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ALKALINE EARTH METAL ION CATALYSIS OF ALCOHOLYSIS OF CROWN ETHER ARYL ACETATES. EFFECT OF THE BASE–SOLVENT SYSTEM

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The effect of strontium and barium ions on the acyl transfer reaction to ethoxide ion from 2-acetoxy-1,3-xylyl-15-crown-4, 2-acetoxy-1,3-xylyl-18-crown-5, 2-acetoxy-1,3-xylyl-21-crown-6 and the model compound phenyl acetate was investigated in ethanol at 25 °C. Significant catalytic effects were observed in all of the studied reactions as a result of stronger metal ion associations with the transition states than with reactants. The rate enhancements observed with the crown ether substrates are much larger than those observed with phenyl acetate, the largest acceleration being displayed by 2-acetoxy-1,3-xylyl-21-crown-6, which reacts with EtOBaBr 5×10^5 times faster than with $EtONMe_4$. These findings provide strong evidence that cooperation of electrostatic binding to the negative charge developing at the carbonyl oxygen and coordinative binding to the polyether chain is highly efficient in the metal-bound transition state. Comparison of rate data reported here with analogous data obtained in methanol solution clearly shows that both modes of interaction contributing to the stability of the metal-bound transition state are much more efficient in ethanol than in methanol solution.

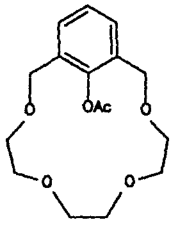
INTRODUCTION

Continuing our studies of reactions catalysed by alkali and alkaline earth metal ions,[1–4] we report here on a detailed kinetic study of the effect of added barium and strontium bromides on transacylation rates from phenyl acetate (PA) and a series of crown ether aryl acetates (2-AcO-15C4, 2-AcO-18C5 and 2-AcO-21C6) to ethoxide ion in anhydrous ethanol at 25·0 °C [equation (1)].

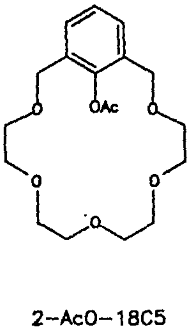
$$ArOAc + EtO^- \xrightarrow{EtOH} ArO^- + EtOAc \qquad (1)$$

The purpose of these studies was to make a comparison with analogous data recently obtained in the MeO^-–MeOH base–solvent system.[3] The strong dependence of the observed catalysis on the nature of

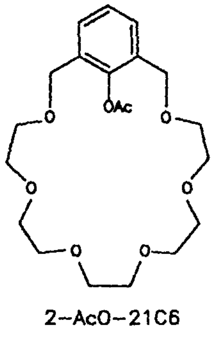
PA



2–AcO–15C4



2–AcO–18C5



2–AcO–21C6

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the cation and the size of the macrocyclic ligand was interpreted on the basis of specific transition-state stabilization arising from multiple binding of the metal ion to the crown ether portion and the negative charge being transferred from methoxide to the ester function. The prediction was that the expected increase in electrostatic anion–cation interaction on changing the solvent from MeOH ($\varepsilon = 32 \cdot 63$) to EtOH ($\varepsilon = 24 \cdot 30$) would produce enhancement of metal ion catalysis.

RESULTS

Kinetic data for transacylation reactions were obtained by monitoring the increase in the aryl oxide absorption in the neighbourhood of 300 nm. Either conventional or stopped-flow spectrophotometry was used, depending on the reaction half-life time. Dilute solutions of the aryl acetates (*ca* 0·1 mM) were reacted with an excess of Me_4NOEt (1–10 mM) in the absence and presence of alkaline earth metal bromides (MBr_2). Close adherence to first-order behaviour was obtained for several half-lives, with infinity readings which corresponded to quantitative conversion in all cases. Pseudo-first-order rate constants obtained in the absence of added salts were translated into second-order rate constants k_0 (Table 1), which were taken to represent free ethoxide ion reactivity.[4,5]

Solutions for rate measurements in the presence of strontium and barium ions were prepared by mixing equimolar amounts of Me_4NOEt and MBr_2. Although the precise nature of the species in solution is unknown, strong evidence was obtained[4] that binding of ethoxide to the metal ions is virtually complete in the investigated concentration range, as formally shown in equation (2).

$$EtONMe_4 + MBr_2 \rightarrow EtOMBr + Me_4NBr \qquad (2)$$

It is uncertain whether the metal–ethoxide complex contains a bromide counter ion, but it is clear that it behaves kinetically as a single species, whose concentration is stoichiometrically determined by that of the added reagents. This is shown by the pseudo-first-order rate constants, k_{obs}, measured in the reactions with PA (Table 2). Plots of k_{obs} vs metal-bound ethoxide [Figure 1(A)] are strictly linear over the whole concentration range, showing that for this reaction the rate equation is

$$v = k_M[EtOMBr]\ [PA] \qquad (3)$$

where $k_M = k_{obs}/[EtOMBr]$.

