Barium(II) complexes of calixcrowns derived from *p-tert*-butylcalix[5]arene as potential transacylation catalysts. Regio- and stereo-selective monoacylation of the calixcrown

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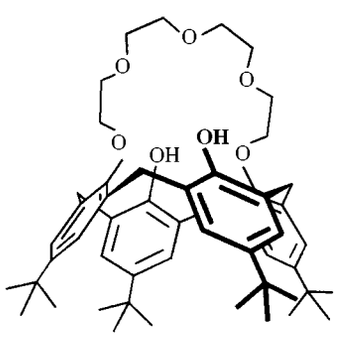
Several crown ethers derived from *tert*-butylcalix[5]arene have been studied in the form of their barium(II) salts as turnover catalysts in the methanolysis of *p*-nitrophenyl acetate in MeCN–MeOH (9:1, v/v) using UV spectroscopy and HPLC. The liberation of *p*-nitrophenol can be interpreted for 1,3-crown ether derivatives by a double displacement mechanism, although their catalytic activity is lower than for the corresponding *tert*-butylcalix[4]arene derivative. Regioselective *O*-acylation of ring 2 has been proved for crown-5 and crown-6 by ^{1}H NMR of the isolated intermediate. Whilst this monoacetyl derivative of crown-6 assumes the expected cone conformation, it is formed exclusively as the partial cone conformer from the crown-5. This observation enables the regio- and stereo-selective monoacylation of the 1,3-crown-5 derivative also on a preparative scale by reaction with *p*-nitrophenyl esters in the presence of one molar equivalent of Ba^{2+} ions.

Introduction

One way to obtain a deeper understanding of naturally occurring processes is to construct and to investigate suitable model systems, which are able to mimic in part the sophisticated reactions occurring in nature. To this end the development of supramolecular systems endowed with catalytic properties ('enzyme-mimics'), remains a constant challenge in contemporary chemistry,[1–3] which may have also some spin-off for other fields of organic chemistry.

We have shown that the barium salt of *p-tert*-butylcalix[4]-arene-crown-5† **1** ($\mathbf{1}^{2-}Ba^{2+}$) may act as a turnover catalyst



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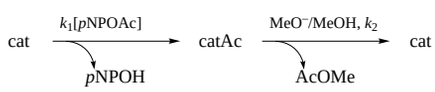
in the methanolysis of *p*-nitrophenyl acetate (*p*NPOAc) [in MeCN–MeOH (9:1, v/v)].[4] The catalyst (generated *in situ* from equimolar amounts of $BaBr_2$ and the parent calixcrown **1**) takes the acetyl group from *p*NPOAc and transfers it to the methoxide ion, thus restoring its active form. This double displacement mechanism is illustrated in Scheme 1, where cat and catAc denote active forms of the catalyst and of the acylated intermediate, respectively.

Fast acylation of cat followed by slow breakdown of catAc to release cat led to biphasic kinetics (burst kinetics)[5] for the liberation of *p*-nitrophenol (*p*NPOH). In this prototype catalyst the key role of the metal ion is twofold: it enhances the acidity of the phenolic OH groups of the catalyst and it provides an electrophilic assistance, both in the acylation step and in the subsequent transfer of the acyl group to the external nucleophile. A similar example of a barium-based transacylation catalyst in which a thiol group is the acyl-receiving and acyl-releasing unit has been also reported recently.[6]



Scheme 1

Crown ethers derived from *p-tert*-butylcalix[5]arene[7] as a molecular platform could provide an interesting extension of our catalytic studies. Therefore, we have investigated several calix[5]crown ethers (**2**–**6**) as catalysts in the methanolysis of *p*NPOAc in the presence of $BaBr_2$. Although these compounds showed in general very poor catalytic properties, the experiments revealed a remarkable regioselective monoacylation of the catalyst, as well as an interesting stereoselective monoacylation in one case. The results of these studies are reported here.

