esters **2**

The title compounds were synthesized according to Scheme 1.

Assignments of the protons and the carbons of the

Scheme 1.

Scheme 2.

various aromatic rings of compounds 2, 3, 11, and 12 are referred to the numbering systems shown in Scheme 2.

2-Allyloxy-1,3-dihydroxybenzene (7). To 240 ml of DMSO, flushed with N₂, 6.3 g (0.16 mol) of powdered NaOH and 20 g (0.16 mol) of 1,2,3-trihydroxybenzene (pyrogallol, 6) were added. The mixture was stirred for 1 h to give an almost clear, slightly brown solution. The reaction mixture was cooled (ice/water bath) and 3-bromo-1-propene (11 ml, 0.13 mol) was added dropwise. The solution was stirred overnight at room temperature. Subsequently the mixture was poured into 750 ml of water, acidified with conc. HCl and extracted with 4 × 200 ml of diethyl ether. The combined organic layer was washed once with water and dried over MgSO₄. After concentration to dryness the crude product was purified by column chromatography (SiO₂; hexane/AcOEt 10:1) obtaining 8.4 g of product (yield 40%; purity 90%). ¹H NMR (250 MHz, CDCl₃) δ 6.85 (t, *J* = 8.3, 1H, Ar H-5), 6.50 (d, *J* = 8.3, 2H, Ar H-4, H-6), 6.15–6.00 (m, 1H, –CH=), 5.75 (bs, 2H, OH), 5.45–5.30 (m, 2H, =CH₂), 4.60–4.50 (m, 2H, OCH₂).

General procedure for the synthesis of 2-allyloxy-1,3-bis(ω-bromoalkoxy)benzene (8). To 150 ml of degassed CH₃CN, 40 g (0.29 mol) of K₂CO₃ and 6.0 g (36 mmol) of 2-allyloxy-1,3-dihydroxybenzene (7) were added. The mixture was heated for 10 min, then cooled and 0.36 mol of 1,2-dibromoethane, or 1,3-dibromopropane, or 1,4-dibromobutane and a catalytic amount of KI were added. The mixture was refluxed overnight and then cooled to room temperature. After filtration of the salts the CH₃CN layer was evaporated and residual dibromoalkane was removed on a vacuum line. The solid residue was poured into 450 ml of water and the aqueous layer was extracted with 4 × 120 ml of diethyl ether. The combined organic layer was dried over MgSO₄, followed by concentration to dryness.

2-Allyloxy-1,3-bis(2-bromoethoxy)benzene (8, n = 2). The crude product was purified by column chromatography (SiO₂; hexane/AcOEt 20:1); yield 22%. ¹H NMR (250 MHz, CDCl₃) δ 6.90 (t, *J* = 8.3, 1H, Ar H-5), 6.55

(d, *J* = 8.3, 2H, Ar H-4, H-6), 6.20–5.95 (m, 1H, –CH=), 5.50–5.10 (m, 2H, =CH₂), 4.60–4.50 (m, 2H, OCH₂–CH=CH₂), 4.25 (t, *J* = 7.6, 4H, OCH₂–CH₂Br), 3.60 (t, *J* = 7.6, 4H, OCH₂–CH₂Br).

2-Allyloxy-1,3-bis(3-bromopropoxy)benzene (8, n = 3). The purification was performed by column chromatography using a mixture of hexane/AcOEt changing from 20:1 to 10:1 during elution; yield 77%. ¹H NMR (250 MHz, CDCl₃) δ 6.95 (t, *J* = 8.3, 1H, Ar H-5), 6.60 (d, *J* = 8.3, 2H, Ar H-4, H-6), 6.20–5.95 (m, 1H, –CH=), 5.35–5.25 (m, 2H, =CH₂), 4.55–4.45 (m, 2H, OCH₂–CH=CH₂), 4.15 (t, *J* = 7.6, 4H, OCH₂–CH₂CH₂Br), 3.65 (t, *J* = 7.6, 4H, OCH₂CH₂–CH₂Br), 2.30 (pent., *J* = 7.6, 4H, OCH₂–CH₂–CH₂Br); MS (FAB) *m/e* 408.8 (M + H)⁺.

2-Allyloxy-1,3-bis(4-bromobutoxy)benzene (8, n = 4). The purification procedure is analogous to that used for 8, n = 3. Yield 56%. ¹H NMR (250 MHz, CDCl₃) δ 6.95 (t, *J* = 8.3, 1H, Ar H-5), 6.60 (d, *J* = 8.3, 2H, Ar H-4, H-6), 6.20–5.95 (m, 1H, –CH=), 5.35–5.25 (m, 2H, =CH₂), 4.55–4.45 (m, 2H, OCH₂–CH=CH₂), 4.15 (t, *J* = 7.6, 4H, OCH₂–CH₂CH₂CH₂Br), 3.65 (t, *J* = 7.6, 4H, OCH₂CH₂CH₂–CH₂Br), 2.15–1.85 (m, 8H, OCH₂–CH₂CH₂–CH₂Br); ¹³C NMR (62.5 MHz, CDCl₃) δ 153.1 (Ar C-1, C-3), 137.8 (Ar C-2), 134.6 (–CH=), 123.6 (Ar C-5), 117.3 (=CH₂), 107.0 (Ar C-4, C-6), 74.1 (OCH₂–CH=CH₂), 68.1 (OCH₂–CH₂CH₂CH₂Br), 33.6 (CH₂Br), 29.6, 28.0 (OCH₂–CH₂CH₂–CH₂Br).

2-Allyloxy-3-(2-bromoethoxy)benzaldehyde (10). To 250 ml of CH₃CN under N₂, 15.5 g (0.112 mol) of K₂CO₃ and 10.0 g (0.056 mol) of 2-allyloxy-3-hydroxybenzaldehyde (9) [4] were added. The mixture was heated for 10 min, then cooled to room temperature and subsequently 48 ml (0.56 mol) of 1,2-dibromoethane were added. The mixture was refluxed overnight and then cooled to room temperature and the salts were filtered off. The solvent was evaporated and residual 1,2-dibromoethane was removed on a vacuum line. The crude product was purified by column chromatography (SiO₂; CH₂Cl₂) to give the product in 53% yield. ¹H NMR (250 MHz, CDCl₃) δ 10.40 (s, 1H, CHO), 7.45–7.35 (m, 1H, Ar H-6), 7.10–7.00 (m, 2H, Ar H-4, H-5), 6.15–5.95 (m, 1H, –CH=), 5.40–5.30 (m, 2H, =CH₂), 4.75–4.65 (m, 2H, OCH₂–CH=CH₂), 4.35 (t, *J* = 7.6, 2H, OCH₂–CH₂Br), 3.70 (t, *J* = 7.6, 2H, OCH₂–CH₂Br); ¹³C NMR (62.5 MHz, CDCl₃) δ 190.1 (CHO), 151.5 (Ar C-2, C-3), 133.1 (CH=), 130.5 (Ar C-1), 124.1, 120.4, 119.8 (Ar C-4, C-5, C-6), 119.0 (=CH₂), 75.4 (OCH₂–CH=CH₂), 69.1 (OCH₂–CH₂Br), 29.1 (CH₂Br); IR (KBr) 1686 (ν_{C=O}) cm^{–1}; MS (EI) *m/e* calc. for C₁₂H₁₃O₃Br: 284.0049, found 284.0030.