Table 1. Second-order rate constants for the reaction of aryl acetates with $EtONMe_4$ in EtOH at 25 °C

Substrate	k_0 ($l\ mol^{-1}\ s^{-1}$)[a]
PA	1·44
2-AcO-15C4	$6 \cdot 64 \times 10^{-2}$
2-AcO-18C5	$4 \cdot 99 \times 10^{-2}$
2-AcO-21C6	$6 \cdot 36 \times 10^{-2}$

[a] Mean errors of the order of ±2%.

Table 2. Rate data for the reactions of aryl acetates with EtOMBr (M = Sr, Ba) in EtOH at 25·0 °C

Substrate	M	[EtOMBr] (mM)	k_{obs} (s^{-1})[a]
PA	Sr	1·02	0·0882
		3·49	0·308
		5·82	0·527
		10·0	0·888
	Ba	1·60	0·102
		2·81	0·182
		5·72	0·373
		8·38	0·542
2-AcO-15C4	Sr	1·26	0·174
		3·42	0·431
		4·97	0·581
		6·45	0·717
		7·74	0·825
	Ba	1·00	0·486
		1·87	0·830
		2·81	1·17
		5·64	2·08
		8·38	2·80
2-AcO-18C5	Sr	1·00	2·18
		2·48	5·25
		3·87	7·75
		6·45	11·3
		10·0	15·4
	Ba	1·00	2·19
		2·81	4·84
		5·64	7·91
		8·38	9·76
2-AcO-21C6	Sr	1·26	3·05
		3·42	6·80
		5·55	9·64
		7·74	12·0
	Ba	1·00	12·7
		1·87	15·8
		2·81	17·4
		3·75	18·6
		5·64	19·5
		8·38	19·6

[a] Mean errors of the order of ±4%.

At variance with the strictly linear dependence experienced by the concentration–rate profiles of the PA reactions, the corresponding profiles of the crown substrates [Figure 1(B)–(D)] show the markedly nonlinear behaviour with negative curvature typical of saturation kinetics, which provides good evidence for the

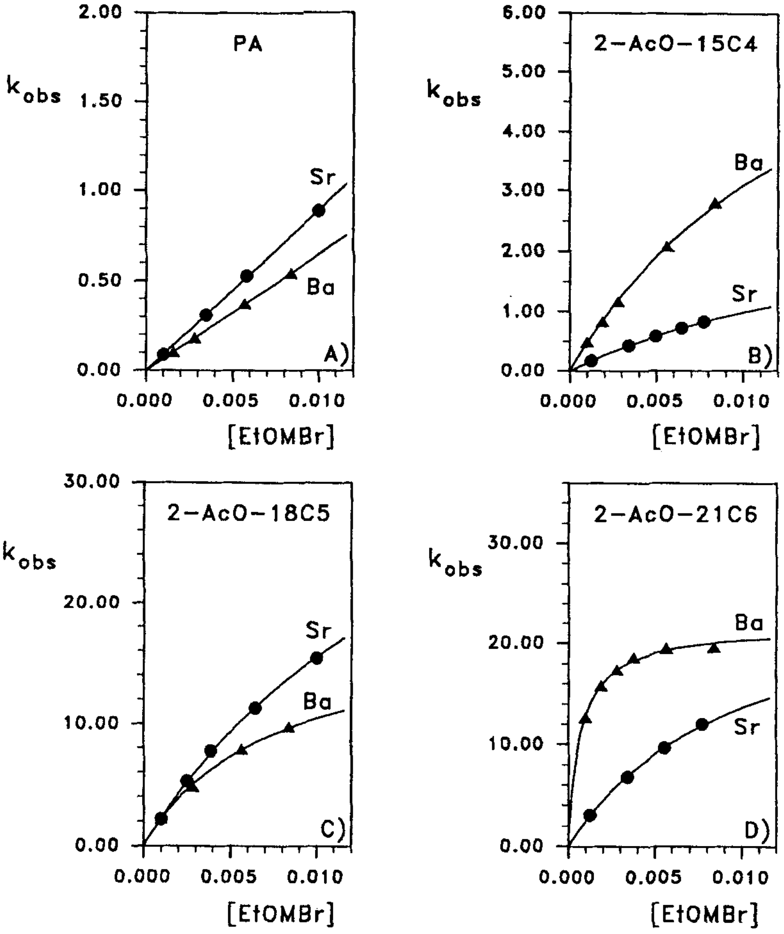


Figure 1. Plots of k_{obs} (s^{-1}) against concentration (M) of metal-bound ethoxide for deacylation of PA and crown ether aryl acetates in EtOH at 25·0 °C. The points are experimental and the curves in B, C, D are plots of equation (5)