Results and discussion

Kinetics and product analyses

The synthesis of crown ethers derived from calix[5]arene and *tert*-butylcalix[5]arene has been described recently.[7,8] Compounds **2**–**6** were tested for catalytic activity under reaction conditions used earlier for crown ether **1**.[4] Concentration–time profiles corrected for the production of *p*NPOH due to background methanolysis are shown in Fig. 1. With the sole exception of the experiment carried out in the presence of the 1,2-crown **6**, the production of *p*NPOH was significantly faster than the background methanolysis (compare also Table 1).

Concentration–time profiles were analysed as a superimposition of an exponential and a linear phase, according to

† IUPAC name: $1^5,3^5,5^5,7^5$-tetra-*tert*-butyl-$1^2,5^2$-dihydroxy-$3^2,7^2$-(1,4,7,10,13-pentoxatridecyl)-1,3,5,7(1,3)-tetrabenzenacyclooctaphane.

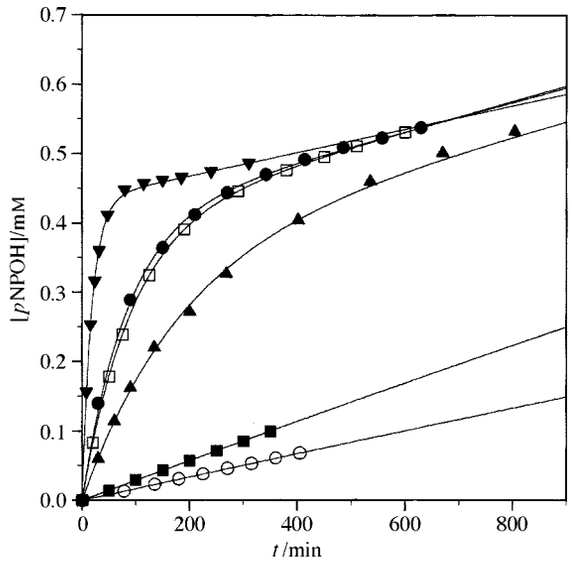


Fig. 1 Effect of various calixcrown–barium(II) complexes on the methanolysis of *p*NPOAc in buffered acetonitrile–methanol (9:1) at 25 °C. Spectrophotometric monitoring of *p*NPOH liberation in the absence (■) and presence of 0.44 mM $BaBr_2$ and 0.44 mM **2** (▼), **3** (●), **4** (▲), **5** (□) and **6** (○), respectively. The points are experimental and the lines are calculated by means of eqn. (1) and the parameters listed in Table 1.

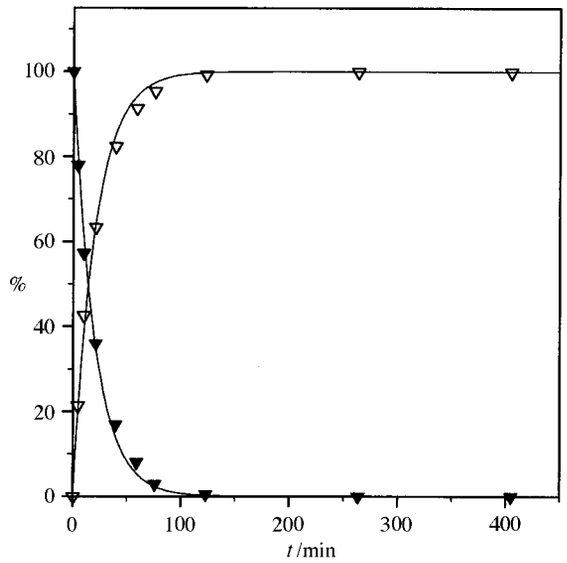


Fig. 2 Monitoring of *p-tert*-butylcalix[5]arene-crown-5 **2** (▼) and of its monoacylated form **7a** (▽) by HPLC during *p*NPOAc methanolysis in the presence of 0.44 mM **2** and 0.44 mM $BaBr_2$. The points are experimental and the curves are plots of the first order equation with $k = 4.83 \times 10^{-2}$ min^{-1} (disappearance of **2**) and $k = 4.95 \times 10^{-2}$ min^{-1} (accumulation of **7a**).

