($CDCl_3$) δ 170.9, 158.5, 155.8, 154.1, 142.6, 107.8, 71.7, 70.8, 70.3, 70.2, 69.9, 58.8, 46.0, 39.5; FABMS *m/e* 971 ($M^+ + 1$); HRMS calcd for $C_{42}H_{79}N_6O_{19}$ 971.5400, found 971.5367.

α-[*N*-[2-[1-[2-Oxo-4-[(triphenylmethyl)amino]pyrimidinyl]]ethyl]amino]-ω-(methoxymethyl)poly(ethylene glycol) (36). Compound **21** (1.19 g, 3.01 mmol) was reacted with compound **26** as described for compound **27** above, except that benzene was used as the solvent. The crude material was purified by column chromatography using 5% MeOH/$CHCl_3$ as the eluent to provide **36** (2.65 g, 75.2%): R_f = 0.48 (system B); ^1H NMR ($CDCl_3$) δ 3.38 (3 H, s, CH_3O), 3.53–3.72 (64 H, m, CH_2O, CH_2CH_2NHCO), 3.86 (2 H, t, *J* = 6.1 Hz, CH_2CH_2NHCO), 4.99 (1 H, d, *J* = 7.3 Hz, C^5H), 7.03 (1 H, d, *J* = 7.3 Hz, C^6H), 7.23–7.37 (15 H, m, Tr*H*), 7.51 (1 H, t, CON*H*); ^{13}C NMR ($CDCl_3$) δ 170.6, 165.3, 155.7, 145.7, 143.6, 128.5, 128.1, 127.4, 94.1, 71.7, 71.0, 70.8, 70.7, 70.6, 70.3, 70.0, 58.8, 48.8, 37.8; CIMS *m/e* 1174 (±*n* × 44 amu) ($M^+ + 1$); HRMS calcd for $C_{60}H_{93}N_4O_9$ 1173.6434, found 1173.6430.

α-[*N*-[2-[1-(4-Amino-2-oxopyrimidinyl)]ethyl]amino]-ω-(methoxymethyl)poly(ethylene glycol) (37). Compound **36** (2.29 g, 1.95 mmol) was dissolved in trifluoroacetic acid (25 mL) and the solution brought to reflux for exactly 30 min. The solvent was then removed in vacuo. Sodium hydroxide (0.5 N in MeOH) was then added to a solution of the residue in MeOH until neutral and the solvent again removed on a rotary evaporator. The crude material was purified by column chromatography using 20% MeOH/$CHCl_3$ as eluent to provide **37** (1.79 g, 98.6%): R_f = 0.59 (20% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.16 (3 H, s, CH_3O), 3.33–3.42 (64 H, m, CH_2O, CH_2CH_2NHCO), 3.70 (2 H, t, CH_2CH_2NHCO), 5.67 (1 H, d, *J* = 7.1 Hz, C^5H), 6.62 (2 H, br s, NH_2), 7.04 (1 H, d, *J* = 7.1 Hz, C^6H), 7.61 (1 H, t, CON*H*); ^{13}C NMR ($CDCl_3$) δ 170.3, 165.9, 156.4, 145.3, 94.1, 71.4, 70.6, 70.0, 69.7, 58.5, 48.5, 37.8; FABMS *m/e* 929 ($M^+ + 1$); HRMS calcd for $C_{41}H_{78}N_4O_{19}K$ 969.4897, found 969.4877.

Determination of Binding Constants. For the dimerization study of **29**, 15 samples of DMSO-d_6 solutions of various concentrations (0.017–0.090 M) were prepared and the chemical shifts of the N^1–H, C^2–NH_2, and C^4–NH_2 protons of **29** recorded using a Nicolet NT-360 NMR (360 MHz) at 23 °C. For the titration of **35** with **37**, six separate aliquots (100–200 μL) of a 0.53 M DMSO-d_6 solution of **37** were added to a 0.086 M solution (500 μL) of **35** and the chemical shifts of the guanine N^1–H and C_2–NH_2 protons recorded as a function of relative nucleobase concentration. Data reduction was then effected using standard Scatchard plots.[21] Because of the low chemical shift (Δδ) values involved, the errors are considered to be significantly larger (<±20%) than might otherwise be expected for this sort of measurement and analysis.

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Supplementary Material Available: ^1H NMR spectra for **9–14, 17–23,** and **26–37**; ^{13}C NMR spectra for **9–14, 17–23, 26–30,** and **32–37**; binding data and equilibrium calculation information for complexes presented in Table I (53 pages). Ordering information is given on any current masthead page.

New Crown Ether-like Macrocycles Containing a Nitrophenol Unit. Synthesis and Metal Ion Effects on the Reactivity of Their Acetates in Transacylation Reactions

Dagmar Kraft,[†] Roberta Cacciapaglia,[‡] Volker Böhmer,*[,†] A. Abu El-Fadl,[§] Sybolt Harkema,[§] Luigi Mandolini,*[,‡] David N. Reinhoudt,*[,§] Willem Verboom,[§] and Walter Vogt[†]

Institut für Organische Chemie, Johannes Gutenberg Universität Mainz, J.-J.-Becher Weg 34 SB1, 6500 Mainz, Germany, Dipartimento di Chimica and Centro CNR sui Meccanismi di Reazione, Università "La Sapienza", Piazza Aldo Moro 5, 00185 Roma, Italy, and Faculty of Chemical Technology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

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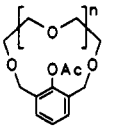
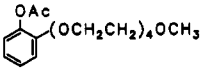
A series of crown ether-like macrocyclic compounds **3** containing the 2,6-dibenzyl-4-nitrophenol substructure have been prepared by cyclization reactions of disalicylideneacetone **4** with ditosylates **7** of oligoethylene glycols, followed by hydrogenation and double aldol condensation with nitromalondialdehyde. These compounds may be regarded as possessing a section of a 1,3-crowned calix[4]arene. X-ray analysis of two examples shows, however, that the three phenolic units linked via *o*-methylene groups adopt a conformation different to the all-cis conformation found in calix[4]arenes. The reaction of the nitrophenyl acetates derived from **3** and from suitable model compounds with ethoxide in ethanol was studied kinetically. This reaction is accelerated by the addition of $SrBr_2$ and $BaBr_2$ in all cases, indicating that the metal ion is bound more strongly to the transition state than to the initial state. Especially high acceleration factors (up to 700 in the case of **10e**) were observed for cyclic and open-chain compounds with longer flexible oligoethylene oxide chains, which means that only in these cases do the ether oxygens contribute effectively to the binding of the metal ion in the transition state.

In recent studies[1-3] of the effect of metal ions on acyl transfer reactions from aryl acetates to methoxide ion it was reported that alkali and alkaline-earth metal ions more or less firmly held in the proximity of the acetoxy group by strategically placed polyether chains, such as those in **1** and **2** (Chart I), greatly enhance reaction rates. The results, which were discussed in terms of differential binding of metal ions to transition state and reactant state, pointed to a selective transition-state stabilization resulting

Chart I



1 (n=2–6)



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[†] Germany.
[‡] Italy.
[§] The Netherlands.

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from a favorable combination of interactions of the metal ion both with the negative charge developing at the carbonyl oxygen (electrophilic catalysis) and the oxygen atoms of the polyether chains. Since it was felt such studies have the potential of providing useful insight into homogeneous catalysis by metal ions, as well as bearing upon the important question of the relationship between binding and catalysis,[4] we were prompted to extend our investigations to additional reacting systems, with the underlying idea that rate-enhancing effects of metal ions should be very sensitive to the mutual distance of the ester group undergoing nucleophilic attack and the proximal arrangement of donor atoms. We therefore synthesized a series of crown ether compounds **3** with an "inwards oriented" phenolic hydroxyl[5] and studied the reactivity of their acetates. These compounds may be regarded as possessing a section of a "calix crown",[6] i.e., a calix[4]arene molecule in which two opposite phenolic oxygen functions are connected by an oligoethylene oxide bridge. In this paper we report the syntheses of the crown ether phenols **3** and a kinetic investigation of the effect of barium and strontium ions on the reactions of their acetates **10** with ethoxide ion in ethanol. For comparison purposes, a series of acyclic model compounds was also considered.

