# Remarkable Metal Ion Catalysis of Methanolysis of *O,O′*-Oxybis(ethyleneoxyethylene)-*tert*-butylcalix[4]arene Monoacetate

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Basic methanolysis of the cone-isomer of *O,O′*-oxybis(ethyleneoxyethylene)-*tert*-butylcalix[4]arene monoacetate **2** is accelerated more than a millionfold by barium and strontium ions.

In the course of our investigations[1] of catalysis of ester cleavage of crown ether arylacetates where the polyether chain holds a metal ion electrophile in proximity to the reacting carbonyl, our attention was attracted by the cone-isomer of the acetate **2**, recently obtained[2] *via* a highly selective metal ion-controlled acetylation of the parent calix[4]arene–crown derivative **1**. Calix[4]arenes diametrically bridged with polyether chains are suitably preorganized hosts[3] whose efficiency and selectivity in cation binding have found useful applications.[4] Since it was felt that ionization of the phenolic hydroxy group of **2** had the potential of providing an additional binding site for holding a metal ion in the crown ether cavity, we have investigated the effect of added hard metal ions on the rate of deacetylation of **2** in $Me_4NOMe$–MeOH at 25 °C. The huge rate accelerations that were observed with barium and strontium ions provide, to the best of our knowledge, the most striking examples of electrophile catalysis by these ions. A preliminary account of our observations is given in the present communication.

The second-order reaction† between **2** and $Me_4NOMe$ in methanol solution at 25 °C affords **1** [eqn. (1)] at an exceedingly low rate, $k_{uncat} = 3.4 \times 10^{-5}$ mol$^{-1}$ dm$^3$ s$^{-1}$.

$$\mathbf{2} \xrightarrow[k_{uncat}]{MeO^-/MeOH} \mathbf{1} \qquad (1)$$

The half-life for the pseudo-first-order reaction of **2** in a 1 mmol dm$^{-3}$ $Me_4NOMe$ solution is 34 weeks, but drops astonishingly to 8 s upon addition of 1 mmol dm$^{-3}$ $BaBr_2$. The magnitude of the observed rate enhancement is a marked function of salt concentration, as shown in Fig. 1. It is apparent that the pseudo-first-order rate constant $k_{obs}$ for ester cleavage in 1 mmol dm$^{-3}$ methanolic $Me_4NOMe$ increases steeply on increasing the salt concentration and approaches a plateau value in the 1 mmol dm$^{-3}$ concentration region (saturation kinetics), where the apparent order in respect to metal salt drops to zero. Strontium bromide promotes the reaction to a lesser extent, but the shape of the rate profile is similar to that of $BaBr_2$. Consistent with previous observations, much lower rate enhancements were brought about by monovalent ions. Methanolysis in 40 mmol dm$^{-3}$ $Me_4NOMe$ was accelerated 3300-fold by 40 mmol dm$^{-3}$ KBr, and 220-fold by 43 mmol dm$^{-3}$ RbBr.

Considerable insight into the reaction mechanism was afforded by UV spectroscopy. In the absence of metal salts **2** remains in its unionized form upon treatment with $Me_4NOMe$, with little or no production of aryloxide absorption in the UV.‡ Upon addition of either barium or strontium bromide, a strong absorption appears at zero time in the 310–350 nm region, whose intensity is a function of the metal salt concentration. The absorption increases further as the reaction proceeds and eventually approaches the value

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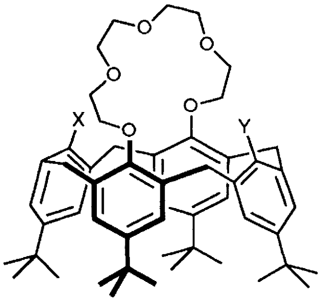
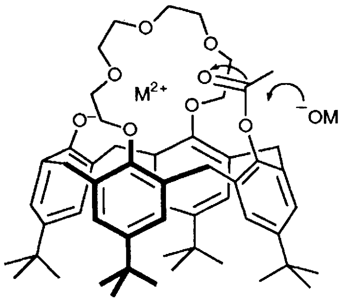
† Because of the extreme sensitivity of the reaction to impurities of alkali (alkaline earth) metal ions present in the commercial samples of tetramethylammonium methoxide, reproducible $k_{uncat}$ values could be obtained only in the presence of excess of [2.2.2]-cryptand.