Table 1 Effect of calixarene–barium(II) complexes in the methanolysis of *p*NPOAc[a] followed by spectrophotometric monitoring of *p*NPOH liberation

Calixcrown[b]	π[c]/mmol dm^{-3}	k[c]/10^{-3} min^{-1}	s[c]/10^{-7} mol dm^{-3} min^{-1}
none	—[d]	—[d]	2.9
2	0.44	52	1.2
3	0.39	13	2.4
4	0.39	4.8	1.7
5	0.39	11	2.4
6	—[d]	—[d]	1.7
1[e]	0.40	121	24

[a] MeCN–MeOH 9:1 (v/v), diisopropylethylamine bromide salt buffer, 25 °C, c(*p*NPOAc) = 3.0 mM. [b] In experiments carried out in the presence of calixcrowns (0.44 mM) an equimolar amount of $BaBr_2$ (0.44 mM) was added to the reaction mixture. The corresponding profiles have been corrected for background methanolysis. [c] For the definition of the parameters see text. Values have been obtained from non-linear least squares fitting of experimental data to eqn. (1). [d] The slope of the linear profile obtained in this case is reported. [e] Data from ref. 4.

eqn. (1), where k is the rate constant of the exponential (first-

$$c_t(p\text{NPOH}) = \pi(1 - e^{-kt}) + st \quad (1)$$

order) phase and s is the slope of the linear (zero-order) phase.[6] The quantity π is the infinity value of the exponential phase, that is approached when $kt > 5$ and eqn. (1) is reduced to the simple form eqn. (2). Therefore π represents the initial 'burst' of *p*NPOH.

$$c_t(p\text{NPOH}) = \pi + st \quad (2)$$

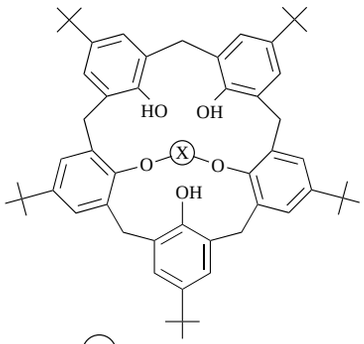
Fitting the data to eqn. (1) by means of a non-linear least squares procedure gave the kinetic parameters listed in Table 1. It was found that π approximately corresponds to the initial concentration of the calixcrown. This suggests that the process for the liberation of *p*NPOH in the exponential phase is acetyl transfer from *p*NPOAc to the calixcrown.

Quantitative conversion of **2** into a single monoacylated derivative was established by combined HPLC and HPLC–ESMS analyses of the reaction progress. These results are plotted in Fig. 2. The first-order rate constant $k = 4.83 \times 10^{-2}$ min^{-1} for the decay of **2** compares well not only with the value of 4.95×10^{-2} min^{-1} obtained for the accumulation of its monoacetylated derivative, but also with the value of 5.16×10^{-2} min^{-1} determined for the exponential liberation of *p*NPOH (Table 1). Analogous HPLC and HPLC–ESMS experiments showed virtually quantitative and selective conversions of calixcrowns **3** and **5** into their corresponding monoacetylated derivatives.

Small samples of the monoacetylated derivatives of calixcrowns **2** and **3** were isolated from scaled up kinetic experiments and studied by ^{1}H NMR spectroscopy. Three signals in the ratio 1:2:2 for the resonances of the *tert*-butyl groups showed that a symmetrical product is formed in both cases, which means that the acetylation occurs at the isolated OH group of ring 2 in the 1,3-crown ethers. This finding strongly suggests that the active forms of the calixcrowns undergoing acetylation are the barium complexes of the dianions derived from **2** and **3**. There seems to be little doubt that the most acidic hydroxy group of the 1,3-crowns is one of the adjacent OH groups of rings 4/5, due to intramolecular hydrogen bond stabilisation of the conjugate base (the monoanion). For the same reason, the isolated OH group at ring 2 ranks next in acidity. In line with these arguments, acylation takes place at the most basic (and most nucleophilic) site of the dianion. (In the presence of weak bases like CsF or Hünig's base the acylation of **2** occurs at ring 4/5, however.[9])

