Remarkable Catalysis by Strontium Ion in S_N2 and E2 Reactions occurring in Proximity to a Crown Ether Structure

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Strontium ion catalyses the reactions of the crown ether derivatives **1** and **2** with methoxide ion in methanol at 40 °C to yield the product of substitution **3** and elimination **4**, respectively.

Metal-ion promoted catalysis in supramolecular systems is of current interest in developing 'artificial enzymes'.[1]

Catalysis in such systems depends, among other things, (solvent, cation, *etc.*) on the reaction type and the position of coordination sites which hold the metal ion in close proximity to the reaction centre. Previous studies of S_N2 reactions have regarded, in particular, the formation of benzo-crown ethers *via* intramolecular Williamson reaction (template effect),[1,2] and methyl-transfer reactions to α-toluenethiolate from substrates in which a crown ether ring is part of the leaving group structure.[3]

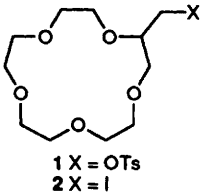
In searching for systems in which rate-enhancing metal-ion effects could arise owing to suitably placed donor atoms, we found that compound **1**[4] reacts with MeO^- in MeOH to yield exclusively the substitution product **3**,[4] whereas compound with a different leaving group **2**,† yields, under the same conditions, exclusively the elimination product **4**.‡ These two systems appeared to us ideally suited for the purpose of comparing rate-enhancing metal-ion effects in S_N2 and E2 reactions. This is the first investigation of this type on an elimination reaction, and on a substitution reaction in which a crown ether is part of the alkyl structure.

Rate measurements were carried out in MeOH at 40.0 °C on very dilute substrate solutions (*ca.* 10^{-4} mol dm^{-3}) in the presence of excess Me_4NOMe (0.100 mol dm^{-3}) and of varying amounts of alkali (Na, K) and alkaline-earth (Sr, Ba) metal bromides. In all cases ionic strength was kept constant by adjusting total salt concentration to 0.2 mol dm^{-3} with Et_4NBr. Reactions were followed spectrophotometrically by monitoring the appearance of tosylate ion in the reaction $\mathbf{1} \rightarrow \mathbf{3}$ (λ 234 nm), and iodide ion in the reaction $\mathbf{2} \rightarrow \mathbf{4}$ (λ 238 nm).

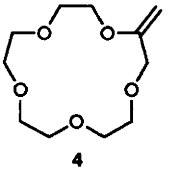
Preliminary rate measurements in the absence of metal salts and with varying amounts of Me_4NOMe in the range *ca.* 5×10^{-2} to 0.2 mol dm^{-3} allowed the evaluation of the second-order rate constants for both the reactions $\mathbf{1} \rightarrow \mathbf{3}$ (k_0 2.6×10^{-5} dm^3 s^{-1} mol^{-1}) and $\mathbf{2} \rightarrow \mathbf{4}$ (k_0 1.5×10^{-4} dm^3 s^{-1} mol^{-1}).

Second-order rate constants k_{obs} for reactions carried out in the presence of metal salts were calculated from the observed pseudo-first-order rate constants and the known concentration of Me_4NOMe. The ratios k_{obs}/k_0 were taken as a measure of the extent of catalysis.

For the substitution reaction $\mathbf{1} \rightarrow \mathbf{3}$, poor rate enhancements were observed in the presence of Na^+ and K^+ ($k_{obs}/k_0 \leq 2$) with no clearly discernible dependence of k_{obs}/k_0 on the metal salt concentration. In contrast (see Fig. 1), the reaction was strongly catalysed by the presence of strontium ion (acceleration *ca.* 37 at [$SrBr_2$] *ca.* 5×10^{-2} mol dm^{-3}). Unfortunately, the study of the barium ion was hampered by the early formation of an unknown precipitate. However, an estimate based on initial rates indicates that the catalytic effects of barium are of the same order of magnitude of those displayed by strontium.