‡ Taking the UV spectrum of the anion derived from 2,4,6-trimethylphenol as a reasonable model for **3**, we found that **2** is 12 and 4% ionized in 0.25 and 0.08 mol dm$^{-3}$ $Me_4NMeO$, respectively. Ionization was negligibly small in 1 mmol dm$^{-3}$ $Me_4NOMe$.



**1**; X = Y = OH
**2**; X = OH, Y = OAc
**3**; X = O⁻, Y = OAc



**4**

expected on the basis of the known absorption of the reaction product **1** in a medium of the same composition. Incidentally, we note that this permitted the metal ion catalysed reactions to be followed by UV spectroscopy, whereas the uncatalysed reaction was monitored by HPLC (initial rates). It was further observed that in the absence of base, binding of either strontium or barium ions to **2** is negligibly small. Therefore the increase in apparent acidity of **2** caused by metal ions can be quantitively expressed by eqn. (2). Here we are faced with the usual difficulty of a quantitative treatment of ionic equilibria involving divalent metal ions.[1a,b] We resorted as in previous studies[1a,b] to the approximation of considering the metal bromides as 1 : 1 strong electrolytes of the type $(MBr)^+Br^-$. Since in all cases the amount of metal ion sequestered by the ionized substrate **3** and by methoxide[1a] is small compared to the total concentration of salt, the concentration of the metal species appearing in eqn. (2) was set equal to the total concentration of salt, $c_{salt}$. Accordingly, the equilibrium constant $K$ can be written as in eqn. (3), with the mean activity coefficient $\gamma$ calculated as before[1a] by an extended Debye–Hückel equation.

$$\mathbf{2} + MeO^- + M^{2+} \xrightleftharpoons{K} \mathbf{3}\cdot M^{2+} \quad (2)$$

$$K = [\mathbf{3}\cdot M^{2+}]/\gamma^2[\mathbf{2}][MeO^-]c_{salt} \quad (3)$$

We assume that the reactive species responsible for the tremendous acceleration caused by the metal salts is the supramolecular complex $\mathbf{3}\cdot M^{2+}$, which undergoes attack of methoxide in a bimolecular step, eqn. (4), whereas in the absence of metal ions attack of methoxide takes place on the unionized form of the substrate, eqn. (5). Combination of eqns. (3)–(5) leads to eqn. (6) which on rearrangement gives eqn. (7).

$$v = k_{cat}[MeO^-][\mathbf{3}\cdot M^{2+}] \quad (4)$$

$$v = k_{uncat}[MeO^-][\mathbf{2}] \quad (5)$$

$$v = \frac{k_{uncat}[\mathbf{2}]_{tot}[MeO^-] + k_{cat}K\gamma^2[\mathbf{2}]_{tot}[MeO^-]^2c_{salt}}{1 + K\gamma^2[MeO^-]c_{salt}} \quad (6)$$