2,2'-Bis(allyloxy)-3,3'-[2-allyloxy-1,3-phenylenebis(oxyethyleneoxy)]dibenzaldehyde (11, n = 2). To 100 ml of

CH₃CN under N₂, 11 g (80 mmol) of K₂CO₃ and 4.6 g (16.2 mmol) of 2-allyloxy-3-(2-bromoethoxy)benzaldehyde (10) were added. The mixture was heated under stirring for 10 min, then cooled to room temperature and 1.34 g (8.07 mmol) of 2-allyloxy-1,3-dihydroxybenzene (7) was added. The mixture was refluxed overnight and then cooled to room temperature. The salts were filtered off and the CH₃CN was evaporated. The crude product was purified by column chromatography (SiO₂; CH₂Cl₂). Yield 50 %. ¹H NMR (250 MHz, CDCl₃) δ 10.44 (s, 2H, CHO), 7.45 (dd, *J* = 7.7, *J* = 2.0, 2H, Ar H-6), 7.23 (dd, *J* = 7.7, *J* = 2.0, 2H, Ar H-4), 7.16 (dd, *J* = 7.7, *J* = 7.7, 2H, Ar H-5), 7.09 (t, *J* = 8.3, 1H, Ar' H-5), 6.67 (d, *J* = 8.3, 2H, Ar' H-4, H-6), 6.11–5.88 (m, 3H, –CH=), 5.35–5.05 (m, 6H, =CH₂), 4.65–4.60 (m, 4H, ArOCH₂–CH=CH₂), 4.58–4.50 (m, 2H, Ar'OCH₂–CH=CH₂), 4.42 (s, 8H, OCH₂); ¹³C NMR (62.5 MHz, CDCl₃) δ 190.4 (CHO), 152.9 (Ar' C-1, C-3), 152.1, 151.8 (Ar C-2, C-3), 138.5 (Ar' C-2), 134.4 (Ar'OCH₂–CH=CH₂), 133.2 (ArOCH₂–CH=CH₂), 130.3 (Ar C-1), 124.1, 123.7, 119.8, 119.7 (Ar C-4, C-5, C-6, Ar' C-5), 118.9 (ArOCH₂–CH=CH₂), 117.4 (Ar'OCH₂–CH=CH₂), 108.3 (Ar' C-4, C-6), 75.2 (ArOCH₂–CH=CH₂), 74.2 (Ar'OCH₂–CH=CH₂), 68.0, 67.9 (OCH₂); IR (KBr) 1688 (ν_{C=O}) cm^{–1}.

2,2'-Bis(allyloxy)-3,3'-[2-allyloxy-1,3-phenylenebis(oxytrimethyleneoxy)]dibenzaldehyde (11, n = 3). To 13 ml of CH₃CN under N₂, 3.5 g (25 mmol) of K₂CO₃ and 870 mg (4.9 mmol) of 2-allyloxy-3-hydroxybenzaldehyde (9) [4] were added. The mixture was heated for 10 min, cooled to room temperature and subsequently 1.0 g (2.45 mmol) of 2-allyloxy-1,3-bis(3-bromopropoxy)benzene (8, *n* = 3) was added. The mixture was refluxed overnight, cooled to room temperature and the salts were filtered off. The solvent was evaporated. The residue was dissolved in CH₂Cl₂ and filtered to remove some of the remaining salts. After evaporation of the solvent the product was purified by crystallization from hexane resulting in a white solid; yield 40%. m.p. 66–68°C. ¹H NMR (250 MHz, CDCl₃) δ 10.40 (s, 2H, CHO), 7.40 (d, *J* = 7.6, 2H, Ar H-6), 7.20–7.05 (m, 4H, Ar H-4, H-5), 6.95 (t, *J* = 8.3, 1H, Ar' H-5), 6.60 (d, *J* = 8.3, 2H, Ar' H-4, H-6), 6.10–5.90 (m, 3H, –CH=), 5.35–5.05 (m, 6H, =CH₂), 4.65–4.55 (m, 4H, ArOCH₂–CH=CH₂), 4.50–4.40 (m, 2H, Ar'OCH₂–CH=CH₂), 4.30, 4.25 (m, 8H, OCH₂–CH₂–CH₂O), 2.35 (pent., *J* = 7.6, 4H, OCH₂–CH₂–CH₂O); ¹³C NMR (62.5 MHz, CDCl₃) δ 190.5 (CHO), 153.0 (Ar' C-1, C-3), 152.2, 151.4 (Ar C-2, C-3), 137.8 (Ar' C-2), 134.6 (Ar'OCH₂–CH=CH₂), 133.1 (ArOCH₂–CH=CH₂), 130.3 (Ar C-1), 124.2, 123.8, 119.3, 119.2 (Ar C-4, C-5, C-6, Ar' C-5), 118.8 (ArOCH₂–CH=CH₂), 117.0 (Ar'OCH₂–CH=CH₂), 107.1 (Ar' C-4, C-6), 75.2 (ArOCH₂–CH=CH₂), 74.1 (Ar'OCH₂–CH=CH₂), 65.6, 65.4 (OCH₂–CH₂–CH₂O), 29.4 (OCH₂–CH₂–CH₂O). MS (FAB) *m/e* 602.2 (M + H)⁺. Anal. Calc. for C₃₅H₃₈O₉: C, 69.75; H, 6.35. Found: C, 69.74; H, 6.52.

2,2'-Bis(allyloxy)-3,3'-[2-allyloxy-1,3-phenylenebis(oxytetramethyleneoxy)]dibenzaldehyde (11, n = 4). This compound was prepared as shown for 11, *n* = 3. The product was purified by column chromatography (SiO₂; CH₂Cl₂); yield 40%. m.p. 58–60°C; ¹H NMR (250 MHz, CDCl₃) δ 10.45 (s, 2H, CHO), 7.40 (dd, *J* = 7.6, *J* = 2.0, 2H, Ar H-6), 7.20–7.05 (m, 4H, Ar H-4, Ar H-5), 6.95 (t, *J* = 8.3, 1H, Ar' H-5), 6.55 (d, *J* = 8.3, 2H, Ar' H-4, H-6), 6.15–5.95 (m, 3H, –CH=), 5.45–5.10 (m, 6H, =CH₂), 4.70–4.60 (m, 4H, ArOCH₂–CH=CH₂), 4.55–4.45 (m, 2H, Ar'OCH₂–CH=CH₂), 4.20–4.00 (m, 8H, OCH₂–CH₂CH₂–CH₂O), 2.05 (s, 8H, OCH₂–CH₂CH₂–CH₂O); ¹³C NMR (62.5 MHz, CDCl₃) δ 190.5 (CHO), 153.2 (Ar' C-1, C-3), 152.4, 151.4 (Ar C-2, C-3), 137.8 (Ar' C-2), 134.7 (Ar'OCH₂–CH=CH₂), 133.2 (ArOCH₂–CH=CH₂), 130.2 (Ar C-1), 124.2, 123.7, 119.1, 119.0 (Ar C-4, C-5, C-6, Ar' C-5), 118.9 (ArOCH₂–CH=CH₂), 117.1 (Ar'OCH₂–CH=CH₂), 106.9 (Ar' C-4, C-6), 75.1 (ArOCH₂–CH=CH₂), 74.1 (Ar'OCH₂–CH=CH₂), 68.7, 68.6 (OCH₂–CH₂CH₂–CH₂O), 26.2 (OCH₂–CH₂CH₂–CH₂O). MS (FAB) *m/e* 630.4 (M + H)⁺. Anal. Calc. for C₃₇H₄₂O₉: C, 70.46; H, 6.71. Found: C, 70.45; H, 6.64.

General procedure for the synthesis of the disalicylaldehyde 12. To 33 ml of a mixture of EtOH/H₂O/THF (5:1:5), 2.5 mmol of HCOOH, 2.5 mmol of Et₃N, 0.06 mmol of Ph₃P, and 0.02 mmol of Pd(OAc)₂ were added, followed by the addition of 0.50 mmol of 11. The mixture was refluxed for 1 h. The completion of the reaction was monitored by TLC (SiO₂; CH₂Cl₂). The solvent was evaporated. The crude product was purified by recrystallization from ethanol, after filtration of the warm solution to remove the insoluble Pd. After the first crystallization the product was recrystallized a second time to give a 50% yield.