occurrence of significant associations between the reactants. If association of substrate S and metal-bound ethoxide takes place reversibly with 1:1 stoichiometry, and the complex which is formed decomposes into products in a monomolecular slow step:

$$S + \mathrm{EtOMBr} \overset{K_S}{\rightleftharpoons} S \cdot \mathrm{EtOMBr}$$

$$S \cdot \mathrm{EtOMBr} \xrightarrow{k_{cat}} \text{products}$$

the rate equation is[4]

$$v = \frac{k_{cat} K_S [\mathrm{EtOMBr}]\,[S]}{1 + K_S [\mathrm{EtOMBr}]} \qquad (4)$$

with

$$k_{obs} = \frac{k_{cat} K_S [\mathrm{EtOMBr}]}{1 + K_S [\mathrm{EtOMBr}]} \qquad (5)$$

The close adherence of the data to equation (5) for all of the reactions investigated is shown graphically in Figure 1(B)–(D) by the good fit to the curves calculated on the basis of the k_{cat} and K_S parameters (Table 3) obtained by standard non-linear least-squares treatment of the k_{obs} values.

Comparison of the effect of the metal ions on the transacylation of the crown substrates with those of the reference compound PA is not straightforward, on account of the differing rate equations. It should be noted, however, that in the limit of very low concentrations of EtOMBr, i.e. when the product K_S[EtOMBr] is small compared with unity, equation (4) reduces to

$$v = k_{cat} K_S [\mathrm{EtOMBr}]\,[S] \qquad (6)$$

which has clearly the same form as equation (3). We believe that the analogy is well beyond the formal

Table 3. Rate and equilibrium parameters

Substrate	EtOSrBr k_{cat} (s^{-1})	K_S ($l\ mol^{-1}$)	k_M[a] ($l\ mol^{-1}\ s^{-1}$)	k_M/k_0[b]	k_{cat}/k_0[b] (M)	EtOBaBr k_{cat} (s^{-1})	K_S ($l\ mol^{-1}$)	k_M[a] ($l\ mol^{-1}\ s^{-1}$)	k_M/k_0[b]	k_{cat}/k_0[b] (M)
PA	—	—	89	62	—	—	—	65	45	—
2-AcO-15C4	3·1	48	$1·5 \times 10^2$	$2·3 \times 10^3$	47	8·9	54	$4·8 \times 10^2$	$7·2 \times 10^3$	130
2-AcO-18C5	42	57	$2·4 \times 10^3$	$4·8 \times 10^4$	840	19	121	$2·3 \times 10^3$	$4·6 \times 10^4$	380
2-AcO-21C6	29	89	$2·6 \times 10^3$	$4·1 \times 10^4$	460	22	1450	$3·2 \times 10^4$	$5·0 \times 10^5$	350

[a] Calculated for reactions of the crown ether substrates as $k_{cat}K_S$.

[b] k_0 values from Table 1.

appearance. Like any bimolecular reaction in solution, the reactions of PA can be thought of as proceeding via an unstable encounter complex,[6] the inherent stability of which is not large enough to affect the kinetics. According to this view, the second-order rate constant k_M is given by the product of the equilibrium constant for encounter complex formation and the first-order rate constant for its decomposition. It appears, therefore, that the $k_{cat}K_S$ products calculated for the substrates exhibiting saturation kinetics have the same mechanistic meaning as the k_M values. They can be used for an assessment of the effect of metal ions on transacylation rates throughout the series investigated under subsaturation conditions.