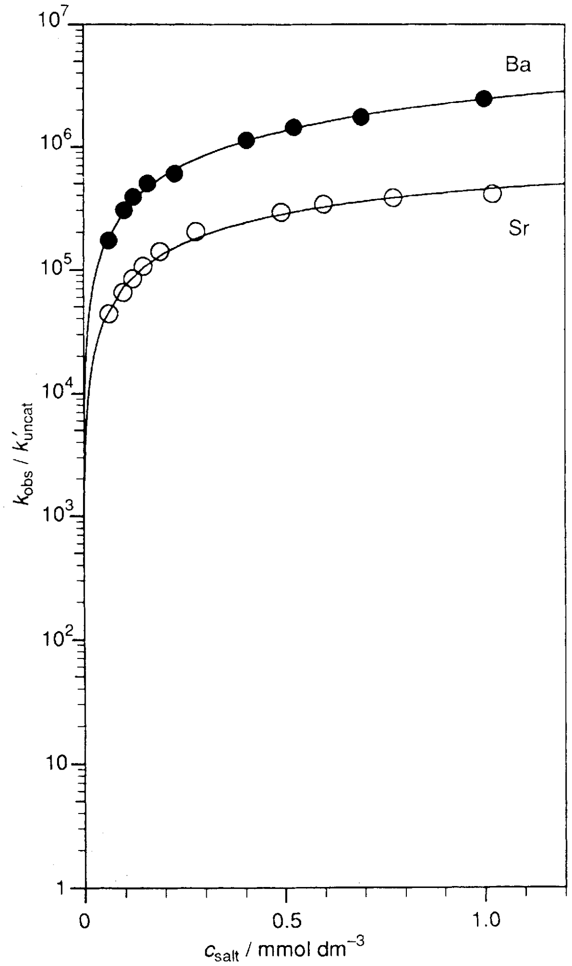


**Fig. 1** Metal ion effects on the methanolysis of **2** in methanolic 1 mmol dm⁻³ $Me_4NOMe$ at 25 °C. $k_{obs}$ is the pseudo-first-order rate constant measured in the presence of added salt. $k'_{uncat}$ (s⁻¹) is calculated as $10^{-3}$ $k_{uncat}$. The points are experimental and the curves are calculated using eqn. (7) and the least-squares parameters in Table 1.

**Table 1** Alkaline earth metal ion assisted basic methanolysis of **2** ($T$ = 25 °C)

| Added salt | $K$/mol⁻² dm⁶ | $k_{cat}$/mol⁻¹ dm³ s⁻¹ | $k_{cat}/k_{uncat}$ |
|---|---|---|---|
| $SrBr_2$ | $8.5 \times 10^5$ | 41 | $1.2 \times 10^6$ |
| $BaBr_2$ | $1.9 \times 10^5$ | 724 | $2.1 \times 10^7$ |

$$\frac{v}{[\mathbf{2}]_{tot}} = k_{obs} = \frac{k_{uncat}[MeO^-] + k_{cat}K\gamma^2[MeO^-]^2c_{salt}}{1 + K\gamma^2[MeO^-]c_{salt}} \quad (7)$$

As shown by the full lines in Fig. 1, eqn. (7) fits the data remarkably well. The root mean square deviation is 8% in the strontium reaction, and 6% in the barium reaction. The best fit parameters are listed in Table 1. Additional kinetic experiments showed that at high salt concentration (>1 mmol dm⁻³) the reaction is first-order in methoxide, whereas at low salt concentration (<0.1 mmol dm⁻³) the reaction is first-order in metal ion and the order in respect to methoxide rises to two. In other words, in the low salt concentration region ($1 \gg K\gamma^2[MeO^-]c_{salt}$) the reaction is overall fourth-order, but the order in metal ion drops to zero and that in methoxide drops to one when the condition $1 \ll K\gamma^2[MeO^-]c_{salt}$ is approached. This is exactly what is predicted by eqn. (7), remembering that in the presence of salt the contribution of the uncatalysed path is negligibly small.

The mechanistic picture which emerges from the data is clearly one where replacement of the ionizable proton of **2** with a divalent metal ion converts a sluggish species into a very reactive one. The metal ion, housed in the hydrophilic cavity delimited by the crown ether bridge and the aryloxide oxygen, strongly activates the carbonyl oxygen towards addition of the nucleophile, as schematically depicted in structure **4**. The resulting transition state stabilization, calculated as $RT\ln(k_{cat}/k_{uncat})$, amounts to 10.0 kcal $mol^{-1}$ (1 cal = 4.184 J) for the barium reaction and to 8.3 kcal $mol^{-1}$ for the strontium reaction.

These findings widen considerably the scope of group 2 metal ions as efficient catalysts of transacylation reactions. Our current work is aimed at putting these remarkable rate enhancements to the purpose of developing supramolecular catalysts with transacylase activity.

This work has been carried out in the frame of an EC joint project, contract No. SC1*-0359. Thanks are due to MURST for financial support.

*Received, 14th May 1992; Com. 2/02528K*

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