3,3'-[2-Hydroxy-1,3-phenylenebis(oxyethyleneoxy)]disalicylaldehyde (12, n = 2). m.p. 107–109°C; ¹H NMR (250 MHz, CDCl₃) δ 11.01 (s, 2H, ArOH), 9.94 (s, 2H, CHO), 7.31–7.20 (m, 4H, Ar H-4, H-6), 6.96 (dd, *J* = 8.3, *J* = 8.3, 2H, Ar H-5), 6.80–6.61 (m, 3H, Ar'), 6.03 (bs, 1H, Ar'OH), 4.43 (s, 8H, OCH₂); ¹³C NMR (62.5 MHz, CDCl₃) δ 196.7 (CHO), 152.6 (Ar C-2), 147.5 (Ar C-3), 146.9 (Ar' C-1, C-3), 126.1, 121.8, 121.7, 120.0, 119.6, 119.1 (Ar C-1, C-4, C-5, C-6, Ar' C-2, C-5), 109.3 (Ar' C-4, C-6), 68.9, 68.8 (OCH₂). IR (KBr) 1653 (ν_{C=O}) cm^{–1}. MS (FAB) *m/e* 482.3 (M + H)⁺. Anal. Calc. for C₂₄H₂₂O₉·EtOH: C, 62.39; H, 5.64. Found: C, 62.90; H, 5.34.

3,3'-[2-Hydroxy-1,3-phenylenebis(oxytrimethyleneoxy)]disalicylaldehyde (12, n = 3). m.p. 127–129°C; ¹H NMR (300 MHz, CDCl₃) δ 11.04 (s, 2H, ArOH), 9.90 (s, 2H, CHO), 7.19–7.13 (m, 4H, Ar H-4, H-6), 6.93 (dd, *J* = 7.9, *J* = 7.9, 2H, Ar H-5), 6.74 (dd, *J* = 9.1, *J* = 7.4, 1H, Ar'

H-5), 6.62 (two overlapping doublets, $J = 9.1$, $J = 7.4$, 2H, Ar' H-4, H-6), 5.65 (bs, 1H, Ar'OH), 4.27 (q, $J = 6.0$, 8H, $\text{OCH}_2\text{---CH}_2\text{---CH}_2\text{O}$), 2.35 (pent., $J = 6.0$, 4H, $\text{OCH}_2\text{---CH}_2\text{---CH}_2\text{O}$); ^{13}C NMR (75 MHz, CDCl_3) δ 197.0 (CHO), 152.5 (Ar C-2), 148.0 (Ar C-3), 147.0 (Ar' C-1, C-3), 136.3, 125.5, 121.5, 120.6, 120.0, 119.6 (Ar C-1, C-4, C-5, C-6, Ar' C-2, C-5), 107.3 (Ar' C-4, C-6), 66.8, 66.6 ($\text{OCH}_2\text{---CH}_2\text{---CH}_2\text{O}$), 29.8 ($\text{OCH}_2\text{---CH}_2\text{---CH}_2\text{O}$). MS (FAB) m/e 482.3 ($\text{M} + \text{H}$)⁺. Anal. Calc. for $\text{C}_{26}\text{H}_{26}\text{O}_9$: C, 64.72; H, 5.43. Found: C, 63.75; H, 5.30.

3,3'-(2-Hydroxy-1,3-phenylenebis(oxytetramethyleneoxy))disalicylaldehyde (12, $n = 4$). m.p. 105–107°C; ^1H NMR (300 MHz, CDCl_3) δ 11.0 (s, 2H, ArOH), 9.91 (s, 2H, CHO), 7.18 (dd, $J = 7.8$, $J = 1.5$, 2H, Ar H-6), 7.13 (dd, $J = 8.0$, $J = 1.5$, 2H, Ar H-4), 6.94 (dd, $J = 7.8$, $J = 8.0$, 2H, Ar H-5), 6.75 (dd, $J = 8.9$, $J = 7.6$, 1H, Ar' H-5), 6.59 (two overlapping doublets, $J = 8.9$, $J = 7.6$, 2H, Ar' H-4, H-6), 5.55 (bs, 1H, Ar'OH), 4.14 (m, 8H, $\text{OCH}_2\text{---CH}_2\text{CH}_2\text{---CH}_2\text{O}$), 2.05 (bs, 8H, $\text{OCH}_2\text{---CH}_2\text{CH}_2\text{---CH}_2\text{O}$). ^{13}C NMR (75 MHz, CDCl_3) δ 196.6 (CHO), 152.1 (Ar C-2), 147.7 (Ar C-3), 146.7 (Ar' C-1, C-3), 135.7, 124.9, 121.1, 120.0, 119.6, 119.1 (Ar C-1, C-4, C-5, C-6, Ar' C-2, C-5), 106.5 (Ar' C-4, C-6), 69.2, 69.0 ($\text{OCH}_2\text{---CH}_2\text{CH}_2\text{---CH}_2\text{O}$), 26.1, 26.0 ($\text{OCH}_2\text{---CH}_2\text{CH}_2\text{---CH}_2\text{O}$). MS (ESP⁺) m/e 533.9 ($\text{M} + \text{Na}$)⁺.

General procedure for the synthesis the uranyl complexes 3. A solution of 0.120 mmol of 12 in 10 ml of THF and a solution of 0.120 mmol of *o*-phenylenediamine in 10 ml of MeOH were added separately over a period of 3 h to a refluxing solution of $\text{UO}_2(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (51 mg, 0.120 mmol) in 30 ml of MeOH. After the addition was completed the solution was refluxed for an additional 30 min. Subsequently the mixture was cooled to room temperature and the solvent was concentrated to about 2 ml, after which the product precipitated. It was filtered off and washed once with MeOH. Yield 45–50%.

[9,10,18,19-Tetrahydro-33-hydroxy-3,7:12,16:21,25-trimetheno-8,11,17,20,1,27-benzotetraoxadiazacyclononacosine-32,34-diolato(2-)-N¹,N²⁷,O³²,O³⁴]dioxouranium (3, $n = 2$). m.p. 210°C (dec.). ^1H NMR (250 MHz, $\text{DMSO}-d_6$) δ 9.64 (s, 2H, CH=N), 7.81–7.70 (m, 2H, Ar''), 7.60–7.52 (m, 2H, Ar''), 7.46 (dd, $J = 7.7$, $J = 2.0$, 2H, Ar H-6), 7.28 (dd, $J = 7.7$, $J = 2.0$, 2H, Ar H-4), 6.70 (s, 3H, Ar'), 6.65 (dd, $J = 7.7$, $J = 7.7$, 2H, Ar H-5), 4.47 (bs, 8H, OCH_2). IR (KBr) 1602 ($\nu_{\text{N}=\text{C}}$), 900 ($\nu_{\text{U}=\text{O}}$) cm^{-1} . MS (FAB) m/e 795.5 ($\text{M} + \text{H}$)⁺, 811.0 ($\text{M} + \text{H}_2\text{O}$)⁺. Anal. Calc. for $\text{C}_{30}\text{H}_{24}\text{N}_2\text{O}_9\text{U} \cdot 2\text{H}_2\text{O}$: C, 43.38; H, 3.40; N, 3.37. Found: C, 43.67; H, 3.34; N, 3.38%.