DISCUSSION

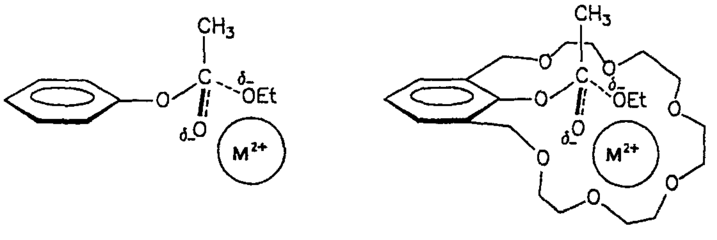
The acetyl transfer reactions reported here provide additional examples of reactions which are dramatically accelerated by divalent metal ions. Kinetic evidence was obtained that these reactions proceed through what might be called a ternary complex (substrate + ethoxide + metal ion), which has the same composition as the rate-limiting transition state and decomposes into products in a monomolecular step. Virtually complete accumulation of this ternary complex in the accessible concentration range was obtained in the barium reaction of 2-AcO-21C6.

A measure of the rate enhancements brought about by the metal ions under subsaturating EtOMBr concentrations is provided by the k_M/k_0 ratios in Table 3, which show rate accelerations of from more than a 10^3-fold to slightly less than 10^6-fold, the largest acceleration being displayed by 2-AcO-21C6, which reacts with EtOBaBr 5×10^5 times faster than with EtONMe$_4$.

Comparison of these exceedingly large rate enhancements with those found in the corresponding reactions of the model compound PA (Table 3) clearly points to the important role of the polyether bridges in determining the observed phenomena. It is remarkable, however, that even in the absence of the polyether bridge the reaction of PA is still 62 and 45 times faster with EtOSrBr and EtOBaBr, respectively, than with EtONMe$_4$. According to transition-state theory,[7] this means that strontium and barium ions bind the transition state 62 and 45 times, respectively, more strongly than the ethoxide reactant. The corresponding figures for deacetylation of *p*-nitrophenyl acetate under the same conditions, namely 8·0 and 7·0, respectively,[4] show that the catalytic efficiency of strontium and barium ions dramatically decreases under the influence of a strong electron-withdrawing group. We interpret these findings by assuming[2–4] that transition-state stabilization by the metal ions is attained by means of a chelate interaction, where the metal ion coordinates both the incoming ethoxide oxygen and the carbonyl oxygen, where the negative charge of the former is being transferred (Figure 2). Without entering into the question of whether alcoholysis of aryl acetates proceeds through a rate-limiting intermediate or, as suggested by Ba-Saif *et al.*[8] and further stressed by Guthrie,[9] via a concerted mechanism with no intermediates of significant lifetimes, we note that our data point to a transition-state structure characterized by a substantial fraction of a negative charge on the carbonyl oxygen and, consequently, with a pronounced degree of tetrahedral geometry. The resulting electrostatic interaction responsible for cation binding in the transition-state complex is very sensitive to the electron-withdrawing property of the nitro group of *p*-nitrophenyl acetate.

No doubt the electrostatic interaction is responsible for only a fraction of the rate enhancements found in the reactions of the crown substrates, which show much larger k_M/k_0 values than PA (Table 3). In the crown substrates, additional stabilization of the transition state arises from coordinative binding of the oxygen donors to the metal ion (Figure 2). It is worth stressing that since k_M refers to subsaturating concentrations of EtOMBr, the reaction rate is related to the concentration of free reactants. As a consequence, the entire binding energy rendered available by the polyether chain is realized in the transition state only, i.e. it is fully utilized in catalysis.[10,11]

A different situation is met with k_{cat}, which relates the reaction rate to the properties of the



(I) (II)

Figure 2. Schematic diagrams of the transition state for the metal ion-assisted ethanolysis of phenyl acetate (I) and 2-AcO-21C6 (II)

substrate–cation–ethoxide complex. Here only a fraction of the available binding energy is utilized in catalysis,[10,11] namely the differential binding energy of transition states and reactants, as clearly shown by the differing orders followed by k_{cat} and k_M (Table 3). Noteworthy is the behaviour of the barium reaction of 2-AcO-21C6, for which k_M and K_S, but not k_{cat}, are the largest in the series, because of the free energy wasted in the complexation of the substrate with the cation–ethoxide pair. A better utilization of binding energy in catalysis is found in the strontium reaction of 2-AcO-18C5, which exhibits the largest k_{cat} value, in spite of the fact that binding in the reactant state is relatively weak.