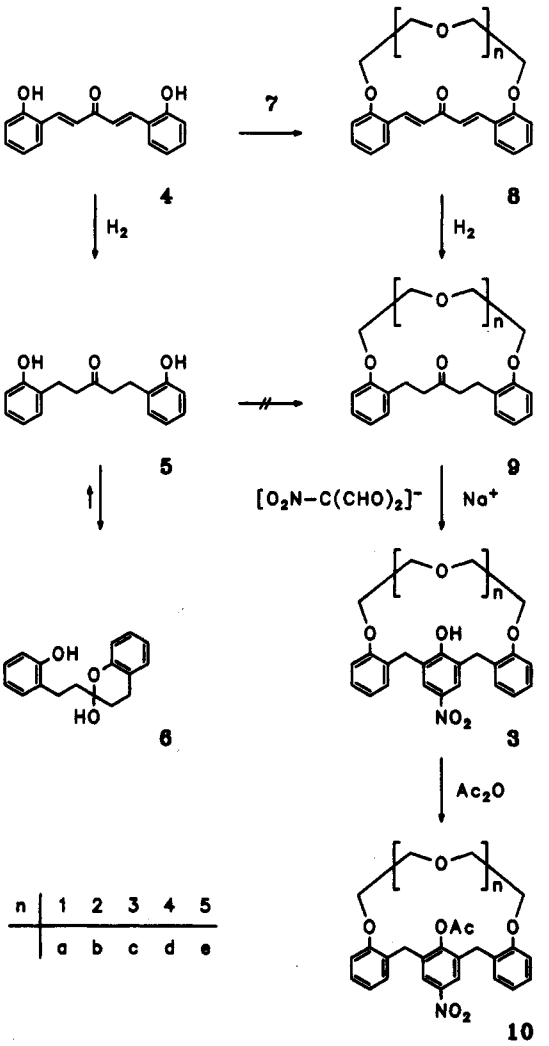
Results

Synthesis. Various trinuclear phenolic oligomers with a nitrophenol unit in the middle have been synthesized.[7,8] However, they cannot be used as educts for the synthesis of **3**, since the phenolic hydroxyl group of this nitrophenol unit should require selective protection during the cyclization step. We therefore thought of a strategy which creates the nitrophenol unit after the crown ether cycle has been formed. This can be done by double aldol condensation of a suitable ketone with nitromalondialdehyde, a reaction which also was used for the synthesis of hemispherands containing a *p*-nitrophenol unit.[9]

The ketone structure needed for the synthesis of **3** is that of a 1,5-diphenylpentan-3-one, which can be easily obtained by aldol condensation of acetone with a benzaldehyde and subsequent selective hydrogenation of the carbon–carbon double bonds. In fact, the model compounds **13a,b** were easily obtained in high overall yields (nearly quantitative yield for the condensation step with nitromalondialdehyde) starting with *o*- or *p*-methoxybenzaldehyde.

In a similar way condensation of salicylaldehyde with acetone and hydrogenation of the disalicylideneacetone **4** should yield a diphenolic compound **5** suitable for cyclization with the ditosylate of an oligoethylene glycol **7**.

Scheme I



According to Mora and Szeki,[10] **4** and **5** have the structure of a cyclic hemiketal (e.g. **6** instead of **5**). In fact, all attempts to cyclize the saturated ketone (which were undertaken in the hope that the open-chain compound **5** probably present in equilibrium with **6** could be trapped) failed. The NMR spectra of **4**, however, show no indication of the presence of significant amounts of cyclic product, and the reaction of **4** with ditosylates **7** gave the cyclic compounds **8** from which the further compounds were obtained as indicated in Scheme I.

Several conditions were checked for the cyclization of **4** with **7**. By far the best results were obtained in acetonitrile in the presence of CsF.[11] Crown ethers **8** were isolated by flash chromatography in yields of 29% to 67% for the analytically pure compounds. No indication for the formation of a cyclic dimer was found not even for the shortest ditosylate **7a**. In a similar way the open-chain compound **11c** was prepared by reaction of **4** with the tosylate of triethyleneglycol monomethyl ether.

Hydrogenation of compounds **8** and **11** was performed at room temperature and normal pressure using Raney nickel as a catalyst, which has been deactivated by treatment with dilute acetic acid. Nevertheless, reduction of the keto group must be considered as a side reaction, and the secondary alcohol was isolated as byproduct (24%) in the case of **9b**, reducing its yield to 48%. In the other

(1) Cacciapaglia, R.; Lucente, S.; Mandolini, L.; van Doorn, A. R.; Reinhoudt, D. N.; Verboom, W. *Tetrahedron* **1989**, *45*, 5293.
(2) Ercolani, G.; Mandolini, L. *J. Am. Chem. Soc.* **1990**, *112*, 423.
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(4) Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; Freeman W. H. and Company: New York, 1985; Chapter 12.
(5) For further examples of crown ethers containing a *p*-nitrophenol unit see for instance: (a) Brown, C. M.; Ferguson, G.; McKervey, M. A.; Mulholland, D. L.; O'Connor, T.; Parvez, M. *J. Am. Chem. Soc.* **1985**, *107*, 2703. (b) Ferguson, G.; Kaitner, B.; Browne, C. M.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1725.
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(7) Böhmer, V.; Deveaux, J.; Kämmerer, H. *Makromol. Chem.* **1976**, *177*, 1745.
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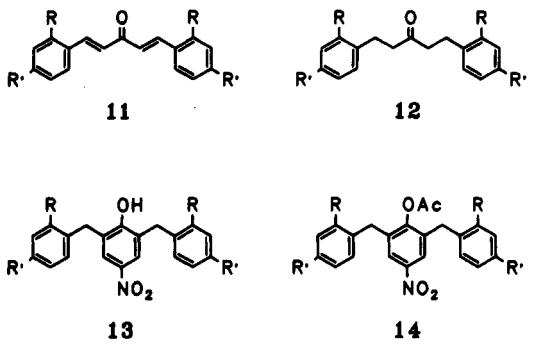
(11) Reinhoudt, D. N.; de Jong, F.; Tomassen, H. P. M. *Tetrahedron Lett.* **1979**, 2067.

Chart II



	a	b	c
R	OCH_3	H	$(OCH_2CH_2)_3OCH_3$
R'	H	OCH_3	H

cases the yield of the desired saturated ketone was in the range of 63–77%.

Condensation with the sodium salt of nitromalondialdehyde was performed in boiling methanol with sodium ethoxide as base. On cooling, the sodium salt of **3** often crystallized out of the reaction mixture. It was easily converted to the free nitrophenol by treatment with dilute hydrochloric acid. In those cases where the sodium salt remained in solution, the nitrophenol could be precipitated (almost in pure form) by acidification. Yields of the nitrophenol crown ethers were practically quantitative.

The acetates **10** were easily obtained by reaction of **3** with acetic anhydride in pyridine at room temperature. It is interesting to note that for $n = 1$ and $n = 2$ the ester group obviously cannot pass through the annulus, since in the ^1H NMR spectrum the benzylic methylene protons appear as an AB quartet.

Similar to the cyclic compounds, the linear analogues **13c** (54%) and its acetate **14c** (88%) were obtained starting with disalicylideneacetone **4** and the tosylate of triethylene glycol monomethyl ether via the linear ketones **11c** (46%) and **12c** (89%; 10% of the secondary alcohol as byproduct).

X-ray Structures. The structures of two cyclic compounds **3c** and **3e** were further confirmed by X-ray analysis. Figure 1 shows their molecular conformation in the crystalline state (in the case of **3c** from two crystallographically independent molecules, with slightly different conformations, only one is shown). As normally found in flexible molecules, bond distances and bond angles are close to usual values (see the supplementary material). The interesting conformational aspect of these molecules is the mutual arrangement of the three phenolic units in comparison with 1,3-calixcrowns, which would be obtained by connecting the phenyl ether rings in ortho position via an additional phenolic unit. According to a proposal by Ugozzoli,[12] the conformation of a calixarene is unequivocally described by pairs of torsion angles for the Ar–CH_2– bonds. The usual cone conformation is then characterized by pairs of angles with alternating sign, while a distortion of the "ideal" 4-fold symmetry is indicated by torsion angles deviating from 90°. Thus, for *tert*-butylcalixcrown-5 the following angles were found:[6] 110, –61; 66, –121; 116, –68; 70, –112 (which are expressed, involving the carbon atoms carrying the phenolic oxygen). The corresponding values for **3c** are 91.3, –161.9; –103.6, 87.7 for the molecule shown in Figure 1a and 89.1, –163.4; –79.0, 102.8 for the second molecule, while for **3e** the following values were found: –66.7, 134.4; –84.5, 162.8. There is not only a stronger deviation from 90° than in calixcrowns, with one of the torsion angles coming close to 180° in both compounds, but there is also a deviation from the alternating sequence of plus/minus in the case of **3c**, which means that the three phenolic units are arranged in a zig–zag like manner. The higher conformational freedom expressed by these findings must be considered also when the results of the kinetic studies are compared with calixcrowns. While the hydroxyl group of the nitrophenol unit in **3c** forms an intramolecular hydrogen bond to the phenol ether oxygen of the adjacent phenolic unit (like in calixcrowns) it forms a hydrogen bond to a water molecule included in the cavity of the macrocycle **3e**. This water molecule in turn is hydrogen bonded to two oxygen atoms of the polyether chain.

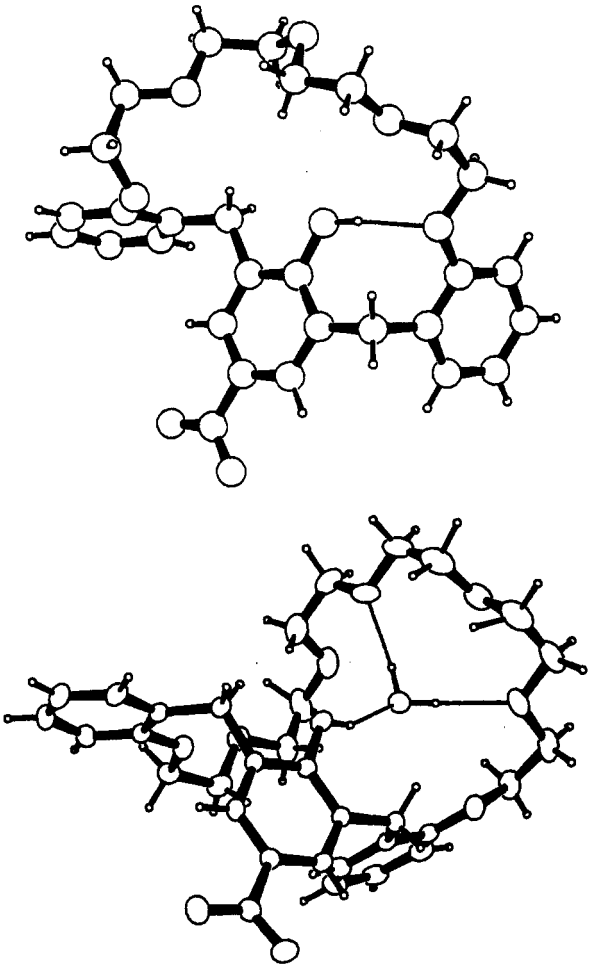


Figure 1. Molecular conformation of crown ethers **3c** (top) and **3e** (bottom).

