Competition between Catalysts and Inhibitors in Crown Ether Formation and Other Reactions of Associated Substrates

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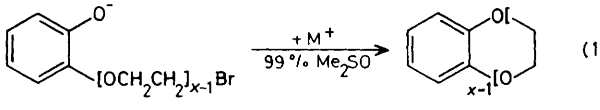
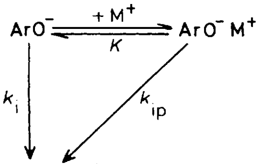
Competition between non-covalent catalysts and/or inhibitors helps quantitative investigation in crown ether formation, and promises to be a useful tool when dealing with associated reactive substrates in general.

In previous work on template effects,[1,2] the observed increase or decrease in the rate of cyclization of compounds (**1**), reacting at low concentration in 99% Me_2SO in the presence of varying amounts of alkali metal salts [equation (1)], was accounted for by Scheme 1 and equation (2). The values of the kinetic and equilibrium constants could be determined.†



(**1**) (**2**)



Scheme 1

$$\frac{k_{\text{obs}}}{k_{\text{i}}} = \frac{1 + (k_{\text{ip}}/k_{\text{i}})\,K\gamma_{\pm}^{2}\,[\text{M}^{+}]}{1 + K\gamma_{\pm}^{2}\,[\text{M}^{+}]} \qquad (2)$$

We now report that when two different alkali metal ions M_1^+ and M_2^+ are present in the solution, but the involvement of two ions in the transition state can safely be excluded, the kinetic scheme is modified as illustrated in Scheme 2, from which equation (3) is obtained. The two cationic species compete with each other for the substrate and in principle three reaction paths can lead to the crown ether. On varying the concentration of the two alkali metal ions, the observed rate of cyclization can be varied at will within the limits imposed by k_i, k_{ip1}, and k_{ip2}.

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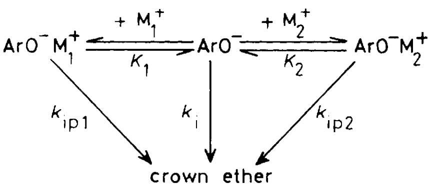
† An equation was also derived to calculate the activity coefficients $\gamma_{\pm}$ in 99% Me_2SO.[1]



Scheme 2

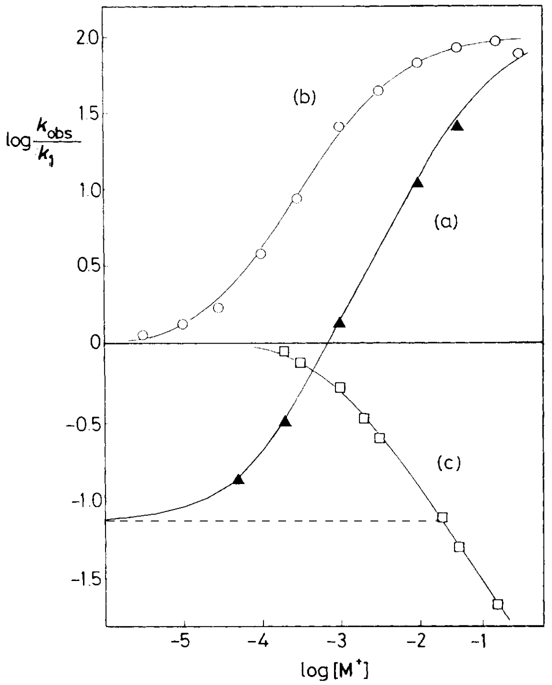


Figure 1. Effect of added Li^+ and K^+ ions on the rate of formation of benzo[18]crown-6 in 99% Me_2SO at 25 °C: (a) effect of K^+ at fixed (0.02 M) Li^+ concentration; (b) effect of the sole K^+ ion; (c) effect of the sole Li^+ ion. The points are experimental and the full lines are calculated using equation (2) (plots b and c) or equation (3) (plot a).

In particular, a given crown ether can be formed in the presence of both an inhibitor and a catalyst, and we report in Figure 1 the profile calculated using equation (3) for the formation of benzo-18-crown-6 in the presence of varying amounts of K^+ ion at fixed Li^+ ion concentration (0.02 M) (curve a). The profiles previously[1] observed for the same reaction catalysed by the sole K^+ ion (curve b) and inhibited by the sole Li^+ ion (curve c) are also reported. The experimental points for the cyclization under the conditions of curve a are very close to the calculated values and the validity of equation (3) is confirmed.

It appears that the catalyst K^+, which can increase the rate of the reaction by up to a factor of 100 under the usual conditions, is more effective when the substrate reactivity is initially lowered by the presence of an inhibitor. A problem solved through the application of this competition method is outlined as follows.

In the formation of compounds (**2**) according to equation (1), a horizontal line was obtained[1,2] as the profile for R_4N^+ ions. Despite an earlier interpretation that no appreciable association takes place between compound (**1**) and the added cations, the possibility that the complex is formed, but k_{ip} is the same as k_i, could not be excluded on a kinetic basis. We then examined whether, in the formation of compound (**2**), $x = 9$, any effect on the reaction rate was brought about by added $Me_4N^+ClO_4^-$, both in the absence and in the presence of a fixed amount (0.05 M) of the inhibitor Li^+ ion. It can be easily calculated by equation (3) that even low K values (for instance 50 M^{-1}) for the association with the Me_4N^+ ion should result in large rate increases of the initially inhibited reaction when $k_{ip} = k_i$ for the Me_4N^+ ion,[‡] and the absence of any significant association can be taken as kinetically proved.[§]

$$\frac{k_{obs}}{k_i} = \frac{1 + (k_{ip1}/k_i)\,K_1\,\gamma_\pm{}^2\,[M_1^+] + (k_{ip2}/k_i)\,K_2\,\gamma_\pm{}^2\,[M_2^+]}{1 + K_1\,\gamma_\pm{}^2\,[M_1^+] + K_2\,\gamma_\pm{}^2\,[M_2^+]} \qquad (3)$$

Most importantly, Scheme 1 and equation (2), [and then also Scheme 2 and equation (3)], are not limited to the template effect of alkali metal ions in the formation of crown ethers, but are expected to hold in a number of circumstances[3] (catalysis by cyclodextrins, rate retardation due to ion pairing, and so on). In these cases the competition between added species can help the kinetic analysis. Moreover in some cases a complexation causing inhibition can actually be the starting point. For instance, under preparative conditions, some anionic nucleophiles are used as the salt most easily generated *in situ* and a rate increase seems likely to be profitably carried out by adding cations which are less effective inhibitors than the initial counter ion.

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References

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2 L. Mandolini and B. Masci, *J. Am. Chem. Soc.*, 1984, **106**, 168 and 3706.
3 For a recent review on complex formation and chemical reactivity, see K. A. Connors, 'Binding Constants,' Wiley Interscience, New York, 1987, ch. 6.

[‡] The values for Li^+ ion, used in equation (3), were as follows: $K = 1040\ M^{-1}$; $k_{ip}/k_i < 0.01 \simeq 0$.

[§] If, on the other hand, effects on rates were present, the K values for association with the Me_4N^+ ion could be obtained by rearranging equation (3).