It is worth emphasising that strong complexation to the barium ion is crucial. In the absence of barium, or when the calixarene lacks an efficient metal binding site, no dissociation of the phenolic hydroxys takes place in the weakly basic diisopropylethylamine buffer. With the calix[4]arene derivative **1**, production of the dianion in the presence of 1 molar equivalent of $BaBr_2$was extensive, but not complete.[4] It is reasonable to assume that the reactivity order in the acylation step, namely **1** > **2** > **3** = **5** > **4** > **6** reflects to some extent the availability of the dianionic form, which in turn is possibly related to a decreasing affinity towards the barium ion in the given order.

The rates of *p*NPOH production in the zero order period of the concentration–time profiles (Fig. 1) are in all cases very similar to each other and comparable in magnitude to the contribution of the background methanolysis. They are significantly lower than the rate of *p*NPOH production in the steady-state period of the reaction catalysed by calix[4]crown **1**



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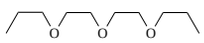
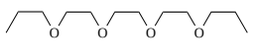
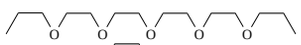
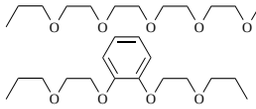
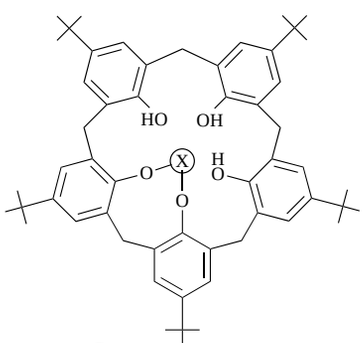
2 

3 

4 

5 



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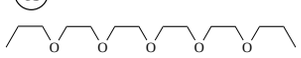
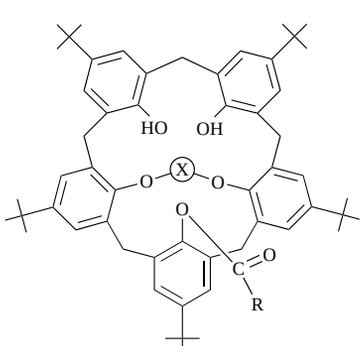
6 



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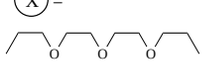
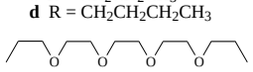
7 

a R = CH_3
b R = CH_2CH_3
c R = $CH_2CH_2CH_3$
d R = $CH_2CH_2CH_2CH_3$

8 

(see the values *s* in Table 1). Maybe these low rates of production of *p*NPOH reflect low deacylation rates of the acetylated calix[5]crowns. However, the possibility that complexation of barium to the (acetylated) calix[5]crowns is not complete and, consequently, that the background methanolysis is enhanced by the fraction of uncomplexed barium should be also considered. For instance, we recently showed that the methanolysis of *p*NPOAc in MeCN–MeOH (9:1, v/v) is enhanced by the addition of $Ba(ClO_4)_2$ to the buffered solution.[6]

This question was investigated in detail for the reaction of calix[5]crown **2**. The deacetylation of its acetylated derivative **7a** was studied (initial rate method) by HPLC analysis under conditions identical to those of the catalytic experiments and found to occur at a rate of $v_0 = 6.6 \times 10^{-9}$ mol dm^{-3} min^{-1}. This is much lower than that expected from the steady state kinetics ($s = 1.2 \times 10^{-7}$ mol dm^{-3} min^{-1}; Table 1). On the basis of this result we conclude that the catalyst turns over, but does so with an exceedingly low efficiency caused by the extreme slowness of the deacylation step. Only a tiny fraction of the production of *p*NPOH in the steady state phase is due to the expected double displacement mechanism. A much larger fraction is probably ascribable to the metal ion not sequestered by the catalyst and available in solution for electrophilic assistance to direct methanolysis of *p*NPOAc.