Kinetics. Acetyl transfer reactions to ethoxide ion from the *p*-NO_2-aryl esters **14a–c**, **10b–e**, and *p*-nitrophenylacetate were carried out in EtOH solution at 25.0 °C. The reaction progress was monitored spectrophotometrically following the increase of the *p*-nitroaryl oxide absorption. Very dilute solutions of the *p*-NO_2-aryl esters (0.03 mM) were reacted with a large excess of ethoxide ion (1–10 mM). In all cases the reactions proceeded quantitatively, and clean first-order behavior was observed up to high conversions. A first series of experiments was carried out using tetramethylammonium ethoxide as reference reactant. Observed pseudo-first-order rate constants, k_{obs}, were

(12) Ugozzoli, F., private communication, lecture at the workshop on calixarenes and related compounds, August 28–30, 1991, Mainz.

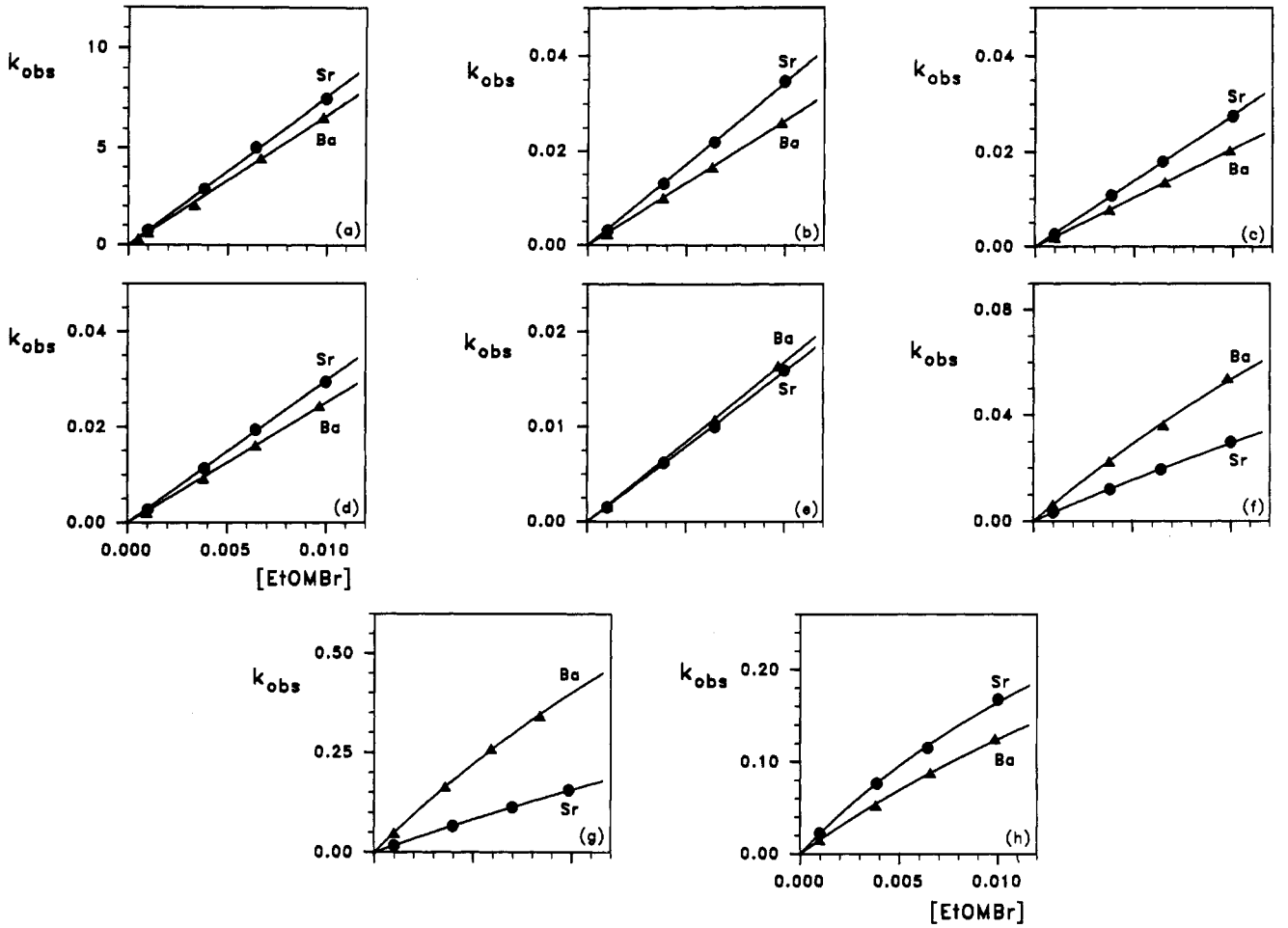


Figure 2. Plots of k_{obs} [s^{-1}] vs concentration [M] of metal-bound ethoxide for the acyl transfer reactions of *p*-nitrophenylacetate (a), **14b** (b), **14a** (c), **10b** (d), **10c** (e), **10d** (f), **10e** (g), and **14c** (h) in EtOH at 25 °C. The curves in f, g, and h are plots of eq 4.

translated into second-order rate constants, k_o, that were taken to represent free ethoxide reactivity.[13] A second series of experiments was carried out in the presence of the alkaline-earth metal ions Sr^{2+} and Ba^{2+}. The sources were $SrBr_2$ and $BaBr_2$. Solutions for kinetic measurements were prepared by mixing equimolar amounts of $EtONMe_4$ and metal bromide. The exact nature of the species in solution is unknown, but the fact that k_{obs} varies in a strictly linear manner with base concentration in the reaction of the model compound *p*-nitrophenylacetate (Figure 2a) may be taken as evidence that the ethoxide ion is completely bound to the metal ion in the investigated concentration range, according to the conventional formulation of eq 1.

$$EtONMe_4 + MBr_2 \rightarrow EtOMBr + Me_4NBr \quad (1)$$

Consistent with this conclusion are experiments where the reaction rate turned out to be insensitive to the amount of added metal salt in stoichiometric excess over $EtONMe_4$. As an example, the rate constant $k_{obs} = 4.47\ s^{-1}$, obtained upon treatment of *p*-nitrophenylacetate with a solution where $[EtONMe_4] = [BaBr_2] = 6.7 \times 10^{-3}$ M, was practically coincident with the value 4.20 s^{-1} obtained when the concentration of added $BaBr_2$ was increased to 1.1×10^{-2} M, the concentration of $EtONMe_4$ being equal. In the MeO^-/MeOH base/solvent system used in previous studies[1,2] association of Ba^{2+} and Sr^{2+} with MeO^- was far from being complete and had to be taken into account for quantitative treatment of rate data. In contrast, the EtO^-/EtOH base/solvent system lends itself to a much simpler kinetic treatment as the metal-bound ethoxide species can be treated as an in situ generated reactant, whose concentration is simply equal to the concentration of added $EtONMe_4$ (and metal salt).

Table I. Rate Data for Acetyl Transfer Reactions from a Series of *p*-Nitrophenyl Acetates to Ethoxide Ion in EtOH at 25 °C

		EtOSrBr		EtOBaBr	
substrate	k_o ($M^{-1}\ s^{-1}$)	k_M ($M^{-1}\ s^{-1}$)	k_M/k_o	k_M ($M^{-1}\ s^{-1}$)	k_M/k_o
p-nitrophenyl-acetate	94.9	7.56×10^2	7.97	6.63×10^2	6.99
14a	0.112	2.78	24.8	2.07	18.5
14b	0.342	3.44	10.1	2.65	7.75
10b	0.177	2.96	16.7	2.50	14.1
10c	0.111	1.58	14.2	1.68	15.1
10d	7.12×10^{-2}	3.32[a]	46.6	6.50[a]	91.3
10e	6.99×10^{-2}	17.4[a]	249	48.3[a]	691
14c	8.23×10^{-2}	23.0[a]	279	15.5[a]	188

[a] Calculated as $k_{cat} K_S$ (from Table II).

Plots of k_{obs} vs concentration of metal-bound ethoxide for reactions of the model compounds **14a** and **14b** and the ring compounds **10b** and **10c** are shown in Figures 2b–e. It is apparent that these plots also are strictly linear, showing that the given reactions closely follow second-order kinetics according to eq 2, where S denotes a *p*-NO_2-aryl ester. The results are summarized in Table I.

$$v = k_M[EtOMBr][S] \quad (2)$$

On the other hand, the corresponding plots for the ring compounds **10d** and **10e**, and for the open chain crown

(13) Buncel, E.; Dunn, E. J.; van Truong, Ng.; Bannard, R. A. B.; Purdon, J. G. *Tetrahedron Lett.* **1990**, *31*, 6513.