[10,11,20,21-Tetrahydro-35-hydroxy-3,7:13,17:23,27-trimetheno-9H,19H-8,12,18,22,1,29-benzotetraoxadiazacyclohentriacontine-34,36-diolato(2-)-N¹,N²⁹,O³⁴,O³⁶] di-

oxouranium (3, $n = 3$). m.p. 190°C (dec.). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.60 (s, 2H, CH=N), 7.85 (s, 1H, OH), 7.77 (dd, $J = 5.9$, $J = 3.4$, 2H, Ar''), 7.53 (dd, $J = 5.9$, $J = 3.4$, 2H, Ar''), 7.42 (d, $J = 7.8$, 2H, Ar H-6), 7.28 (d, $J = 7.8$, 2H, Ar H-4), 6.72 (d, $J = 7.8$, 2H, Ar' H-4, H-6), 6.67–6.58 (m, 3H, Ar H-5, Ar' H-5), 4.38–4.28 (m, 8H, $\text{OCH}_2\text{---CH}_2\text{---CH}_2\text{O}$), 2.27–2.22 (m, 4H, $\text{OCH}_2\text{---CH}_2\text{---CH}_2\text{O}$); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 166.4 (CH=N), 161.4 (Ar C-2), 150.1 (Ar C-3), 148.0 (Ar' C-1, C-3), 146.6 (Ar'' C-1, C-2), 140.1 (Ar' C-2), 128.7, 127.9 (Ar C-6, Ar'' C-4, C-5), 124.5 (Ar C-1), 120.4, 120.1, 118.2, 115.9 (Ar C-4, C-5, Ar' C-5, Ar'' C-3, C-6), 113.1 (Ar' C-4, C-6), 69.3, 66.9 ($\text{OCH}_2\text{---CH}_2\text{---CH}_2\text{O}$), 29.5 ($\text{OCH}_2\text{---CH}_2\text{---CH}_2\text{O}$). MS (FAB) m/e 823.2 ($\text{M} + \text{H}$)⁺. Anal. Calc. for $\text{C}_{32}\text{H}_{28}\text{N}_2\text{O}_9\text{U} \cdot 1.5\text{H}_2\text{O}$: C, 45.24; H, 3.68; N, 3.30. Found: C, 44.92; H, 3.73; N, 3.21.

[9,10,11,12,20,21,22,23-Octahydro-37-hydroxy-3,7:14,18:25,29-trimetheno-8,13,19,24,1,31-benzotetraoxadiazacyclotritriacontine-36,38-diolato(2-)-N¹,N³¹,O³⁶,O³⁸]di-oxouranium (3, $n = 4$). m.p. 198°C (dec.) ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.57 (s, 2H, CH=N), 8.19 (s, 1H, OH), 7.76 (dd, $J = 5.9$, $J = 3.4$, 2H, Ar''), 7.52 (dd, $J = 5.9$, $J = 3.4$, 2H, Ar''), 7.37 (dd, $J = 7.9$, $J = 1.4$, 2H, Ar H-6), 7.22 (dd, $J = 7.8$, $J = 1.4$, 2H, Ar H-4), 6.65–6.55 (m, 5H, Ar H-5, Ar' H-4, H-5, H-6), 4.22–4.12 (m, 8H, $\text{OCH}_2\text{---CH}_2\text{CH}_2\text{---CH}_2\text{O}$), 2.05–1.85 (m, 8H, $\text{OCH}_2\text{---CH}_2\text{CH}_2\text{---CH}_2\text{O}$); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 166.4 (CH=N), 160.9 (Ar C-2), 150.4 (Ar C-3), 147.2 (Ar' C-1, C-3), 146.7 (Ar'' C-1, C-2), 137.2 (Ar' C-2), 128.6, 127.1 (Ar C-6, Ar'' C-4, C-5), 124.1 (Ar C-1), 120.1, 118.2, 116.0, 115.9 (Ar C-4, C-5, Ar' C-5, Ar'' C-3, C-6), 107.7 (Ar' C-4, C-6), 68.5 ($\text{OCH}_2\text{---CH}_2\text{CH}_2\text{---CH}_2\text{O}$), 25.8, 25.7 ($\text{OCH}_2\text{---CH}_2\text{CH}_2\text{---CH}_2\text{O}$). MS (ESP⁺) m/e 872.3 ($\text{M} + \text{Na}$)⁺.

General procedure for the synthesis of the uranyl complexes 2. To a solution of 0.12 mmol of 3 in 10 ml of dry CH_2Cl_2 under Ar, 0.15 mmol of Et_3N were added, turning the solution from orange to dark red. Subsequently 0.13 mmol of AcCl were added, while keeping the temperature <30°C. After completion of the reaction (TLC, SiO_2 ; $\text{CH}_2\text{Cl}_2/\text{EtOH}$ 20:1) the mixture was poured into 150 ml of CH_2Cl_2 and washed with 2×70 ml of water. The organic layer was dried with MgSO_4 and concentrated to dryness. The crude red product was purified by column chromatography (SiO_2 ; $\text{CH}_2\text{Cl}_2/\text{EtOH}$ 50:1).

[33-Acetoxy-9,10,18,19-tetrahydro-3,7:12,16:21,25-trimetheno-8,11,17,20,1,27-benzotetraoxadiazacyclononacosine-32,34-diolato(2-)-N¹,N²⁷,O³²,O³⁴]dioxouranium (2, $n = 2$). Yield 55%. ^1H NMR (250 MHz, $\text{DMSO}-d_6$) δ 9.60 (s, 2H, CH=N), 7.83–7.79 (m, 2H, Ar''), 7.55–7.52 (m, 2H, Ar''), 7.40 (dd, $J = 7.8$, $J = 2.0$, 2H, Ar H-6), 7.24 (dd, $J = 7.8$, $J = 2.0$, 2H, Ar H-4), 7.25 (bs, 1H, Ar' H-5), 6.92 (s, 2H, Ar' H-4, H-6), 6.61 (dd, $J = 7.8$, $J = 7.8$, 2H,

Ar H-5), 4.40 (bs, 8H, OCH₂), 0.67 (bs, 3H, OAc). IR (KBr) 1762 ($\nu_{\text{C=O}}$ [non-coord], medium), 1720 ($\nu_{\text{C=O}}$ [coord], medium), 1602 ($\nu_{\text{N=C}}$, strong), 900 ($\nu_{\text{U=O}}$, strong) cm⁻¹. MS (FAB) *m/e* 837.4 (M + H)⁺, 795.4 [metastable from 837.4 (M + 2H - Ac)⁺]. Anal. Calc. for C₃₂H₂₆N₂O₁₀U·EtOH: C, 46.27; H, 3.65, N, 3.17. Found: C, 46.59; H, 4.08, N, 2.69.

[35-Acetoxy-10,11,20,21-tetrahydro-3,7:13,17:23,27-trimetheno-9H,19H-8,12,18,22,1,29-benzotetraoxadiazacyclohentriacontine-34,36-diolato(2-)-N¹,N²⁹,O³⁴,O³⁶] dioxouranium (2, *n* = 3). Yield 75%. m.p. 170°C (dec.). ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.59 (s, 2H, CH=N), 7.78 (dd, *J* = 5.8, *J* = 3.4, 2H, Ar''), 7.54 (dd, *J* = 5.8, *J* = 3.4, 2H, Ar''), 7.44 (d, *J* = 7.8, 2H, Ar H-6), 7.31 (d, *J* = 7.8, 2H, Ar H-4), 7.17 (bs, 1H, Ar' H-5), 6.91 (bs, 2H, Ar' H-4, H-6), 6.62 (dd, *J* = 7.8, *J* = 7.8, 2H, Ar H-5), 4.50–4.19 (m, 8H, OCH₂-CH₂-CH₂O), 2.18 (bs, 4H, OCH₂-CH₂-CH₂O), 1.15 (bs, 3H, OAc); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 168.4 (C=O), 166.4 (CH=N), 161.5 (Ar C-2), 151.6 (Ar' C-1, C-3), 150.1 (Ar C-3), 146.7 (Ar'' C-1, C-2), 133.3 (Ar' C-2), 128.6, 128.3, 126.0 (Ar C-6, Ar' C-5, Ar'' C-4, C-5), 124.7 (Ar C-1), 121.2, 120.1, 116.0 (Ar C-4, C-5, Ar'' C-3, C-6), 111.5 (Ar' C-4, C-6), 68.7, 67.7 (OCH₂-CH₂-CH₂O), 54.8 (CH₃), 29.2 (OCH₂-CH₂-CH₂O). IR (KBr) 1764 ($\nu_{\text{C=O}}$ [non-coord], weak), 1700 ($\nu_{\text{C=O}}$ [coord], strong), 1603 ($\nu_{\text{N=C}}$, strong), 896 ($\nu_{\text{U=O}}$, strong) cm⁻¹. MS (FAB) *m/e* 865.8 (M + H)⁺, 887.5 (M + Na)⁺. Anal. Calc. for C₃₄H₃₀N₂O₁₀U·2H₂O: C, 45.34; H, 3.80, N, 3.11. Found: C, 45.49; H, 3.57, N, 2.95.