The acylated catalyst

The ^{1}H NMR spectra ($CDCl_3$) of the monoacetyl derivatives **7a** and **8** of crown ethers **2** and **3**, respectively, also revealed interesting structural information. Whereas the signal of the CO–CH_3 protons is slightly downfield shifted in **8** ($\delta = 2.75$) relative to phenyl acetate ($\delta = 2.40$) the corresponding signal of **7a** is found at $\delta = -0.74$, which represents a strong upfield shift of more than 3 ppm. This can be understood by the assumption that the acetyl residue is embedded in the calixarene cavity in the case of the crown-5 derivative **7a**, which consequently must adopt a sort of 'partial cone' or 'flattened cone' conformation.[10,11] Similar self-inclusion phenomena have been also reported for substituted calix[6]arenes[12] and cyclodextrins.[13–16]

Unfortunately we were not able to grow single crystals and to establish by X-ray analysis the conformational difference between **7a** and **8** for which we assume a cone conformation on the basis of the ^{1}H NMR spectrum. We therefore extended the kinetic studies to the methanolysis of *p*-nitrophenyl propionate catalysed by the barium complex of **2**, which is the only catalytically promising calix[5]arene derivative (Table 1). Here the acylation of the catalyst ($k = 8.3 \times 10^{-3}$ min^{-1}, determined from spectroscopic measurement of *p*NPOH liberation) is about six times slower than with *p*-nitrophenyl acetate. The slope of the profile of *p*NPOH liberation obtained at steady state in the presence of the barium(II) salt of the calixcrown ($s = 1.0 \times 10^{-7}$ mol dm^{-3} min^{-1}) is also in this case close to the slope of the background process ($s = 2.3 \times 10^{-7}$ mol dm^{-3} min^{-1}).

In preparative experiments under conditions similar to the kinetic runs all monoester derivatives **7a**–**7d** (acetate to pentanoate) could be synthesised in yields of 84–95% by acylation of **2** (in form of its barium salt $\mathbf{2}^{2-}Ba^{2+}$) with the corresponding *p*-nitrophenyl esters. In all cases the signals for the acyl residue are strongly shifted upfield, as shown in Fig. 3. This suggests for all monoesters a similar 'partial cone' conformation, in which the acyl residue of the 'inverted' phenyl ester ring is embedded in the calixarene cavity, as illustrated in Fig. 4 for **7d**.

The different chemical shifts for the different protons of the acyl groups not only reflect differences in shielding by the aromatic residues of the calixarene part but also the deshielding by the ester carbonyl group. This latter effect is most pronounced if the propionate **7b** ($\delta = -0.86$ for $-CH_3$ and $\delta = -0.33$ for $-CH_2-$) is compared with the acetate **7a** ($\delta = -0.74$ for $-CH_3$). While the shielding of the terminal methyl group is similar in **7b** and **7c** ($\delta = -0.88$) the methyl group is less shielded again in **7d** ($\delta = -0.20$) in which now the γ-CH_2 group is most shielded ($\delta = -0.62$). Although slight differences in the calixarene conformation will be also caused by the different size of the included acyl group, it is reasonable to assume that, in the case of the pentanoate **7d**, the acyl chain is already long enough, to protrude from the calixarene cavity (compare Fig. 4). This may be considered as an additional proof for the postulated 'partial cone' conformation of monoesters.

From variable temperature studies of calix[5]arene pentaesters Gutsche concluded[11] that an acetyl, propanoyl and even *n*-butanoyl group can pass the annulus of a calix[5]arene while