1 X = OTs
2 X = I
3 X = OMe



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In the elimination reaction $\mathbf{2} \rightarrow \mathbf{4}$, K^+ proved to be ineffective as catalyst, whereas Na^+ showed a regular catalytic profile with evidence of saturation at [NaBr] *ca.* 0.1 mol dm^{-3}. However, even at this concentration the catalytic effect was a modest 3. As shown in Fig. 2, strontium ion exerts a remarkable catalysis in the elimination reaction also, the maximum observed catalytic effect being *ca.* 47 at [$SrBr_2$] ~ 4 × 10^{-2} mol dm^{-3}. Attempts to study the effect of barium were hampered by the same difficulties encountered in the substitution reaction, but also in this case initial rates suggest catalytic effects similar to those of strontium ions.

Rate measurements of S_N2 reaction on ethyl tosylate and E2 + S_N2 (87% + 13%) reaction on isobutyl iodide did not show, under the same conditions, any significant rate variations as a function of the metal salt concentration thus indicating that the catalytic effects observed with **1** and **2** are structure specific and not mere medium effects.

In brief, the results of the kinetic experiments have shown that a doubly charged cation, namely strontium ion, exerts a remarkable catalysis on both S_N2 and E2 reactions occurring in proximity to a crown ether ring, whereas in the case of monovalent cations, such as sodium or potassium ions, the catalytic effects are less pronounced or even absent.

It has long been recognised that catalysis is due to a greater stabilisation of the transition state relatively to the reactants.[5] It is known that MeO^- binds alkaline-earth cations by electrostatic interactions,[6] while the crown ether substrates **1** and **2** can coordinate both alkali and alkaline-earth metal ions

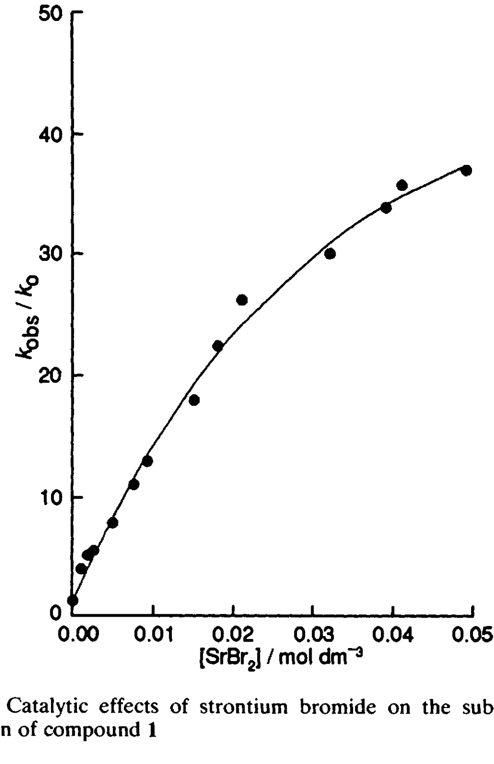


Fig. 1 Catalytic effects of strontium bromide on the substitution reaction of compound **1**

via their oxygen atoms. The rationale for the greater transition-state stabilisation by the metal ion is that it is the result of cooperation of electrostatic binding to the (somewhat delocalised) negative charge and coordinative binding to the polyether moiety. In this respect, the greater catalytic effect of strontium ion points to the importance of electrostatic interactions between the transition state and the metal ion, which are clearly stronger with divalent cations than with monovalent cations. Qualitatively similar results have been observed in the base-induced methanolysis of esters having a polyether chain[6] or ring.[7]