Table II. Kinetic Parameters for Substrates Exhibiting Saturation Kinetics

	EtOSrBr		EtOBaBr	
substrate	K_S (M^{-1})	k_{cat} (s^{-1})	K_S (M^{-1})	k_{cat} (s^{-1})
10d	12	0.28	20	0.32
10e	11	1.6	23	2.1
14c	39	0.59	25	0.62

analogue **14c** shown in Figure 2f–h exhibit slightly negative curvatures (downwards drifts). These may be taken as being diagnostic of weak but appreciable associations between the reactants. Therefore, the data have been analyzed on the basis of the mechanism in eq 3, where the substrate S associates in a reversible fast step with the ethoxide-bound metal species to give what might be called a ternary complex (substrate + ethoxide + metal ion), which decomposes in a slow monomolecular step into products. Equations 3a,b lead to eq 4, which has the same

$$S + EtOMBr \overset{K_s}{\rightleftharpoons} S{\cdot}EtOMBr \quad (3a)$$

$$S{\cdot}EtOMBr \xrightarrow{k_{cat}} \text{products} \quad (3b)$$

form as the Michaelis–Menten equation (with $K_s = K_M^{-1}$).

$$k_{obs} = \frac{k_{cat}K_s[EtOMBr]}{1 + K_s[EtOMBr]} \quad (4)$$

Initial values of the k_{cat} and K_s parameters, obtained from double reciprocal (Lineweaver–Burk) plots, were further refined by a nonlinear least-squares procedure to give the best fit to eq 4. The optimized parameters are listed in Table II.

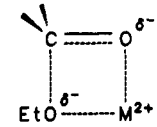
It is worth noting that in the low concentration region, i.e., when $K_s[EtOMBr] \ll 1$, eq 4 reduces to the form of eq 5, which shows that when there is negligible formation of the ternary complex, the reactions follow second-order kinetics. Given the low values of the K_s quantities, this

$$k_{obs} = k_{cat}K_s[EtOMBr] \quad (5)$$

condition is practically met in the kinetic runs where [EtOMBr] = 1 mM. On the other hand, whenever $K_s < 10\ M^{-1}$ the denominator of eq 4 is indistinguishable from unity in the whole concentration range, as clearly shown by the rate profiles for the strontium reactions of **10d** and **10e** (Figure 2), where the curvature is hardly noticeable on account of the fact that the pertinent K_s values (Table II) are close to the lower detection limit.

It seems very unlikely that the fact that some of the compounds of the series under examination follow a certain kinetic equation, whereas the others follow a different equation, is the result of a mechanistic change occurring along the series. We assume, therefore, that the mechanism of eq 3 conveniently applies also to the substrates exhibiting linear rate profiles, the ternary complex being a common intermediate. Whereas the reactions of *p*-nitrophenylacetate and **14b**, like any bimolecular reaction in solution, may be viewed as proceeding through something of the nature of an inherently unstable encounter complex ($K_s \ll 10$),[14] the presence of an increasing number of oxygen donors increases the stability of the associated species up to the point that a true complex accumulates to such an extent as to affect the kinetics. An important consequence of this view is that the $k_{cat}K_s$ products determined for the substrates exhibiting nonlinear rate profiles (Table I) have the same meaning as the k_M quantities determined for the other substrates and can be used for a meaningful comparison of reactivity throughout the series under subsaturating conditions.

Chart III



Discussion

The first observation made is that addition of the alkaline-earth metal bromides causes significant rate accelerations in all of the studied reactions, as shown by the k_M/k_o values listed in Table I. With some of the substrates, barium ion is more effective than strontium ion, and the reverse holds for the others, but no explanation for that curious inversion can be offered. The magnitude of the observed rate enhancements ranges from 1 order of magnitude, or nearly so, with the model compounds *p*-nitrophenylacetate and **14b**, to a remarkable 700-fold in the barium reaction of **10e**. It is thus apparent that the metal-bound ethoxide is much more reactive than free ethoxide, in contrast with the widespread belief that naked anions are more reactive than metal bound anions.[15] In fact, the rule holds for nucleophilic substitutions at saturated carbon[16] but can fail for nucleophilic additions to carbonyl[1,2] and phosphoryl[13] groups.

The guiding mechanistic concept is that the metal ion, strongly bonded to ethoxide ion in the initial state, becomes increasingly bonded to the carbonyl oxygen during the activation process, as a result of the negative charge being transferred from the incoming nucleophile to the carbonyl oxygen itself. Clearly, a strong interaction between the metal ion and the carbonyl oxygen in the initial state is not a necessary prerequisite for the metal ion to act as an efficient electrophilic catalyst. What is important is that, according to transition-state theory, the metal ion interacts with the transition state more strongly than with the initial state. This condition is clearly fulfilled in the reaction series under investigation. The picture which emerges is one where the rate-determining tetrahedral intermediate is attained via a transition state where the metal ion is chelated through coordination to both the ethoxide oxygen and the carbonyl oxygen,[2] as schematically depicted in Chart III, and where this chelate interaction is stronger than the initial state cation–anion interaction. The presence of additional donor atoms close to the reaction zone provides additional stabilization of the transition state through coordinative interactions with the metal ion. This is clearly shown, for example, by the fact that **14a**, where the two OCH_3 donors are closer to the acetoxy group, displays rate enhancements significantly larger than those of the para isomer. The k_M/k_o values listed in Table I show a general tendency to increase on increasing the number of oxygen atoms, but flexibility of the polyether chain is also important, as suggested by the fact that the two methoxy groups in **14a** are more effective than the 4-oxygen and 5-oxygen bridges in **10b** and **10c**, respectively. As suggested by CPK molecular models, the polyether bridges of the conformationally rigid macrocycles **10b** and **10c** are inaccessible for coordination to a metal bound to the reaction zone, but a more favorable situation is apparent in the more flexible macrocycles **10d** and **10e**, as well as in their open-chain analogue **14c**.

(14) Typical values estimated for the equilibrium constants of complexes due to random association are in the order of 0.1–1 M^{-1}. See: Connors, K. A. *Binding Constants*; Wiley: New York, 1987; p 89.

(15) Lefour, J.-M.; Loupy, A. *Tetrahedron* 1978, *34*, 2597.

(16) Gordon, J. E. *The Organic Chemistry of Electrolyte Solutions*; Wiley: New York, 1975; pp 465–469.

It is highly significant that the magnitude of the observed rate enhancements upon addition of the alkaline-earth metal salts is similar for *p*-nitrophenylacetate and **14b**, in spite of the fact that the latter is nearly 300 times less reactive than the former. It would appear, therefore, that the significant steric effect of the bulky *o*-benzyl groups does not alter to a significant extent the charge distribution in the transition state. As a consequence, the observed variations of the k_M/k_o vaues are solely due to additional stabilization of the transition state resulting from binding of the metal ion with (at least some of) the ether oxygens.

Since k_M refers to the unassociated reactants, the k_M/k_o values show that there is some stabilization of the transition state but are uninformative as to whether such stabilization is stronger in the reactant state complex (S·EtOMBr) or in the transition state complex (S·EtOMBr‡).[4] But the data listed in Table II clearly show that the additional binding energy available in **10e** and **14c** as compared to **10d** is realized much more efficiently in the transition state. In other words, variations of $k_{cat}K_s$ are mainly due to variations of k_{cat} and only to a minor extent to variations of K_s. In the language of the enzyme kineticist, the metal ions display a greater complementarity to the transition state than to the reactant state.

The substrate for which the utilization of binding energy in catalysis is at a maximum is **10e**, as shown by the pertinent k_{cat} values, which are the highest in the lot.

Conclusions

We have shown that acyl transfer reactions from *p*-nitroarylacetates to ethoxide ion are subject to significant accelerations upon addition of barium and strontium ions, which specifically stabilize the transition state via two major modes of interaction. One is due to electrostatic attraction of the metal ion by the negative charge being transferred from the ethoxide oxygen to the carbonyl oxygen. The other results from additional binding energy which is made available by the proximal oxygen donors through coordination of the metal ion. What is highly significant is that during the activation process cation binding enhancement results from either mode of interaction. In other words, barium and strontium ions function as electrophilic catalysts with all of the substrates investigated, but their efficiency is much greater for those substrates having a multidentate ligand structure, such as **10d,e** and **14c**. These are very weak binders as such, but the altered substrates in the transition state behave as strong ligands, thus providing an illustration of the well-established, but not intuitively obvious, notion that strong binding in the reactant state is not an important component of catalysis.[4]

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with Me_4Si as internal standard. An unambiguous assignment of all individual signals in the ^{1}H NMR spectra was not possible in all cases. The ^{13}C NMR data are summarized in the supplementary material (the assignment of ^{13}C NMR data for aromatic carbon atoms was calculated on the basis of increment tables[17]). IR spectra were obtained from KBr pellets.

Starting Materials. Disalicylideneacetone **4**,[10] pentaethylene glycol,[18,19] hexaethylene glycol,[19] the oligoethylene glycol ditosylates **7** (n = 1–3),[20] **7** (n = 4, 5),[18] triethyleneglycol monomethyl ether tosylate,[21] and 2-nitromalondialdehyde sodium salt[22] were prepared according to the literature cited. Ketones **11a** (1,5-bis(2′-methoxyphenyl)-1,4-pentadien-3-one) and **11b** (1,5-bis(4′-methoxyphenyl)-1,4-pentadien-3-one) were obtained by aldol condensation of *o*- and *p*-methoxybenzaldehyde with acetone in methanol in yields of 80–96%. (**11a**, mp 120–121 °C; **11b**, mp 126 °C (126.5–127 °C)[23].) The saturated ketones **12a** (1,5-bis(2′-methoxyphenyl)pentan-3-one) and **12b** (1,5-bis(4′-methoxyphenyl)pentan-3-one) were prepared by hydrogenation of **11a** and **11b** in ethanol, using Raney nickel as a catalyst, in yields of 60–78%. (**12a**, mp 87–89 °C; **12b**, mp 53.5 °C (54–55 °C)[24].)