So far the discussion has been focused on transition-state stabilization due to interaction with the metal ion as the entire and sole source of catalytic power.[11] In a more pictorial, canonical formulation,[11] the catalytic activity of strontium and barium ions can be interpreted as arising from the ability of the metal ions to bring the two reactants together in a reactive ternary complex, whereby the entropically disfavoured bimolecular attack of free ethoxide on free substrate is changed into a more favoured intramolecular (intracomplex) reaction. The effective molarity (*EM*)[12,13] values listed in Table 3, which were calculated as k_{cat}/k_O, provide a measure of the efficiency of the metal-bound ethoxide ion in the intracomplex reaction compared with an external free ethoxide in its 1 M standard state. The relatively high efficiencies which are observed arise not only from the close proximity of the reactive groups in the complex, but also from the ability of the metal ion to act as a built-in electrophile catalyst for nucleophilic attack at carbonyl carbon. We believe, however, that this pictorial description of catalysis adds little to the discussion based on transition-state stabilization.[11]

Let us now turn to the original plan of the present investigation, namely a comparison with analogous rate data obtained in MeOH solution.[2,3] The first observation is that metal ion catalysis is much stronger in EtOH than in MeOH, but again a quantitative comparison is faced with difficulties arising from the markedly differing rate equations found in the two solvent systems. In MeOH solution, binding of methoxide to the metal ions is weak, and had to be taken into account by means of a proper term in the rate equation. Further, no indication emerged from the kinetics of the involvement of ternary complexes as intermediates of significant stability. Instead, evidence was obtained that in addition to the metal–ethoxide pairs, metal–substrate complexes of appreciable stability also played a role as separate entities with 2-AcO-21C6 ($K_{ass} \approx 3\ l\,mol^{-1}$ with $SrBr_2$ and $50\ l\,mol^{-1}$ with $BaBr_2$ in MeOH at 25 °C). With 2-AcO-15C4 and 2-AcO-18C5, complexation of the metal species was insignificant.

It appears, therefore, that the only possible comparison of the quantitative nature of metal ion catalysis in the two given solvents is one where reference is made to the reaction of the free substrate with the metal-bound alkoxide, thus avoiding the complicating interference of various association equilibria which specifically occur in one of the solvents, but not in the other. The required data in EtOH are already available in Table 3 as k_M/k_O values. The corresponding data in MeOH, which were calculated from previously published data[2,3b] by extrapolation to infinite metal ion concentration, are listed in Table 4.

Table 4. Metal ion catalysis of deacylation in MeOH solution at 25·0 °C: comparison with rate data in EtOH

Substrate	M	$(k_M/k_O)_{MeOH}$[a]	$\dfrac{(k_M/k_O)_{EtOH}}{(k_M/k_O)_{MeOH}}$
PA	Sr	4·7	13
	Ba	3·7	12
2-ACO-15C4	Sr	60	38
	Ba	150	48
2-AcO-18C5	Sr	303	158
	Ba	1180	39
2-AcO-21C6	Sr	327	125
	Ba	1780	281

[a] Calculated as $K_T{}^{\neq}/K_{MeO}$, where K_{MeO} is the equilibrium constant for binding of MeO^- to the metal species and $K_T{}^{\neq}$ is the corresponding quantity for the formal equilibrium which involves the transition state $T^{\neq}$. $K_T{}^{\neq}$ and K_{MeO} values are from Ref. 2 for PA and from Ref. 3b for the crown ether substrates.

As shown by the last column in Table 4, rate enhancements are much larger in EtOH than in MeOH, and differences in the two solvents are more pronounced with the crown substrates than with the model compound PA. Therefore, the expected increase in electrostatic binding energy caused by the decrease in dielectric constant on going from MeOH to EtOH provides only a partial answer to the question of why metal ion catalysis of deacylation of the crown ether substrates is much stronger in the latter solvent. Noting that the strength of association between the crown ether substrates and the metal species turns out to be much larger in EtOH solution, and remembering that the rate data listed in Table 4 refer to conditions where the entire binding energy arising from metal ion binding to the polyether chains is utilized in catalysis, the extra stabilization of the metal-bound transition states in EtOH solution is easily understood.

CONCLUSION

The remarkable influence of strontium and barium ions on deacylation of crown ether aryl acetates arises from specific stabilization by the metal ion of the negatively charged transition state compared with the neutral reactant. The former behaves as a negatively charged host, where cation binding is strongly enhanced by cation–anion electrostatic interaction. The results reported here clearly demonstrate that the magnitude of catalysis is not only dependent on the nature of the cation and the ring size of the crown ether host, but also is affected to a surprisingly large extent by replacement of MeOH for EtOH as the solvent.

EXPERIMENTAL

Materials, apparatus and techniques were as reported previously.[3,4]

Non-linear least-squares calculations were carried out with the program Sigma Plot (Jandel Scientific).

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