[37-Acetoxy-9,10,11,12,20,21,22,23-octahydro-3,7:14,18:25,29-trimetheno-8,13,19,24,1,31-benzotetraoxadiazacyclotritriacontine-36,38-diolato(2-)-N¹,N³¹,O³⁶,O³⁸] dioxouranium (2, *n* = 4). Yield 65%; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.58 (s, 2H, CH=N), 7.76 (dd, *J* = 6.0, *J* = 3.4, 2H, Ar''), 7.52 (dd, *J* = 6.0, *J* = 3.4, 2H, Ar''), 7.37 (dd, *J* = 7.9, *J* = 1.4, 2H, Ar H-6), 7.22 (dd, *J* = 7.9, *J* = 1.4, 2H, Ar H-4), 7.05 (t, *J* = 8.4, 1H, Ar' H-5), 6.80 (d, *J* = 8.4, 2H, Ar' H-4, H-6), 6.59 (dd, *J* = 7.9, *J* = 7.9, 2H, Ar H-5), 4.25–4.10 (m, 8H, OCH₂-CH₂-CH₂-CH₂O), 2.10–1.90, 2.05 (overlapping peaks: m, 8H, OCH₂-CH₂-CH₂-CH₂O, s, 3H, OAc); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 168.4 (C=O), 166.4 (CH=N), 160.9 (Ar C-2), 151.4 (Ar' C-1, C-3), 150.5 (Ar C-3), 146.7 (Ar'' C-1, C-2), 130.4 (Ar' C-2), 128.6, 127.1 (Ar C-6, Ar'' C-4, C-5), 126.1 (Ar' C-5), 124.1 (Ar C-1), 120.2, 117.9, 115.9 (Ar C-4, C-5, Ar'' C-3, C-6), 107.6 (Ar' C-4, C-6), 68.7, 68.4 (OCH₂-CH₂-CH₂-CH₂O), 25.7, 25.6 (OCH₂-CH₂-CH₂-CH₂O), 20.1 (CH₃). IR (KBr) 1734 ($\nu_{\text{C=O}}$ [non-coord], medium), 1700 ($\nu_{\text{C=O}}$ [coord], medium), 1603 ($\nu_{\text{N=C}}$, strong), 903 ($\nu_{\text{U=O}}$, strong) cm⁻¹. MS (FAB) *m/e* 893.3 (M + H)⁺, 915.3 (M + Na)⁺. Anal. Calc. for C₃₆H₃₄N₂O₁₀U·H₂O: C, 47.48; H, 3.98, N, 3.08. Found: C, 47.97; H, 3.93, N, 2.94.

2.2.2. Synthesis of 2,6-diethoxyphenyl acetate (4)

To 15 ml of dry CH₂Cl₂ flushed with Ar, 300 mg (1.65 mmol) of 2,6-diethoxyphenol (5) [8] were added. Then 1.0 ml (7.2 mmol) of triethylamine and 500 μ l (7.1 mmol) of acetyl chloride were added. The mixture was stirred overnight at room temperature. Then the mixture was dissolved in 40 ml of CH₂Cl₂ and shaken with 40 ml of water (that should result weakly basic). The aqueous phase was neutralized and extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated to dryness. The crude product was purified by column chromatography (SiO₂; hexane/AcOEt 100:3) obtaining a white solid. Yield 35%. m.p. 50–51°C. ¹H NMR (300 MHz, CDCl₃) δ 7.05 (t, *J* = 8.4, 1H, Ar H-4), 6.58 (d, *J* = 8.4, 2H, Ar H-3, H-5), 4.04 (q, *J* = 7.0, 4H, OCH₂-CH₃), 2.33 (s, 3H, OAc), 1.37 (t, *J* = 7.0, 6H, OCH₂-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 169.3 (C=O), 152.2 (Ar C-2, C-6), 130.0 (Ar C-1), 126.5 (Ar C-4), 106.5 (Ar C-3, C-5), 65.0 (OCH₂), 20.8 (CO-CH₃), 15.2 (OCH₂-CH₃).

2.3. Equilibrium measurements

Solutions have been prepared and handled under argon to minimize contamination by atmospheric carbon dioxide. Unnecessary or prolonged exposure to light of solutions containing the salophen-uranyl substrates was avoided to prevent decomposition processes. Spectrophotometric determinations of association constants were carried out at 25.0°C in a 10.0 mm quartz cuvette. A known amount of tetramethylammonium alkoxide in the parent alcohol was added by means of a microsyringe to a dilute (0.015–0.020 mM) solution of the substrate in the same solvent. The absorbance value at 360 or 350 nm was recorded after thermal equilibration and corrected for dilution. Reaction of alkoxide ion with the acetyl group of compounds 2 was in all cases slow enough to allow meaningful determinations of the association constants. To minimize complications arising from alcoholysis of the ester function, incremental addition of aliquots of alkoxide to the same substrate solution was avoided. A new substrate solution was employed in all experiments for each point in the titration curve. The data were fitted by means of non-linear least-square procedure to Eq. (3). The fraction of alkoxide ion sequestered by the substrate was calculated by means of an iteration procedure, and whenever required, the total alkoxide ion concentration was corrected accordingly.

2.4. Spectrophotometric rate measurements

Methanolysis and ethanolysis of compounds 2, *n* = 2–4, were monitored spectrophotometrically at 390 nm. Methanolysis of compound 4 was followed by monitoring the increase of absorption at 292 nm due to accumulation of the anionic form of the phenol product 5. The same

2.5. HPLC rate measurements

Samples of the reaction mixtures were withdrawn at time intervals, quenched with dilute perchloric acid, and subjected to HPLC analysis. Internal standard, column, eluent, and flow rate are indicated in the given order for the different substrates. Compound **2**, $n=2$: 2,6-dimethylanisole, 25 cm $\times$ 4.6 mm Alltech C-18 5U, MeOH/H₂O 70:30 (v/v), 0.5 ml min⁻¹. Compounds **2**, $n=3$ and **2**, $n=4$: 1-ethylnaphthalene, 25 cm $\times$ 4.6 mm Supelcosil LC-18-DB, CH₃CN/H₂O 70:30 (v/v), 0.9 ml min⁻¹. Compound **4**: 2,6-dimethylanisole, 25 cm $\times$ 4.6 mm Supelcosil LC-18-DB, CH₃CN/H₂O 1:1 (v/v), 0.8 ml min⁻¹. In all cases complete resolution of the peaks due to the acetate reactant **2** or **4**, phenol product **3** or **5** and internal standard was observed.

2.6. Molecular mechanics calculations

The molecular mechanics calculations have been performed using Quanta/CHARMM [13]. The coordinates of the salophen moiety with the complexed uranyl cation were taken from the literature [4,14] and kept constant during the minimizations by imposing atomic constraints. The non-bonded parameters for the uranyl cation were taken from literature [4,14]: $q_o = 0.0$ and $q_u = 2.0$, $R_{\min} = 3.00 \text{ \AA}$ and $E_{\min} = -1.00 \text{ kcal mol}^{-1}$. These parameters correctly reproduce the hydration energy of the uranyl cation in water and the coordination distances are similar to those in crystal structures [4,14]. The pyrogallol moiety was generated with Quanta and attached to the salophen unit. The TIP3P model of water has been used. The charges used are the so-called charge templates as provided by Quanta; except for the uranyl cation and the phenolate oxygen ($q_{\text{phenolate}} = -0.9$) [14b]. Small 'excess' charge was smoothed to non-polar carbons and hydrogens. The hydrated structures were made by rotating away the intramolecularly coordinated carbonyl in the minimized structures and placing the water at approximately the coordination distance to the uranium. Minimizations were run with a dielectric constant of 1 and no cutoff was applied to the non-bonded interactions. The structures were minimized by Adopted-Basis set Newton-Raphson until the RMS on the gradient was $<0.01 \text{ kcal (mol \AA)}^{-1}$.