Acetonitrile was dried over molecular sieves (4 Å). CsF was dried for 1 h at 100 °C in a vacuum oven before use. The macrocyclization reactions were carried out in a dry nitrogen atmosphere. The chromatographic separations were performed on silica gel 60 (SiO_2), E. Merck, particle size 0.040–0.063 mm, 70–230 mesh ASTM.

General Procedure for the Preparation of Compounds 8. CsF (19 g, 0.125 mol) was added to a solution of disalicylideneacetone **4** (6.66 g, 0.025 mol) in dry acetonitrile (600 mL). The mixture was stirred for 1 h at 40–45 °C. Then a solution of the corresponding oligoethylene glycol ditosylate **7** (0.025 mol) in acetonitrile (400 mL) was added dropwise to the refluxing mixture over a 4-h period (in the case of **8e** over a 24-h period). The reaction mixture was refluxed for 20–40 h and then cooled to room temperature. After filtration by suction the solvent was evaporated under reduced pressure and the residue dried on a vacuum-line. Flash column chromatography ($CHCl_3$) of the crude products afforded the pure compounds **8**, which in some cases were additionally recrystallized.

8,9:15,16-Dibenzo-1,4,7-trioxacyclohexadeca-8,10,13,15-tetraen-12-one (8a): yellow needles from ethanol (67%); mp 161–164 °C; ^{1}H NMR (200 MHz) δ 8.02 (d, J = 16.4 Hz, 2 H, ArCH), 7.54 (dd, ^3J = 7.8 Hz, 2 H, ArH), 7.53 (d, J = 16.5 Hz, 2 H, CHCO), 7.33 (dt, ^3J = 7.9 Hz, 2 H, ArH), 7.02 (br t, ^3J = 7.6 Hz, 2 H, ArH), 6.97 (br d, ^3J = 8.2 Hz, 2 H, ArH), 4.32–4.28 (m, 4 H, CH_2), 3.92–3.88 (m, 4 H, CH_2); MS m/z 336 (M^+, 34). Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.97; H, 6.00. Found: C, 74.92; H, 6.01.

11,12:18,19-Dibenzo-1,4,7,10-tetraoxacyclononadeca-11,13,16,18-tetraen-15-one (8b): yellow needles from aqueous acetone (63%); mp 98.5–100 °C; ^{1}H NMR (200 MHz) δ 7.78 (d, J = 16.0 Hz, 2 H, ArCH), 7.53 (d, J = 16.0 Hz, 2 H, CHCO), 7.46 (dd, ^3J = 7.6 Hz, 2 H, ArH), 7.30 (br t, ^3J = 8.1 Hz, 2 H, ArH), 6.97 (br t, ^3J = 8.0 Hz, 2 H, ArH), 6.88 (br d, ^3J = 8.2 Hz, 2 H, ArH), 4.24–4.19 (m, 4 H, $ArOCH_2CH_2$), 3.97–3.93 (m, 4 H, $ArOCH_2CH_2$), 3.78 (s, 4 H, OCH_2CH_2O); MS m/z 380 (M^+, 2). Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.60; H, 6.36. Found: C, 72.51; H, 6.36.

14,15:21,22-Dibenzo-1,4,7,10,13-pentaoxacyclodocosa-14,16,19,21-tetraen-18-one (8c): yellow solid (29%); mp 94–96 °C; ^{1}H NMR (200 MHz) δ 7.89 (d, J = 16.1 Hz, 2 H, ArCH), 7.51 (br d, ^3J = 7.6 Hz, 2 H, ArH), 7.33 (br t, ^3J = 7.7 Hz, 2 H, ArH), 7.23 (d, J = 16.1 Hz, 2 H, CHCO), 6.99 (br t, ^3J = 7.5 Hz, 2 H, ArH), 6.93 (br d, ^3J = 8.1 Hz, 2 H, ArH), 4.27–4.22 (m, 4 H, $ArOCH_2CH_2$), 3.95–3.90 (m, 4 H, $ArOCH_2CH_2$), 3.73–3.59 (m, 8 H, OCH_2CH_2O); MS m/z 424 (M^+, 7).

17,18:24,25-Dibenzo-1,4,7,10,13,16-hexaoxacyclopentacosa-17,19,22,24-tetraen-21-one (8d): yellow solid (30%); mp 103–106 °C; ^{1}H NMR (200 MHz) δ 8.10 (d, J = 16.0 Hz, 2 H, ArCH), 7.59 (dd, ^3J = 7.6 Hz, 2 H, ArH), 7.33 (br t, ^3J = 8.1 Hz, 2 H, ArH), 7.13 (d, J = 16.1 Hz, 2 H, CHCO), 6.97 (br t, ^3J = 7.4 Hz, 2 H, ArH), 6.90 (br d, ^3J = 8.3 Hz, 2 H, ArH), 4.22–4.18 (m, 4 H, $ArOCH_2CH_2$), 3.93–3.89 (m, 4 H, $ArOCH_2CH_2$), 3.76–3.60 (m, 8 H, OCH_2CH_2O), 3.58 (s, 4 H, OCH_2CH_2O); MS m/z 468 (M^+, 92).

20,21:27,28-Dibenzo-1,4,7,10,13,16,19-heptaoxacyclooctacosa-20,22,25,27-tetraen-24-one (8e): yellow solid (48%); mp 87 °C; ^{1}H NMR (200 MHz) δ 8.06 (d, J = 16.1 Hz, 2 H, ArCH),

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7.59 (dd, ^3J = 7.7 Hz, 2 H, ArH), 7.32 (br t, ^3J = 8.3 Hz, 2 H, ArH), 7.18 (d, J = 16.1 Hz, 2 H, CHCO), 6.97 (br t, ^3J = 7.5 Hz, 2 H, ArH), 6.91 (br d, ^3J = 8.5 Hz, 2 H, ArH), 4.23–4.19 (m, 4 H, $ArOCH_2CH_2$), 3.95–3.91 (m, 4 H, $ArOCH_2CH_2$), 3.76–3.60 (m, 8 H, OCH_2CH_2O), 3.58 (s, 8 H, OCH_2CH_2O); MS m/z 512 (M^+, 53).

1,5-Bis(2′-(1,4,7,10-tetraoxaundecanyl)phenyl)-1,4-pentadien-3-one (11c). By analogy to the syntheses of compounds 8 a solution of triethylene glycol monomethyl ether tosylate (22.3 g, 0.07 mol) in acetonitrile (200 mL) was added to a mixture of disalicylideneacetone 4 (7.98 g, 0.03 mol) in dry acetonitrile (500 mL) and NaH (2.59 g, 0.09 mol; 80% in paraffin). Conditions and working up were as described for compounds 8. Flash column chromatography (petroleum ether/ethyl acetate, 1/5) of the crude product afforded a yellow oil (46%), which was pure enough for the following reaction step. Some impurities are detected in the ^1H NMR: ^1H NMR (200 MHz) δ 8.05 (d, J = 16.1 Hz, 2 H, ArCH), 7.60 (br d, ^3J = 7.6 Hz, 2 H, ArH), 7.33 (br t, ^3J = 7.8 Hz, 2 H, ArH), 7.17 (d, J = 16.1 Hz, 2 H, CHCO), 6.98 (br t, ^3J = 7.5 Hz, 2 H, ArH), 6.93 (br d, ^3J = 8.2 Hz, 2 H, ArH), 4.24–3.33 (m, 24 H, CH_2CH_2), 3.33 (s, 6 H, CH_3).

General Procedure for the Preparation of Compounds 9. Compound 8 (5 mmol) was dissolved in acetone (80 mL) in the case of **8a** and **8b** or methanol (200 mL) in the case of **8c–d** and hydrogenated at 15–30 °C in the presence of 1 tsp of Raney nickel (which was slightly deactivated by washing with 5% acetic acid (3 × 30 mL). The H_2 consumption was monitored and the reaction was complete after 0.5–3 h. After filtration the solvent was evaporated under reduced pressure. The crude white products were purified by recrystallization in the case of **9a** and **9b** and flash column chromatography ($CHCl_3$/acetone, 10/1) in the case of **9c–d**. In addition to **9c**, 24% of the corresponding secondary alcohol was isolated, in which the keto group is reduced to the alcohol function.

8,9:15,16-Dibenzo-1,4,7-trioxacyclohexadeca-8,15-dien-12-one (9a): white crystals from acetone (63%); mp 125–126 °C; ^1H NMR (200 MHz) δ 7.22–7.13 (m, 4 H, ArH), 6.91–6.79 (m, 4 H, ArH), 4.19–4.15 (m, 4 H, $ArOCH_2CH_2$), 3.94–3.87 (m, 4 H, $ArOCH_2CH_2$), 2.96–2.76 (m, 8 H, $ArCH_2CH_2$); MS m/z 340 (M^+, 42). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.08; H, 7.11. Found: C, 73.70; H, 6.99.

11,12:18,19-Dibenzo-1,4,7,10-tetraoxacyclononadeca-11,18-dien-15-one (9b): white crystals from acetone (64%); mp 126–128 °C; ^1H NMR (200 MHz) δ 7.16–7.11 (m, 4 H, ArH), 6.89–6.77 (m, 4 H, ArH), 4.15–4.11 (m, 4 H, $ArOCH_2CH_2$), 3.88–3.84 (m, 4 H, $ArOCH_2CH_2$), 3.75 (s, 4 H, OCH_2CH_2O), 2.87–2.77 (m, 8 H, $ArCH_2CH_2$); MS m/z 384 (M^+, 96). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.84; H, 7.34. Found: C, 71.76; H, 7.13.