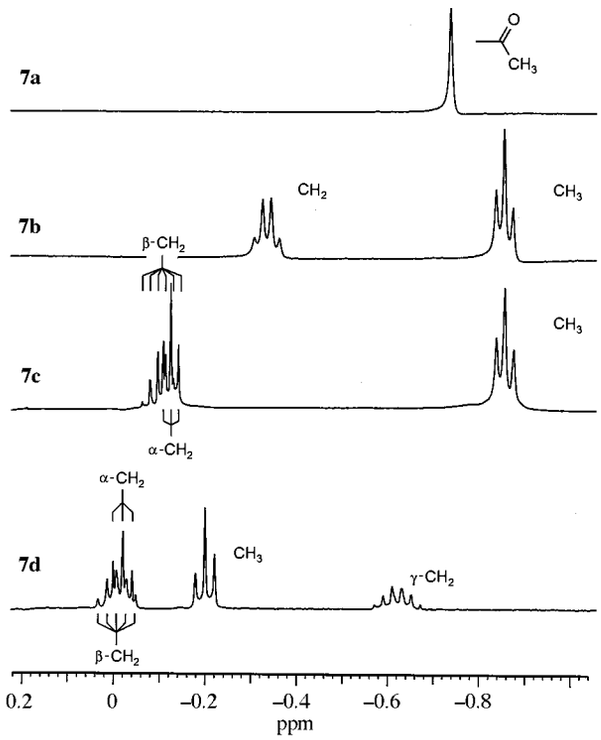


Fig. 3 Section of the ^{1}H NMR spectra ($CDCl_3$, 200 MHz) of monoesters **7a**–**7d**

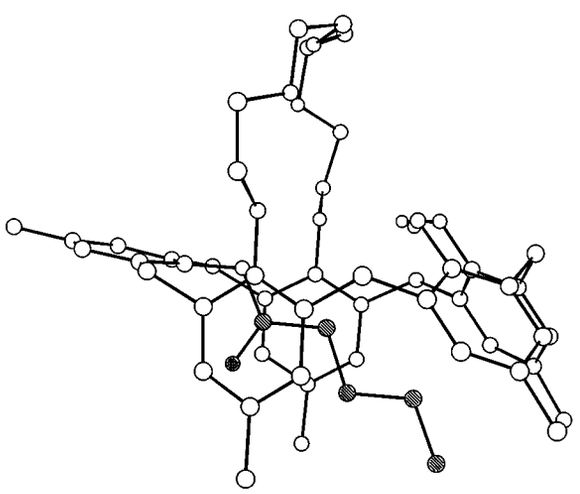


Fig. 4 Illustration of a 'flattened partial cone' conformation of **7d** which explains the high field shift of the signals of the pentanoyl residue

an isobutanoyl or pentanoyl group cannot. This is not necessarily true for a partial ester where an additional conformational stabilisation is possible from intramolecular hydrogen bonds, and especially not for monoesters like **7** or **8**. Although one could assume that the conformational difference of **7a** and **8** is due to the different stability of conformationally mobile compounds, such a conformational interconversion seems impossible for **7c/7d**. It is reasonable therefore, to assume that all esters **7** are directly formed in the 'partial cone' conformation and that the conformational difference to **8** reflects the different conformation of barium salts $\mathbf{2}^{2-}Ba^{2+}$ and $\mathbf{3}^{2-}Ba^{2+}$ (or of the transition states during their monoacylation). Unfortunately, all the attempts to study the conformation of these barium salts by NMR in a medium similar to that of the methanolysis experiments were frustrated by severe solubility problems.

Conclusions

Several crown ethers derived from *tert*-butylcalix[5]arene have been studied in the presence of a stoichiometric amount of barium(II) as catalysts for the methanolysis of *p*-nitrophenyl acetate. Although burst kinetics have been observed for the liberation of *p*-nitrophenol for all 1,3-crown ethers **2** to **5**, these calix[5]arene derivatives cannot compete in their catalytic activity with the barium(II) salt of the corresponding calix[4]arene derivative **1**. Regioselective *O*-acylation of ring 2 of the catalyst has been proved for **2** and **3** by isolation of the acylated intermediates **7** and **8**, but the liberation of *p*-nitrophenol under steady state conditions (corrected for the uncatalysed background methanolysis) is only partly due to turnover of the catalyst, and a direct catalysis by Ba^{II} cannot be excluded. Surprisingly, the 2-acyl derivatives **7a**–**d** are formed exclusively in a (fixed) 'partial cone' conformation with the acyl residue embedded in the cavity, which may explain the low deacylation rates. While the monoacylation of 1,3-crown ethers of *tert*-butylcalix[5]arene in the presence of weak bases usually occurs in the 4/5-position, the regio- and stereo-selective preparation of 2-acyl derivatives by acylation of their barium(II) salts with *p*-nitrophenyl esters is also possible on a preparative scale. This provides another example for the rich and sophisticated stereochemistry of calixarenes in general, and of *tert*-butylcalix[5]arene in particular.