3. Results and discussion

Because the kinetics disclosed a complicated dependence of reaction rates on alkoxide ion concentration, a great experimental effort was devoted to the collection of rate data over a wide concentration range. Parallel to the above rate measurements, investigation of the association equilibria between the salophen-uranyl substrates **2** and the alkoxide ions were carried out in the two base-solvent systems. Knowledge of the binding constants proved to be crucial to disentangle the intricate dependence of reaction rates upon base concentration, and to assess the role played by the proximal uranyl centre as a built-in electrophilic catalyst in the ester cleavage process. Structural information arising from IR and ^1H NMR spectroscopy, as well as from molecular mechanics calculations, was used to establish a link between ground state interactions and rate enhancements brought about by the metal centre.

3.1. Association equilibria

Addition of increasing amounts of either $\text{MeO-Me}_4\text{N}^+$ or $\text{EtO-Me}_4\text{N}^+$ to solutions of **2** in the parent alcohol caused small, but reproducible changes in the UV-VIS absorption spectra. Variations of absorbance (ΔA) were well described by the binding isotherm of Eq. (3), which applies to the case of association of 1:1 stoichiometry between RO^- and the substrate **S**. Here ΔA_∞ is the limiting value of ΔA and K is defined in Eq. (4) in terms of concentrations rather than activities because extensive cancellation of activity coefficients of negatively charged species is expected. A typical titration curve is shown in Fig. 1.

$$\Delta A = \frac{\Delta A_{\infty} K[\text{RO}^-]}{1 + K[\text{RO}^-]} \quad (3)$$

$$K = \frac{[\text{S} \cdot \text{RO}^-]}{[\text{S}] [\text{RO}^-]} \quad (4)$$

In view of the well-known ability of salophen-uranyl complexes to bind anions, interpretation of the above associations in terms of binding of the alkoxide species to the uranyl centre in the fifth equatorial coordination site ($2\cdot\text{RO}^-$) is straightforward.

Fig. 1. Spectrophotometric titration of 0.02 mM **2**, $n = 3$ with $\text{Me}_4\text{N}^+\text{MeO}^-$ in MeOH, at 25.0°C ($\lambda = 350$ nm).

The results of equilibrium measurements are summarized in Table 1. It is apparent that associations are 3–4 times stronger in the less polar ethanol and that the smaller macrocycle **2**, $n = 2$ binds the alkoxide ions an order of magnitude less strongly than its higher homologous, most likely because the alkoxide guests can be less easily accommodated in the smaller cavity.

3.2. Kinetics

3.2.1. Rate measurements

Because of the extremely low solubility of substrates **2**, $n = 2$ –4 in methanol and in ethanol, rate measurements were carried out on very dilute substrate solutions (0.015–0.020 mM) in the presence of excess alkoxide ion to allow for first-order time dependence. Reactions at very low methoxide concentration were carried out in the presence of a buffer formed by $(i\text{-Pr})_2\text{NEt}$ (Hünig base, 5.4 mM) and its perchlorate salt (0.54 mM). We found that in a buffer solution formed by equimolar quantities of the Hünig base and its conjugate acid the dissociation degree of *p*-nitrophenol is 0.45. Combination of this value with the $\text{p}K_a$ of the *p*-nitrophenol indicator ($\text{p}K_a = 11.5$ in MeOH at 25°C [15]) and the autoprotolysis constant of

Table 1

Equilibrium constants K (M^{-1})^a for 1:1 association between compounds **2**, $n = 2$ –4 and RO^- ($\text{R} = \text{Me}, \text{Et}$) in the parent alcohol, at 25.0°C^b

Compound	K (MeO^-/MeOH)	K (EtO^-/EtOH)
2 , $n = 2$	75	330
2 , $n = 3$	1300	3800
2 , $n = 4$	900	2600

^aError limits are in the order of $\pm 15\%$.

^bApproximate K values (M^{-1}) for the parent compound **1** are $\geq 1 \times 10^4$ in MeO^-/MeOH and $\geq 5 \times 10^4$ in $\text{EtOH}^-/\text{EtOH}$.

Fig. 2. Variation of absorbance for the ethanolysis of 0.015 mM **2**, $n = 4$ in the presence of 13.2 mM $\text{Me}_4\text{N}^+\text{EtO}^-$. Lower curve, time zero; upper curve, time infinite.

MeOH ($\text{p}K_{\text{MeOH}} = 16.9$ at 25°C [16]) led to an estimate of 3.0×10^{-5} for the molar concentration of methoxide ion in the given buffer solution. Whereas acid-base reactions in MeOH are well documented to be free from the complicating interference of homo- and heteroconjugation [17], we suspect [18] that in EtOH significant association exists between ethoxide ion and the acid form of the buffer to give the hydrogen bonded ion pair $\text{R}_3\text{NH}^+\cdots\text{OEt}$. Therefore, in the absence of a reliable way to estimate the ethoxide concentration in any buffer solution, rate measurements in EtOH in the presence of extremely dilute base could not be carried out.

Because conversion of the aryl acetate reactants **2** into phenol products **3** consistently resulted in a slight absorption increase over a wide range of wavelengths in the UV-VIS spectra (Fig. 2), we conveniently resorted to a spec-

Fig. 3. Variation of absorbance at 390 nm versus time for the ethanolysis of 0.015 mM **2**, $n = 4$ in the presence of 13.2 mM $\text{Me}_4\text{N}^+\text{EtO}^-$, at 25.0°C.

Fig. 4. Normalized plots of reactant and product versus time for the ethanolysis of 0.020 mM **2**, $n=3$ in the presence of 6.6 mM $\text{Me}_4\text{N}^+\text{EtO}^-$, as monitored by HPLC. The points are experimental and the curves are plots of the first-order equation [$(k_1)_{\text{obs}} = 1.16 \times 10^{-4} \text{ s}^{-1}$ from product accumulation and $(k_1)_{\text{obs}} = 1.22 \times 10^{-4} \text{ s}^{-1}$ from reactant disappearance].

trophotometric technique to monitor the reaction progress. From a set of preliminary measurements in which a photodiode array spectrophotometer was used, it was apparent that prolonged illumination induced a subsequent transformation of the phenol products, causing irreproducible results and more or less pronounced deviations from first-order behaviour. The above complication was largely overcome by monitoring the kinetics in a conventional spectrophotometer at the fixed wavelength of 390 nm, thus avoiding exposure of kinetic solutions to UV radiations. A typical spectrophotometric run is shown in Fig. 3.

A number of control experiments were carried out by monitoring the reaction progress by HPLC analysis of quenched reaction samples withdrawn at selected time intervals (Fig. 4). These experiments not only showed that conversion of **2** into **3** was virtually quantitative, but also afforded first-order rate constants in reasonably good agreement with those obtained from the spectrophotometric experiments.

The results of the kinetic experiments are summarized in Table 2 (MeOH) and Table 3 (EtOH) and graphically shown as $\log(k_2)_{\text{app}}$ versus alkoxide concentration in Fig. 5. It should be stressed that because of a series of difficulties, including (i) the inherent slowness of many reactions, requiring in some cases observation times of up to 4 weeks, (ii) the modest absorbance variations, typically in the order of about 0.03 absorbance units and, even more importantly, (iii) the inherent lability of the phenol products under prolonged illumination, the precision of the determined first-order rate constants is moderate, being in the order of 10–15%. Nevertheless, consistency with the HPLC experiments shows that the spectropho-

tometric measurements are meaningful over the entire ranges of alkoxide ion concentration.