14,15:21,22-Dibenzo-1,4,7,10,13-pentaoxacyclodocosa-14,21-dien-18-one (9c): white powder (48%); mp 55–57 °C; ^1H NMR (200 MHz) δ 7.17–7.10 (m, 4 H, ArH), 6.88–6.74 (m, 4 H, ArH), 4.11–4.07 (m, 4 H, $ArOCH_2CH_2$), 3.85–3.78 (m, 4 H, $ArOCH_2CH_2$), 3.68 (br s, 8 H, OCH_2CH_2O), 2.90–2.84 (m, 4 H, $ArCH_2CH_2$), 2.75–2.68 (m, 4 H, $ArCH_2CH_2$); MS m/z 428 (M^+, 2).

As a side product, the corresponding secondary alcohol was obtained:

14,15:21,22-Dibenzo-1,4,7,10,13-pentaoxa-18-hydroxycyclodocosa-14,21-diene: white powder (24%); mp 69.5–71 °C; MS m/z 430 (M^+, 2).

17,18:24,25-Dibenzo-1,4,7,10,13,16-hexaoxacyclopentacosa-17,24-dien-21-one (9d): white powder (77%); mp 60–61.5 °C; ^1H NMR (200 MHz) δ 7.19–7.10 (m, 4 H, ArH), 6.89–6.77 (m, 4 H, ArH), 4.13–4.08 (m, 4 H, $ArOCH_2CH_2$), 3.86–3.82 (m, 4 H, $ArOCH_2CH_2$), 3.72–3.67 (m, 8 H, OCH_2CH_2O), 3.64 (s, 4 H, OCH_2CH_2O), 2.93–2.85 (m, 4 H, $ArCH_2CH_2$), 2.76–2.69 (m, 4 H, $ArCH_2CH_2$); MS m/z 472 (M^+, 8). Anal. Calcd for $C_{27}H_{36}O_7$: C, 68.61; H, 7.68. Found: C, 68.61; H, 7.76.

20,21:27,28-Dibenzo-1,4,7,10,13,16,19-heptaoxacyclooctacosa-20,27-dien-24-one (9e): colorless oil (70%); ^1H NMR (200 MHz) δ 7.18–7.08 (m, 4 H, ArH), 6.87–6.77 (m, 4 H, ArH), 4.12–4.08 (m, 4 H, $ArOCH_2CH_2$), 3.86–3.81 (m, 4 H, $ArOCH_2CH_2$), 3.71–3.64 (m, 8 H, OCH_2CH_2O), 3.61 (br s, 8 H, OCH_2CH_2O), 2.91–2.83 (m, 4 H, $ArCH_2CH_2$), 2.75–2.67 (m, 4 H, $ArCH_2CH_2$); MS m/z 516 (M^+, 21).

1,5-Bis(2′-(1,4,7,10-tetraoxaundecanyl)phenyl)pentan-3-one (12c). Compound **11c** (5.3 g, 9.5 mmol) dissolved in methanol (500 mL) was hydrogenated for 5 h at 20 °C under the conditions described for compounds **9**. After filtration the solvent was evaporated under reduced pressure. The crude white residue contained in addition to the desired product **12c** the corresponding secondary alcohol. Separation by flash column chromatography ($CHCl_3$/acetone, 6/1) afforded the pure compounds.

12c: colorless oil (89%); IR 1710 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ 7.18–7.07 (m, 4 H, ArH), 6.88–6.78 (m, 4 H, ArH), 4.14–4.08 (m, 4 H, $ArOCH_2CH_2$), 3.86–3.81 (m, 4 H, $ArOCH_2CH_2$), 3.70–3.48 (m, 16 H, OCH_2CH_2O), 3.36 (s, 6 H, CH_3), 2.91–2.82 (m, 4 H, $ArCH_2CH_2$), 2.73–2.67 (m, 4 H, $ArCH_2CH_2$).

A side product, the corresponding secondary alcohol, was isolated:

1,5-Bis(2′-(1,4,7,10-tetraoxaundecanyl)phenyl)-3-hydroxypentane: colorless oil (10%); IR 3490 (OH) cm^{-1}.

General Procedure for the Preparation of Compounds 3. The cyclic ketone **9** (3 mmol) was dissolved in hot methanol (15 mL), 2-nitromalondialdehyde sodium salt (0.83 g, 6 mmol) was added, and a solution of Na (0.35 g, 0.015 mol) in ethanol (5.4 g) was dropped slowly to the boiling mixture. After 20 h under reflux the reaction mixture was filtered hot (with suction), the solvent was evaporated under reduced pressure, and the residue was taken up in water/methanol. Neutralization with diluted HCl afforded a precipitate which, in the case of **3e**, was recrystallized from aqueous ethanol. In all the other cases the mixture was extracted with $CHCl_3$, and the organic phase was washed with water and dried over $MgSO_4$. After evaporation of the solvent the crude product was purified by flash column chromatography ($CHCl_3$) in the case of **3a** and **3c** and by recrystallization in the case of **3b** and **3d**.

2″-Hydroxy-5″-nitro-8,9:11,13:15,16-tribenzo-1,4,7-trioxacyclohexadeca-8,11,15-triene (3a): pale yellow cottonlike fibers from methanol (72%); mp 213–214 °C; ^1H NMR (200 MHz) δ 8.00 (s, 3 H, OH, ArH), 7.31 (dd, ^3J = 7.4 Hz, 2 H, ArH), 7.18 (dt, ^3J = 8.0 Hz, 2 H, ArH), 6.93 (br t, ^3J = 7.2 Hz, 2 H, ArH), 6.82 (br d, ^3J = 8.2 Hz, 2 H, ArH), 4.31–4.28 (m, 4 H, $ArOCH_2CH_2$), 3.94 (s, 4 H, $ArCH_2Ar$), 3.89–3.86 (m, 4 H, $ArOCH_2CH_2$); MS m/z 421 (M^+, 100).

2″-Hydroxy-5″-nitro-11,12:14,16:18,19-tribenzo-1,4,7,10-tetraoxacyclononadeca-11,14,18-triene (3b): white cottonlike fibers from methanol (72%); mp 179–181 °C; ^1H NMR (200 MHz) δ 8.02 (s, 1 H, OH), 7.99 (s, 2 H, ArH), 7.23 (br d, ^3J = 6.7 Hz, 2 H, ArH), 7.18 (br t, ^3J = 6.6 Hz, 2 H, ArH), 6.92 (br t, ^3J = 8.1 Hz, 2 H, ArH), 6.85 (br d, ^3J = 8.2 Hz, 2 H, ArH), 4.19–4.16 (m, 4 H, $ArOCH_2CH_2$), 4.00 (s, 4 H, $ArCH_2Ar$), 3.89–3.84 (m, 4 H, $ArOCH_2CH_2$), 3.84 (s, 4 H, OCH_2CH_2O); MS m/z 465 (M^+, 69). Anal. Calcd for $C_{26}H_{27}NO_7$: C, 67.07; H, 5.85; N, 3.01. Found: C, 66.82; H, 5.68; N, 3.21.

2″-Hydroxy-5″-nitro-14,15:17,19:21,22-tribenzo-1,4,7,10,13-pentaoxacyclodocosa-14,17,21-triene (3c): white powder (68%); mp 143–144 °C; ^1H NMR (200 MHz) δ 8.27 (s, 1 H, OH), 7.81 (s, 2 H, ArH), 7.25–7.19 (m, 4 H, ArH), 6.96 (br t, ^3J = 7.3 Hz, 2 H, ArH), 6.87 (br d, ^3J = 8.5 Hz, 2 H, ArH), 4.17–4.13 (m, 4 H, $ArOCH_2CH_2$), 4.02 (s, 4 H, $ArCH_2Ar$), 3.75–3.70 (m, 12 H, OCH_2CH_2O); MS m/z 509 (M^+, 100). Anal. Calcd for $C_{28}H_{31}NO_8$: C, 65.99; H, 6.14; N, 2.75. Found: C, 66.26; H, 6.22; N, 2.79.

2″-Hydroxy-5″-nitro-17,18:20,22:24,25-tribenzo-1,4,7,10,13,16-hexaoxacyclopentacosa-17,20,24-triene (3d): white cottonlike fibers from aqueous methanol or ethanol (68%); mp 83–85 °C; ^1H NMR (200 MHz) δ 8.31 (s, 1 H, OH), 7.79 (s, 2 H, ArH), 7.26–7.14 (m, 4 H, ArH), 6.97–6.86 (m, 4 H, ArH), 4.18–4.14 (m, 4 H, $ArOCH_2CH_2$), 4.02 (s, 4 H, $ArCH_2Ar$), 3.78–3.74 (m, 4 H, $ArOCH_2CH_2$), 3.63 (br s, 12 H, OCH_2CH_2O); MS m/z 553 (M^+, 21). Anal. Calcd for $C_{30}H_{35}NO_9$: C, 65.07; H, 6.38; N, 2.53. Found: C, 64.80; H, 6.52; N, 2.51.

2″-Hydroxy-5″-nitro-20,21:23,25:27,28-tribenzo-1,4,7,10,13,16,19-heptaoxacyclooctacosa-20,23,27-triene (3e): pale yellow crystals from aqueous ethanol (76%); mp 94–96 °C; ^1H NMR (200 MHz) δ 8.64 (s, 1 H, OH), 7.81 (s, 2 H, ArH), 7.25–7.09 (m, 4 H, ArH), 6.94–6.84 (m, 4 H, ArH), 4.16–4.12 (m, 4 H, $ArOCH_2CH_2$), 4.03 (s, 4 H, $ArCH_2Ar$), 3.78–3.74 (m, 4 H, $ArOCH_2CH_2$), 3.65–3.58 (m, 16 H, OCH_2CH_2O); MS m/z 597 (M^+, 48).