Experimental

Kinetic measurements

Methanolysis of *p*NPOAc was carried out in MeCN–MeOH (9:1, v/v) containing a buffer composed of 62 mmol dm^{-3} diisopropylethylamine and 20 mmol dm^{-3} diisopropylethylammonium bromide [c(B)/c(BH$^+$) = 3.1] at 25 °C. Solutions for rate measurements contained 0.44 mmol dm^{-3} calixcrown, 0.44 mmol dm^{-3} $BaBr_2$, and 3.0 mmol dm^{-3} *p*NOPAc. The liberation of *p*NPOH was monitored at 450 nm (ε_{app} = 1600 dm^{-3} mol^{-1} cm^{-1}), using a HP 8452 diode array spectrophotometer. Further details have been previously described.[4,6]

For liquid chromatography either a Hewlett Packard 1050 or a Varian Model 9010 (Walnut Creek, CA) instrument was used, fitted with a UV–VIS detector operating at 230 nm. Samples of the reaction mixture were withdrawn at appropriate time intervals, quenched with dilute trifluoroacetic acid or hydrobromic acid and subjected to quantitative analysis: Supelcosil LC-18-DB column (25 cm × 4.6 mm ID; particle size 5 μm), methanol as eluent, flow rate 1 ml min^{-1}, **6** as an internal standard.

HPLC–MS experiments were carried out on a Fisons Instruments VG-Platform benchtop mass spectrometer equipped with a pneumatically assisted electrospray LC–MS interface and a single quadrupole. The mass spectrometer was operated in the positive-ion mode by applying to the capillary a voltage of 3.8 kV, while the skimmer cone voltage was set at 20 V. The mass spectrometry data handling system used was the Mass Lynx software from Fisons Instruments. The calixcrowns as well as their monoacetates were detected as their $(M + Na)^+$ and $(M + K)^+$ ions.

Syntheses

The preparation of the crown ethers has been described elsewhere.[7,8] The *p*-nitrophenyl esters were obtained by reaction of stoichiometric amounts of *p*-nitrophenol, the corresponding acid and dicyclohexylcarbodiimide in dry ethylacetate.

General procedure for the monoacylation of 2. To a solution of **2** (145.5 mg, 0.15 mmol), $Ba(ClO_4)_2$ (50.5 mg, 0.15 mmol), diisopropylethylamine (5.05 ml, 29 mmol) and HBr (7.0 mmol in form of a 9 M aqueous solution) in 315 ml acetonitrile and 35 ml methanol, 1.0 mmol of the required *p*-nitrophenyl ester was added (in form of 0.2 M stock solution). After 3 h at 25 °C the reaction was quenched by the addition of 2 ml conc. HCl and 400 ml of water. The aqueous phase was extracted three times with 100 ml $CHCl_3$. The organic phases were combined, dried ($MgSO_4$), evaporated, and the residue puri-

fied by chromatography (100 g silica gel, chloroform–acetone 20:1).

Monoester **7a**.—Yield 95%; mp 180 °C; δ_H(400 MHz, $CDCl_3$) 7.92 (br s, 2 H, OH), 7.14 (br s, 2 H, ArH), 7.08 (d, *J* 2.0, 2 H, ArH), 7.01 (d, *J* 2.0, 2 H, ArH), 6.86 (br s, 2 H, ArH), 6.66 (d, *J* 1.7, 2 H, ArH), 4.41 (d, *J* 14.7, 2 H, $ArCH_2Ar$), 4.01–3.33 (m, 22 H, $OCH_2CH_2O/ArCH_2Ar$), 3.31 (d, *J* 14.6, 2 H, $ArCH_2Ar$), 1.37 (s, 9 H, Bu^t), 1.22 (s, 18 H, Bu^t), 1.01 (s, 18 H, Bu^t), −0.74 (s, 3 H, CH_3); *m*/*z* (FD) 1011.7 (100%, M^+. Calc. for $C_{65}H_{86}O_9$: 1011.4).