3.2.2. Treatment of rate data and reaction mechanism

Only for reactions of the model compound **4** are the quantities $(k_2)_{\text{app}}$ listed in Tables 2 and 3 independent of alkoxide ion concentration, which clearly means that only the model compound reacts according to clean second-order kinetics. Reactions of the uranyl complexes **2** show $(k_2)_{\text{app}}$ values which are far from being constant. This is not surprising, as reactions of substrates **2** involve association equilibria between reactants.

A simple kinetic scheme (Scheme 3) involving fast and reversible preassociation followed by rate-limiting second-order reaction (k_2^A) of the alkoxide ion with un-

Table 2

Rate data for the basic methanolysis of **2**, $n=2-4$ and **4** at 25.0°C

$[\text{MeO}^-]$ (mM)	$(k_1)_{\text{obs}}$ (s^{-1})	$(k_2)_{\text{app}}$ ($\text{s}^{-1} \text{ M}^{-1}$) ^a
Compound 2 , $n=2$		
0.030 ^b	6.0×10^{-6c}	0.20
4.59	7.3×10^{-4}	0.16
9.09	1.3×10^{-3}	0.14
17.8	2.0×10^{-3}	0.11
27.0	2.5×10^{-3}	9.2×10^{-2}
50.7	3.4×10^{-3}	6.6×10^{-2}
Compound 2 , $n=3$		
0.030 ^b	5.9×10^{-7c}	2.0×10^{-2}
0.54	7.7×10^{-6}	1.4×10^{-2}
4.59	2.3×10^{-5}	5.0×10^{-3}
4.62	2.5×10^{-5c}	5.4×10^{-3}
9.09	4.2×10^{-5}	4.6×10^{-3}
10.1	4.8×10^{-5c}	4.8×10^{-3}
15.0	7.3×10^{-5c}	4.9×10^{-3}
17.8	9.3×10^{-5}	5.3×10^{-3}
17.8	9.6×10^{-5}	5.4×10^{-3}
20.7	1.2×10^{-4c}	5.8×10^{-3}
25.6	1.7×10^{-4c}	6.6×10^{-3}
27.0	1.7×10^{-4}	6.4×10^{-3}
34.1	2.2×10^{-4}	6.6×10^{-3}
34.1	2.3×10^{-4}	6.7×10^{-3}
Compound 2 , $n=4$		
0.030 ^b	9.1×10^{-7c}	3.0×10^{-2}
4.59	4.2×10^{-5}	9.2×10^{-3}
9.09	6.3×10^{-5}	6.9×10^{-3}
17.8	8.6×10^{-5}	4.8×10^{-3}
27.0	1.4×10^{-4}	5.1×10^{-3}
27.9	1.5×10^{-4c}	5.2×10^{-3}
50.7	2.9×10^{-4}	5.8×10^{-3}
Compound 4		
0.030 ^b	5.3×10^{-7c}	1.8×10^{-2}
11.5	1.9×10^{-4}	1.7×10^{-2}
15.5	2.3×10^{-4}	1.5×10^{-2}
22.3	3.7×10^{-4}	1.7×10^{-2}

^aCalculated as $(k_1)_{\text{obs}}/[\text{MeO}^-]$.

^b10:1 Hünig base/perchlorate salt buffer.

^cHPLC data.

Table 3

Rate data for the basic ethanolysis of 2, $n = 2$ –4 and 4 at 25.0°C

[EtO ⁻] (mM)	(k_1) _{obs} (s ⁻¹)	(k_2) _{app} (s ⁻¹ M ⁻¹) ^a
Compound 2, $n = 2$		
0.49	4.1×10^{-4}	0.84
0.49	4.4×10^{-4}	0.90
0.49	4.8×10^{-4}	0.99
0.68	6.6×10^{-4}	0.97
0.94	7.7×10^{-4}	0.82
2.25	1.3×10^{-3}	0.58
2.25	1.4×10^{-3}	0.63
2.68	1.6×10^{-3b}	0.61
3.00	1.8×10^{-3}	0.62
6.69	1.8×10^{-3}	0.27
13.2	2.5×10^{-3}	0.19
Compound 2, $n = 3$		
0.11	1.6×10^{-5}	0.15
0.49	3.5×10^{-5}	7.2×10^{-2}
2.25	7.9×10^{-5}	3.5×10^{-2}
4.48	8.9×10^{-5}	2.0×10^{-2}
6.56	1.2×10^{-4b}	1.9×10^{-2}
6.69	1.4×10^{-4}	2.0×10^{-2}
6.69	1.4×10^{-4}	2.1×10^{-2}
19.5	5.1×10^{-4}	2.6×10^{-2}
Compound 2, $n = 4$		
0.53	8.5×10^{-6}	1.6×10^{-2}
1.15	1.0×10^{-5}	9.0×10^{-3}
4.48	1.1×10^{-5}	2.6×10^{-3}
6.69	1.7×10^{-5}	2.5×10^{-3}
6.69	1.8×10^{-5}	2.7×10^{-3}
13.2	3.6×10^{-5}	2.7×10^{-3}
Compound 4		
13.2	4.5×10^{-5}	3.4×10^{-3}
28.7	1.0×10^{-4}	3.6×10^{-3}
32.4	1.1×10^{-4}	3.5×10^{-3}

^aCalculated as (k_1)_{obs}/[EtO⁻].^bHPLC data.

complexed substrate (path A) to give the reaction product P¹ proved to be unsatisfactory to describe the observed dependence of rates on alkoxide ion concentration. Therefore the reaction scheme was modified with the inclusion of an additional reaction pathway involving a second-order reaction (k_2^B) of the alkoxide ion with the complexed substrate (path B). Scheme 3 is easily translated into the corresponding rate expression (Eq. (5)), in which v is the rate of reaction, $[S]_{\text{tot}}$ is the sum of free and complexed substrate, $\gamma_A = \gamma_B$ is the activity coefficient of a singly charged anion, γ_* is the activity coefficient of the doubly charged anionic transition state and k_2^B refers to zero ionic strength. Thus the product $k_2^B(\gamma_A\gamma_B/\gamma_*)$ is the

¹ It is clear that there is no observable kinetic difference between the mechanism described as path A and one in which P is formed by a first-order reaction (k_1) of S·RO⁻. It can be easily shown that $k_2^A = Kk_1$. Our preference for a mechanism in which S·RO⁻ is an unproductive intermediate will be clarified later on.

Scheme 3.

quantity predicted by the Brønsted equation for the primary salt effect on the rate of reaction between two univalent ions having the same sign of charge.

$$\frac{v}{[S]_{\text{tot}}} = (k_1)_{\text{obs}} = \frac{k_2^A [RO^-] + k_2^B (\gamma_A \gamma_B / \gamma_*) K [RO^-]^2}{1 + K [RO^-]} \quad (5)$$

It should be noted that a negligible salt effect is predicted for the anion-(neutral molecule) reaction of path A.

Activity coefficients were calculated from the extended Debye–Hückel equation (Eq. (6)).

$$\log \gamma_i = -\frac{z_i^2 A \sqrt{\mu}}{1 + b \sqrt{\mu}} \quad (6)$$

$$A = 1.826 \times 10^6 (\epsilon T)^{-3/2} \quad (7)$$

$$b = 50.3 (\epsilon T)^{-1/2} d \quad (8)$$

The quantities A and b are defined by Eqs. (7) and (8), respectively, d being the Bjerrum distance. Combination of Eqs. (5) and (6) leads to Eq. (9), where the quantity Y is defined by Eq. (10).

$$\frac{(k_1)_{\text{obs}}}{[RO^-]} = (k_2)_{\text{app}} = \frac{k_2^A + k_2^B K [RO^-] 10^Y}{1 + K [RO^-]} \quad (9)$$

$$Y = \frac{2A \sqrt{\mu}}{1 + b \sqrt{\mu}} \quad (10)$$

Eq. (9) was used to fit the experimental data. Upon introduction of the known K values from Table 1, using a Bjerrum distance of 5 Å, and with the ionic strength μ given by the concentration of tetramethylammonium alkoxide, Eq. (9) reduced to an equation with two adjustable parameters, namely k_2^A and k_2^B , whose numerical values were optimized by means of a non-linear least-square procedure. The calculated profiles in Fig. 5 were obtained from Eq. (9) and the optimized parameters collected in Tables 4 and 5, respectively. Since the standard deviations of the data from the regression line (Tables 4 and 5) are comparable to the experimental uncertainties of the individual rate constants, fit of Eq. (9) to the data is more than satisfactory.