2,6-Bis(2′-methoxybenzyl)-4-nitrophenol (13a). A solution of Na (0.57 g, 25 mmol) in ethanol (9 mL) was added to the boiling solution of compound **12a** (1.49 g, 5 mmol) and 2-nitromalon-

dialdehyde sodium salt (1.39 g, 10 mmol) in methanol (25 mL). The mixture was heated under reflux for 20 h and filtered hot with suction. From the cooled filtrate a yellow precipitate separated which was stirred with dilute HCl. The crude white product thus obtained was recrystallized from aqueous acetic acid to give white crystals (53%): mp 125–127 °C. Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.36; H, 5.79; N, 3.80.

2,6-Bis(4′-methoxybenzyl)-4-nitrophenol (13b). The synthesis was carried out as described for compound **13a**: pale yellow needles from aqueous acetic acid (85%); mp 134.5–135 °C; ^{1}H NMR (200 MHz) δ 7.96 (s, 2 H, ArH), 7.12 (d, J = 8.6 Hz, 4 H, ArH), 6.87 (d, J = 8.6 Hz, 4 H, ArH), 5.47 (s, 1 H, ArOH), 3.95 (s, 4 H, $ArCH_2Ar$), 3.78 (s, 6 H, CH_3). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.53; H, 5.62; N, 3.48.

2,6-Bis(2′-(1,4,7,10-tetraoxaundecanyl)benzyl)-4-nitrophenol (13c). A solution of Na (0.21 g, 9 mmol) in ethanol (3.2 mL) was dropped slowly into the boiling mixture of compound **12c** (1 g, 1.8 mmol) and 2-nitromalondialdehyde sodium salt (0.5 g, 3.6 mmol) in methanol (9 mL). The reaction was carried out as described for compounds **3**. The crude product was purified by flash column chromatography ($CHCl_3$/acetone, 10/1): yellow oil (54%); ^{1}H NMR (200 MHz) δ 8.22 (s, 1 H, OH), 7.94 (s, 2 H, ArH), 7.23–7.08 (m, 4 H, ArH), 3.96 (s, 4 H, $ArCH_2Ar$), 4.20–3.47 (m, 24 H, CH_2CH_2), 3.33 (s, 6 H, CH_3).

General Procedure for the Preparation of Compounds 10 and 14. Acetic anhydride (14 mL) was added to a solution of **3** or **13** (1 mmol) in dry pyridine (12 mL). The mixture was stirred overnight, poured on ice, and allowed to stand for several hours. In most cases a white solid could be filtered off by suction and dried on a vacuum line. In some cases an oil was formed and the crude product was obtained by extraction with $CHCl_3$ and the usual workup procedure. Purification was achieved by flash column chromatography in the case of **10a** ($CHCl_3$), **10c** ($CHCl_3$/acetone, 10/1), and **14c** ($CHCl_3$/acetone, 6/1) and by recrystallization in the other cases.

5″-Nitro-8,9:11,13:15,16-tribenzo-1,4,7-trioxacyclohexadeca-8,11,15-trien-12-yl acetate (10a): white powder from benzene (70%); mp 259 °C; ^{1}H NMR (200 MHz) δ 7.53 (s, 2 H, ArH), 7.34–7.22 (m, 4 H, ArH), 6.99 (br t, ^3J = 7.3 Hz, 2 H, ArH), 6.76 (br d, ^3J = 8.0 Hz, 2 H, ArH), 4.30 (d, ^2J = 15.3 Hz, 2 H, $ArCH_2Ar$), 3.95–3.90 (m, 4 H, $ArOCH_2CH_2$), 3.80–3.60 (m, 4 H, $ArOCH_2CH_2$), 3.43 (d, ^2J = 15.3 Hz, 2 H, $ArCH_2Ar$), 2.45 (s, 3 H, CH_3); MS m/z 463 (M^+, 100). Anal. Calcd for $C_{26}H_{25}NO_7$: C, 67.36; H, 5.44; N, 3.02. Found: C, 67.60; H, 5.57; N, 3.19.

5″-Nitro-11,12:14,16:18,19-tribenzo-1,4,7,10-tetraoxacyclononadeca-11,14,18-trien-15-yl acetate (10b): pale yellow, shining crystals from benzene/petroleum ether (80%); mp 156 °C; ^{1}H NMR (200 MHz) δ 7.49 (s, 2 H, ArH), 7.35–7.20 (m, 4 H, ArH), 6.99 (dt ^3J = 7.3 Hz, 2 H, ArH), 6.88 (br d, ^3J = 8.2 Hz, 2 H, ArH), 4.19 (d, ^2J = 16.2 Hz, 2 H, $ArCH_2Ar$), 4.07–4.03 (m, 4 H, $ArOCH_2CH_2$), 3.74–3.70 (m, 4 H, $ArOCH_2CH_2$), 3.61 (d, ^2J = 16.3 Hz, 2 H, $ArCH_2Ar$), 3.33 (br s, 4 H, CH_2CH_2O), 2.36 (s, 3 H, CH_3); MS m/z 507 (M^+, 17). Anal. Calcd for $C_{28}H_{29}NO_8$: C, 66.25; H, 5.76; N, 2.76. Found: C, 66.11; H, 5.77; N, 2.86.

5″-Nitro-14,15:17,19:21,22-tribenzo-1,4,7,10,13-pentaoxacyclodocosa-14,17,21-trien-18-yl acetate (10c): white powder (99%); mp 128–130 °C; ^{1}H NMR (200 MHz) δ 7.71 (s, 2 H, ArH), 7.25 (dt, ^3J = 9.1 Hz, 2 H, ArH), 7.11 (dd, ^3J = 7.4 Hz, 2 H, ArH), 6.93 (br t, ^3J = 6.7 Hz, 2 H, ArH), 6.87 (br d, ^3J = 8.4 Hz, 2 H, ArH), 4.09–4.10 (m, 4 H, $ArOCH_2CH_2$), 3.92 (s, 4 H, $ArCH_2Ar$), 3.76–3.68 (m, 4 H, $ArOCH_2CH_2$), 3.56–3.48 (m, 8 H, OCH_2CH_2O), 2.26 (s, 3 H, CH_3); MS m/z 551 (M^+, 11). Anal. Calcd for $C_{30}H_{33}NO_9$: C, 65.31; H, 6.03; N, 2.54. Found: C, 65.32; H, 6.30; N, 2.55.

5″-Nitro-17,18:20,22:24,25-tribenzo-1,4,7,10,13,16-hexaoxacyclopentacosa-17,20,24-trien-21-yl acetate (10d): white powder from benzene/petroleum ether (61%); mp 112 °C; ^{1}H NMR (200 MHz) δ 7.85 (s, 2 H, ArH), 7.23 (dt, ^3J = 7.7 Hz, 2 H, ArH), 7.07 (dd, ^3J = 7.4 Hz, 2 H, ArH), 6.95 (dt, ^3J = 7.3 Hz, 2 H, ArH), 6.85 (br d, ^3J = 7.5 Hz, 2 H, ArH), 4.10–4.06 (m, 4 H, $ArOCH_2CH_2$), 3.92 (s, 4 H, $ArCH_2Ar$), 3.76–3.72 (m, 4 H, $ArOCH_2CH_2$), 3.58 (s, 4 H, OCH_2CH_2O), 3.54 (br s, 8 H, OCH_2CH_2), 2.28 (s, 3 H, CH_3); MS m/z 595 (M^+, 6).

5″-Nitro-20,21:23,25:27,28-tribenzo-1,4,7,10,13,16,19-heptaoxacyclooctacosa-20,23,27-trien-24-yl acetate (10e): white needles from benzene (63%); mp 108–109 °C; ^{1}H NMR (200 MHz) δ 7.86 (s, 2 H, ArH), 7.23 (dt, ^3J = 7.9 Hz, 2 H, ArH), 7.08 (br d, ^3J = 7.4 Hz, 2 H, ArH), 6.94–6.83 (m, 4 H, ArH), 4.10–4.05 (m, 4 H, $ArOCH_2CH_2$), 3.91 (s, 4 H, $ArCH_2Ar$), 3.76–3.71 (m, 4 H, $ArOCH_2CH_2$), 3.58–3.57 (m, 16 H, OCH_2CH_2O), 2.31 (s, 3 H, CH_3); MS m/z 639 (M^+, 5).

2,6-Bis(2′-methoxybenzyl)-4-nitrophenylacetate (14a): white crystals from toluene/petroleum ether (75%); mp 79–80 °C; ^{1}H NMR (200 MHz) δ 7.81 (s, 2 H, ArH), 7.29–7.22 (m, 2 H, ArH), 7.05 (br d, ^3J = 6.7 Hz, 2 H, ArH), 6.93–6.86 (m, 4 H, ArH), 3.88 (s, 4 H, $ArCH_2Ar$), 3.77 (s, 6 H, OCH_3), 2.29 (s, 3 H, $COCH_3$). Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.38; H, 5.50; N, 3.32. Found: C, 68.21; H, 5.43; N, 3.40.

2,6-Bis(4′-methoxybenzyl)-4-nitrophenylacetate (14b): white crystals from petroleum ether (71%); mp 95–96 °C; ^{1}H NMR (200 MHz) δ 7.83 (s, 2 H, ArH), 7.06 (d, J = 8.5 Hz, 4 H, ArH), 6.85 (d, J = 8.6 Hz, 4 H, ArH), 3.84 (s, 4 H, $ArCH_2Ar$), 3.79 (s, 6 H, OCH_3), 2.24 (s, 3 H, $COCH_3$). Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.38; H, 5.50; N, 3.32. Found: C, 68.06; H, 5.48; N, 3.39.