A simple distribution scheme considering the associations of the metal ion with reactants and transition state quantitatively accounts for the observed rate enhancements.[1,6] The curves shown in Figs 1 and 2 were calculated according to this model with the following values of the association constants (in $dm^3\ mol^{-1}$): reaction **1** → **3**, $K_{MeO^-} = 30$, $K_1 = 20$, $K_T{}^‡ = 6000$; reaction **2** → **4**, $K_{MeO^-} = 20$, $K_2 = 30$, $K_T{}^‡ = 9000$. However, since both the profiles shown in Figs. 1 and 2 are far from saturation, too much confidence should not be put in these figures. It is clear, however, that the catalytic effects displayed by strontium ion in the substitution reaction are similar to those observed in the elimination reaction. This result can be easily explained using molecular modelling. Comparing the radius of strontium ion (1.27 Å)[8] with that of the 15-crown-5 cavity (0.92 Å),[8] it is obvious that the metal ion is too big to fit inside the cavity, and that it must be located asymmetrically on one side of the crown ring. Considering that in the S_N2 transition state the negative charge is mainly delocalised on the nucleophile and on the leaving group, strontium ion can interact with either of them, but not with both, as illustrated by the structures **5** and **6**. Of course, the concentrations of two transition state structures depends on their relative energy. Analogous considerations can be made for the elimination reaction, the two suggested transition state structures being **7** and **8**. As one can see in all of the cases illustrated by the structures **5**–**8**, the distance between the metal ion and the nearest centre carrying a fraction of the negative charge is similar, thus suggesting similar electrostatic interactions in both S_N2 and E2 transition states.

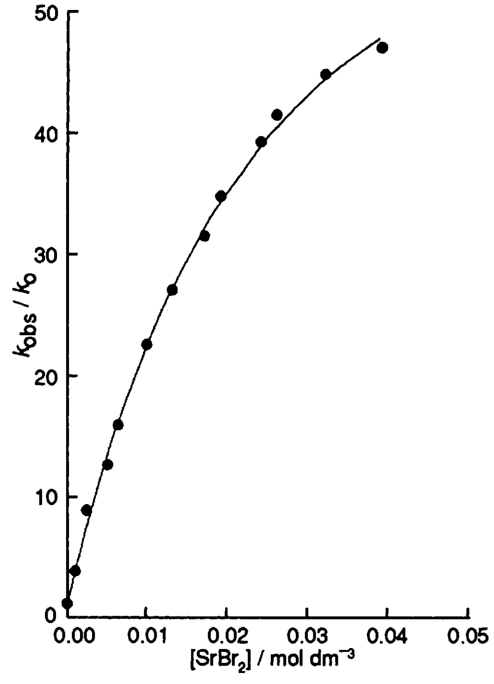
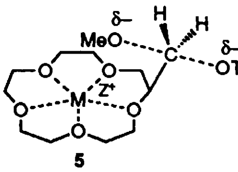


Fig. 2 Catalytic effects of strontium bromide on the elimination reaction of compound **2**



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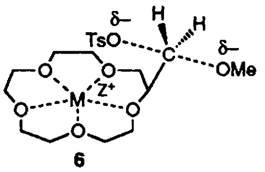

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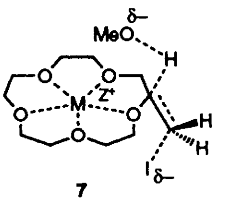

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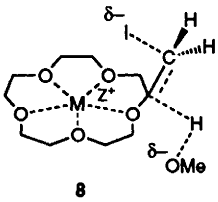

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Footnotes

† Prepared refluxing for 48 h an acetone solution of **1** and NaI (1 : 4), yield 83%, after chromatography on silica gel with acetone. ^1H NMR ($CDCl_3$) δ 3.40 (2H, m, CH_2I), 3.5–3.8 (19H, m). MS *m/z* 360.2. UV (MeOH) λ_{max}/nm 220, 250 (sh).

‡ ^1H NMR (CD_3OD) δ 3.6 (12H, m), 3.8–4.0 (4H, m), 4.1 (2H, s, CH_2–C=), 4.3 (2H, s, CH_2=C), ^{13}C NMR (CD_3OD) δ 69.62, 71.67, 71.86, 71.97, 72.35 (2C), 73.40, 73.46, 74.94, 89.97 (CH_2=C), 160.62 (CH_2=*C*). MS *m/z* = 232. UV (MeOH) λ_{max}/nm 224.

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