It is not surprising that rate constants for reactions occurring through path A are invariably larger than the cor-

Fig. 5. Apparent second-order specific rates (k_2)_{app} ($M^{-1} s^{-1}$) as a function of alkoxide concentration. The points are experimental (full symbols, UV data; empty symbols, HPLC data) and the curves were calculated from Eq. (9) and the parameters listed in Tables 4 and 5. The horizontal lines represent the second-order rate constants for reactions of the model compound 4.

It is not surprising that rate constants for reactions occurring through path A are invariably larger than the corresponding quantities for reactions occurring through path B, because the latter are affected by electrostatic repulsions between negatively charged reactants.

In the last columns of Tables 4 and 5, a comparison is made between rates of alcoholysis of uncomplexed substrates 2, $n = 2-4$ and rates of alcoholysis of the model compound 4. In EtOH solution, the observed rate accelerations, grading regularly from a 310-fold for $n = 2$ to a 9-fold for $n = 4$, point to a definite role played by the proximal uranyl centre as Lewis acid catalyst. Because of the negative charge being transferred from the incoming alkoxide to the ester carbonyl, the oxygen atom of the latter becomes a much better donor (stronger Lewis base) in the transition state than in the initial state.

Table 4

Basic methanolysis at 25.0°C: least-squares kinetic parameters

Compound	k_2^A ($s^{-1} M^{-1}$)	k_2^B ($s^{-1} M^{-1}$)	$\sigma\%$	k_{rel}
2, $n = 2$	$(2.2 \pm 0.2) \times 10^{-1}$	$(9 \pm 3) \times 10^{-3}$	8	14
2, $n = 3$	$(2.0 \pm 0.2) \times 10^{-2}$	$(2.0 \pm 0.2) \times 10^{-3}$	9	1.2
2, $n = 4$	$(3.3 \pm 0.4) \times 10^{-2}$	$(1.5 \pm 0.2) \times 10^{-3}$	8	2.1
4	$(1.6 \pm 0.2) \times 10^{-2}$	—	—	1.0

Much smaller rate accelerations are observed in MeOH. Here a modest 14-fold increase in rate still shows up for the smaller macrocycle, but marginal 1.2- and 2.1-fold accelerations are found for the higher homologues in the given order.

The acceptor numbers AN of MeOH and EtOH are 41.5 and 37.9, respectively [19]. It appears therefore that the demand for electrophilic assistance from the uranyl centre is stronger in the solvent (EtOH) which has less pronounced electron pair acceptor (EPA) [19] properties. This might explain the different sensitivity experienced by reaction (1) to the presence of the uranyl electrophile in the two given solvents, but other factors such as ground state solvation of the uranyl complexes may play a role. A

Table 5

Basic ethanolysis at 25.0°C: least-squares kinetic parameters

Compound	k_2^A ($s^{-1} M^{-1}$)	k_2^B ($s^{-1} M^{-1}$)	$\sigma\%$	k_{rel}
2, $n = 2$	1.1 ± 0.1	$\leq 1 \times 10^{-2a}$	12	310
2, $n = 3$	$(2.0 \pm 0.4) \times 10^{-1}$	$(6 \pm 1) \times 10^{-3}$	13	57
2, $n = 4$	$(3.2 \pm 0.8) \times 10^{-2}$	$(4 \pm 2) \times 10^{-4}$	19	9
4	$(3.5 \pm 0.2) \times 10^{-3}$	—	—	1

^aThe goodness of fit, as measured by the σ parameter, is very nearly the same using for k_2^B any numerical value lower than 1×10^{-2} .

Fig. 6. Calculated structures for compounds $2, n = 2, 4$ and their hydrated forms.

similar phenomenon, namely, a much stronger metal ion catalysis in EtOH than in MeOH was recently reported for the alkaline-earth metal ion assisted basic alcoholysis of esters [6].

3.3. Structural information

The structures of $2, n = 2-4$ were studied by molecular mechanics using Quanta/CHARMm (Fig. 6). The minimized structure of $2, n = 2$ (Fig. 6, top left) has two features that deserve attention. The first is that the ester carbonyl group is coordinated to the electrophilic uranyl cation. The second is that because of this intramolecular coordination the methyl group of the acetate function is positioned over the pyrogallol ring. On this basis an upfield shift of the methyl resonance in the 1H NMR spectrum is anticipated. The hydrated form of $2, n = 2$ was generated and minimized. The calculated structure (Fig. 6, top right) shows that this macrocycle can accommodate a water molecule without severe distortion of the salophen-uranyl unit. In addition to coordination of the water oxygen to the uranyl cation, hydrogen bonding to the oxygens of the host is observed.

The minimized structure of $2, n = 4$ (Fig. 6, bottom left) shows that intramolecular coordination of the carbonyl group is still possible with the methyl group close to the pyrogallol ring. Not surprisingly $2, n = 4$ can easily accommodate a molecule of water (Fig. 6, bottom right). Compound $2, n = 3$ (structure not reported) showed intermediate behaviour.

Consistent with the above molecular mechanics calculations, the signal of the methyl protons are found at δ 0.67 (broad singlet) for $2, n = 2$, 1.15 (broad singlet) for $2, n = 3$ and 2.05 (sharp singlet) for $2, n = 4$, whereas the methyl signal of **4** is found at δ 2.33 (sharp singlet). Equally consistent are the FT-IR spectra (KBr). Compound $2, n = 2$ displays two C=O stretching vibrations at 1762 and 1720 cm^{-1} . Whereas the former can be attributed to a non-coordinated carbonyl group, possibly belonging to a water complexed molecule, the latter is most likely due to a carbonyl group intramolecularly coordinated to the metal. The corresponding bands for the higher homologues are shown at 1764 and 1700 cm^{-1} $2, n = 3$ and 1734 and 1700 cm^{-1} $2, n = 4$.

Thus there is compelling evidence both of direct (IR) and indirect (1H NMR) nature that there is significant binding of the carbonyl group to the metal centre in the ground state. As long as the magnitude of the upfield shifts of the methyl signals in the 1H NMR spectra reflect the extent of complexation, a close parallelism is found between ground state interactions and rate accelerations measured in EtOH.

Finally we note that a glance to the calculated structures in Fig. 6 suggests that a mechanism in which a metal-complexed alkoxide is intramolecularly transferred to the ester carbonyl is unlikely, particularly in the smallest macrocycle $2, n = 2$ whereas addition of external alkoxide seems more plausible.

4. Conclusions

In summary, we have synthesized a series of model ester substrates composed of a pyrogallol acetate moiety and a salophen-uranyl moiety incorporated into the same metallomacrocycles by means of polymethylene bridges of variable length. A thorough kinetic investigation of the base-induced methanolysis and ethanolysis of the synthesized substrates provides unequivocal evidence that the uranyl centre does play a role as a built-in Lewis acid catalyst of ester cleavage. Not unexpectedly, the size of the acceleration markedly decreases on increasing the length of the connecting polymethylene bridges, and is critically dependent on solvent polarity. Rate enhancements are much larger in EtOH than in MeOH, probably on account of the less pronounced EPA property of the former solvent. This finding deserves careful consideration in future studies aimed at designing supramolecular catalysts based on the salophen-uranyl unit.

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