2,6-Bis(2′-(1,4,7,10-tetraoxaundecanyl)benzyl)-4-nitrophenylacetate (14c): white oil (88%); ^{1}H NMR (400 MHz) δ 7.88 (s, 2 H, ArH), 7.20 (br t, ^3J = 7.5 Hz, 2 H, ArH), 7.03 (br d, ^3J = 7.4 Hz, 2 H, ArH), 6.89–6.84 (m, 4 H, ArH), 4.07 (br t, ^3J = 4.7 Hz, 4 H, $ArOCH_2CH_2$), 3.87 (s, 4 H, $ArCH_2Ar$), 3.74 (br t, ^3J = 5.1 Hz, 4 H, $ArOCH_2CH_2$), 3.65–3.58 (m, 12 H, OCH_2CH_2O), 3.51–3.49 (m, 4 H, OCH_2CH_2O), 3.33 (s, 6 H, OCH_3), 2.26 (s, 3 H, $COCH_3$).

X-ray Crystallography. The crystal structure of compound **3c** and **3e** was determined by X-ray diffraction.

Compound 3c. Crystal data: $C_{28}H_{31}NO_8$, monoclinic, space group $P2_1/n$; a = 23.598 (2) Å, b = 14.694 (2) Å, c = 14.381 (2) Å, β = 93.07 (2)°; V = 4964 (3) Å^3; Z = 8; d_{calc} = 1.36 g cm^{-3}, μ = 0.94 cm^{-1}. Reflections were measured at 125 (5) K in the $\omega/2\vartheta$ scan mode [3.0° < ω < 25.0°], using graphite monochromated Mo Kα radiation [scan width (ω) 0.80 + 0.34 tan ϑ]. The structure was solved by direct methods[25] and refined with full-matrix least-squares methods. A total of 4837 reflections with $F_o^2 > 3\sigma(F_o^2)$ was used in the refinement. The crystal structure contains two crystallographically independent molecules, one of which is shown in Figure 1. In both molecules the phenolic hydrogen atom is involved in hydrogen bonding to oxygen atoms of the ring. The conformation of the two molecules is different in the non-hydrogen bonded part of the ring. The numbers of parameters refined was 675 [scale factor, positional parameters, and anisotropic thermal parameters for the non-hydrogen atoms]. Hydrogen atoms were put in calculated positions and were treated as riding atoms in the refinements with fixed thermal parameters. The position of the phenolic hydrogens was found from a difference Fourier synthesis. Positions and thermal parameters of these atoms were refined. The final R factors were R = 5.2%, R_w = 5.7%. All calculations were done with SDP.[26]

Compound 3e. Crystal data: $C_{32}H_{39}NO_{10}\cdot H_2O$, triclinic, space group $P\bar{1}$; a = 8.893 (2) Å, b = 13.143 (5) Å, c = 14.226 (5) Å, α = 81.73 (4)°, β = 79.94 (4)°, γ = 80.61 (4)°; V = 1604 (1) Å^3; Z = 2; d_{calc} = 1.28 g cm^{-3}, μ = 0.90 cm^{-1}. Reflections were measured at 293 (2) K in the $\omega/2\vartheta$ scan mode [3.0° < ω < 25.0°], using graphite monochromated Mo Kα radiation [scan width (ω) 1.00 + 0.35 tan ϑ]. A total of 3570 reflections with $F_o^2 > 3\sigma(F_o^2)$ was used in the refinement. In the cavity of the macrocycle a water molecule was found, which accepts a hydrogen bond from the phenolic H atom and is hydrogen bonded to oxygen atoms of the ring. The crystal structure of compound **3e** is shown in Figure 1. The number of parameters refined was 562 [scale factor, extinction parameter, positional parameters and thermal parameters (anisotropic for the non-hydrogen atoms, isotropic for the hydrogens)]. The final R factors were R = 4.5%, R_w = 5.9%.

Materials for Kinetic Measurements. Absolute ethanol (Erba RP), fractionally distilled over magnesium ethoxide and then over anhydrous copper(II) sulfate, was stored in an automatic burette under argon. Alkaline-earth metal bromides were from a previous investigation.[1] Ethanolic solutions of tetramethylammonium ethoxide were prepared from a commercial sample

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of $Me_4NOH·5H_2O$ (Fluka). The water contained in the solid sample was removed by repeated azeotropic distillations with benzene under vacuum.[1] The residue was then repeatedly taken up with anhydrous ethanol, evaporated to dryness, and eventually dissolved in a calculated amount of dry ethanol. All operations were carried out under argon. *p*-Nitrophenylacetate (Fluka) was used without further purification.

Kinetics. Rate measurements were carried out by using either conventional or stopped flow spectrophotometry. Solutions were prepared and handled under argon to prevent contamination by atmospheric carbon dioxide. The kinetic runs were started by adding a calculated amount of an ethanolic solution of the *p*-NO_2-aryl acetate to an ethanolic solution of base and added salt. On standing, a white crystalline material precipitated from the more concentrated solutions of alkaline-earth metal bromides and Me_4NOEt. The nature of the solid material was not investigated. Solutions for kinetic runs were prepared immediately before use. Occasional checks showed strictly reproducible results in all cases.

Fitting of k_{obs} to eq 4 was carried out by a nonlinear least-squares procedure.[1]

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Registry No. **3a**, 137794-10-6; **3b**, 137794-11-7; **3c**, 137794-12-8; **3d**, 137794-13-9; **3e**, 137794-14-0; **4**, 2150-52-9; **7a**, 6315-52-2; **7b**, 7460-82-4; **7c**, 19249-03-7; **7d**, 37860-51-8; **7e**, 42749-27-9; **8a**, 137794-15-1; **8b**, 137794-16-2; **8c**, 137794-17-3; **8d**, 137794-18-4; **8e**, 137794-19-5; **9a**, 137794-20-8; **9b**, 137794-21-9; **9c**, 137794-22-0; **9c** alcohol, 137794-23-1; **9d**, 137794-24-2; **9e**, 137794-25-3; **10a**, 137794-26-4; **10b**, 137794-27-5; **10c**, 137794-28-6; **10d**, 137794-29-7; **10e**, 137794-30-0; **11c**, 137822-75-4; **12a**, 41973-43-7; **12b**, 74882-32-9; **12c**, 137794-31-1; **13a**, 137794-32-2; **13b**, 137794-33-3; **13c**, 137794-34-4; **14a**, 137794-35-5; **14b**, 137794-36-6; **14c**, 137794-37-7; triethylene glycol monoethyl ether tosylate, 62921-74-8; 1,5-bis-(2'-(2,4,7,10-tetraoxaundecanyl)phenyl)-3-hydroxypentane, 137794-38-8; 2-nitromalondialdehyde sodium salt, 34461-00-2.

Supplementary Material Available: First order rate constants k_{obs} (s^{-1}) at various metal-bound ethoxide concentrations, tables of positional and thermal parameters, bond distances and angles, and ^{13}C NMR data (23 pages). Ordering information is given on any current masthead page.

The Regioselective Cleavage of Aryl Tosylates by Electrochemical Reduction

Edgar R. Civitello and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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The electrochemical reductions of eight bis(tosyloxy)benzenoid compounds were studied as a method for the regioselective cleavage of aryl tosylates. For the methyl bis(tosyloxy)benzoate isomers, a strong preference was observed for cleavage of the tosyl group in conjugation with the electron-withdrawing ester moiety. Thus it was possible to selectively cleave tosyl groups to the ortho or para positions over tosyl groups at the meta positions. The bis(tosyloxy)anisole isomers displayed the opposite regioselectivity favoring cleavage of tosyl groups that were meta to the electron-donating methoxy substituent. The general electrochemical process for the reduction of aryl tosylates has been shown to be selective, high yielding, and reproducible on gram quantities.

Introduction

Background. The cleavage of arenesulfonates and sulfonamides by electrochemical reduction was originally observed in 1965,[1] and although it has been the subject of several studies,[2] it has not found widespread application in synthesis as a deprotection method. The existing literature can be organized into the following two categories: the selective cleavage of different arenesulfonyl derivatives from the same type of functional group and the selective cleavage of the same arenesulfonyl from two different functional groups. With respect to the former category, different ring substituents in the para position of both alkyl and aryl benzenesulfonates have been shown to have a dramatic effect on the half-wave potential.[3] Selectivity in the electrochemical reduction of two differently substituted benzenesulfonates was possible when the difference between their half-wave potentials was sufficiently large. The following trend among para substituents was observed going toward more negative $E_{1/2}$ values:

$$EtO_2C \gg Cl > CH_3CONH > CH_3O$$

The difference in $E_{1/2}$ between the two extremes was approximately 800 mV. The second category deals with selectivity between different functional groups protected with the same arenesulfonyl group. For example, the *O,N*-bis(toluenesulfonyl)-protected methyl ester of serine has been shown to be regiospecifically deprotected at oxygen, preserving the toluenesulfonamide.[4] For the electrochemical cleavage of the tosyl group, the ease of S–X bond cleavage has been shown to decrease in the following sequence:[5]

Ts-O-aryl > Ts-O-alkyl, Ts-NH-aryl > Ts-NH-alkyl > Ts-NH-CH(alkyl)-COOR

Conspicuously missing from the existing literature is a study of the selective monocleavage of tosylated poly-

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