Monoester **7b**.—Yield 91%; mp 227 °C; δ_H(400 MHz, $CDCl_3$) 8.52 (s, 2 H, OH), 7.15 (s, 2 H, ArH), 7.11 (d, *J* 2.2, 2 H, ArH), 7.09 (d, *J* 2.0, 2 H, ArH), 6.92 (d, *J* 2.0, 2 H, ArH), 6.68 (d, *J* 2.1, 2 H, ArH), 4.35 (d, *J* 14.0, 2 H, $ArCH_2Ar$), 4.36–3.43 (m, 22 H, $OCH_2CH_2O/ArCH_2Ar$), 3.39 (d, *J* 14.0, 2 H, $ArCH_2Ar$), 1.37 (s, 9 H, Bu^t), 1.26 (s, 18 H, Bu^t), 1.02 (s, 18 H, Bu^t), −0.33 (q, *J* 7.3, 2 H, $COCH_2$), −0.86 (t, *J* 7.3, 3 H, CH_3); *m*/*z* (FD) 1025.8 (100%, M^+. Calc. for $C_{66}H_{88}O_9$: 1025.4).

Monoester **7c**.—Yield 84%; mp 244 °C; δ_H(400 MHz, $CDCl_3$) 8.79 (s, 2 H, OH), 7.20 (d, *J* 2.3, 2 H, ArH), 7.19 (s, 2 H, ArH), 7.16 (d, *J* 2.3, 2 H, ArH), 7.11 (d, *J* 2.2, 2 H, ArH), 6.70 (d, *J* 2.2, 2 H, ArH), 4.40 (d, *J* 14.2, 2 H, $ArCH_2Ar$), 4.38–3.45 (m, 22 H, $OCH_2CH_2O/ArCH_2Ar$), 3.41 (d, *J* 14.0, 2 H, $ArCH_2Ar$), 1.41 (s, 9 H, Bu^t), 1.31 (s, 18 H, Bu^t), 1.09 (s, 18 H, Bu^t), −0.10 (h, *J* 7.1, 2 H, $CH_2CH_2CH_3$), −0.12 (t, *J* 7.0, $COCH_2$), −0.88 (t, *J* 7.1, CH_3); *m*/*z* (FD) 1039.9 (100%, M^+. Calc. for $C_{67}H_{90}O_9$: 1039.5).

Monoester **7d**.—Yield 88%; mp 236 °C; δ_H(400 MHz, $CDCl_3$) 8.75 (s, 2 H, OH), 7.18 (s, 2 H, ArH), 7.16 (d, *J* 2.2, 2 H, ArH), 7.10 (d, *J* 2.3, 2 H, ArH), 7.04 (d, *J* 2.2, 2 H, ArH), 6.77 (d, *J* 1.7, 2 H, ArH), 4.42–3.32 (m, 26 H, $OCH_2CH_2O/ArCH_2Ar$), 1.38 (s, 9 H, Bu^t), 1.29 (s, 18 H, Bu^t), 1.08 (s, 18 H, Bu^t), 0.01 (p, *J* 7.1, 2 H, $COCH_2CH_2$), −0.02 (t, *J* 7.0, 2 H, $COCH_2$), −0.20 (t, *J* 7.2, 3 H, CH_3), −0.62 (h, *J* 7.1, 2 H, CH_2CH_3); *m*/*z* (FD) 1053.7 (100%, M^+. Calc. for $C_{68}H_{92}O_9$: 1053.5).

Acknowledgements

These studies were carried out in the frame of the COST action D7. R. A., V. B. and W. V. are grateful to the Deutsche Forschungsgemeinschaft for financial support. R. C. and L. M. gratefully acknowledge financial contributions from MURST and from CNR, Progetto Strategico Tecnologie Chimiche Innovative.

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Paper 7/03966B
Received 6*th June* 1997
Accepted 25*th September* 1997