Associations of alkali and alkaline earth metal ions with cyclic transition states having crown-ether-like structure

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Abstract - The template effect of alkali and alkaline earth metal ions on the formation of crown ethers is believed to arise from the ability of the metal ion to organize the open chain reactant in a conformation favourable to ring closure. The template effect is conveniently discussed in terms of relative ligation abilities of reactants and transition states for ring closure. It is shown that the latter are well-behaved macrocyclic ligands, closely conforming to the ion-in-the-hole model.

INTRODUCTION

The study of associations between alkali and alkaline earth metal ions with polyether ligands is a well developed subject of interdisciplinary nature (ref. 1 and 2). Perhaps the most interesting feature is the well established concept of the fit between the cation and macrocyclic ligand cavity size, which leads to remarkable selectivities in cation associations.

It is well known that a large number of chemical phenomena are deeply and selectively influenced by coordinative interactions with alkali and alkaline earth metal ions (ref. 3). Among these, the findings that certain cations may strongly and specifically facilitate the formation of crown ethers have attracted our attention as remarkable examples of homogeneous catalysis by metal ions. It is the purpose of this lecture to review our quantitative work in the field. The systems chosen for our investigations are phenolic substrates (ArOH) having an ortho polyether side-chain bearing an α-bromo leaving group, which under the influence of base undergo cyclisation to the corresponding benzo-3x-crown-x ethers (B3xCx).

Our earliest published work in this field involved an examination of the effect of alkali (Li, Na, K) and alkaline earth (Sr, Ba) metal ions on the rate of formation of B1806 in alkaline water solution (ref. 4). Significant rate enhancements were observed with Sr++, Ba++, K⁺, and Na⁺, but not with Li⁺. Although limitations of varying nature prevented a complete analysis of the kinetic data, it was nevertheless clear that the template effect is a kinetically detectable phenomenon. Moreover, the suggestion was strong that under the conditions of the kinetic experiments a simple distribution scheme was operating, i.e., a scheme which involves a pre-equilibrium with 1:1 stoichiometry between ArO⁻ and the metal ion and two parallel reaction paths. This was fully confirmed by subsequent works in MeOH and in 99% Me₂SO solution, in which more extensive investigations of reaction (1) could be carried out.
The influence of metal ions on the rate of the investigated reactions could be quantitatively accounted for in terms of classical kinetics (Scheme 1) by the hypothesis that the overall reaction rate $v$ is given by independent contributions from the free anion $\text{ArO}^-$ and the ion pair $\text{ArOM}^+$, according to eq. (2). Equation (2) is equivalent to eq. (3), where $K_{\text{ArO}^-}$ is the equilibrium constant for association defined by eq. (4), and $k_{\text{obs}} = \frac{v}{[\text{ArO}^-] + [\text{ArOM}^+]}$ is time-independent provided $[\text{M}^+]$ does not suffer from major variations in a given run. If $k_i$ can be directly measured and a suitable expression for the activity coefficient $\gamma$ is available, eq. (3) shows that the measured $k_{\text{obs}}$ values are related to the concentration of metal ion through an equation with two unknown parameters, $k_{\text{ip}}$ and $K_{\text{ArO}^-}$. These are the relevant quantities which determine the magnitude of the template effect and its dependence upon cation concentration.

According to the transition state theory, eq. (3) is equivalent to eq. (5), in which $K_T$, given by eq. (6), has the meaning of the equilibrium constant for conversion of the transition state $T$ that does not contain $M^+$ into one that contains $M^+$, i.e., the ion pairing association constant of the transition state (Scheme 2). According to eq. (6) catalysis ($k_{\text{ip}} > k_i$) or inhibition ($k_{\text{ip}} < k_i$) occurs if the transition state binds cations more strongly ($K_T > K_{\text{ArO}^-}$) or less strongly ($K_T < K_{\text{ArO}^-}$) than the reactant. Thus, the problem of the influence of the metal ion on the magnitude of the template effect resolves itself into questions of the response to the metal ion of the relative ligation abilities of reactant and transition state.
Associations of alkali metal ions with cyclic transition states

TEMPLATE EFFECT IN MeOH SOLUTION

Cyclisation of ArO⁻, x = 6 to B18C6 has been found to be strongly accelerated by alkali and alkaline earth bromides in MeOH solution. Direct measurement of the specific rates of reaction of the free ion and ion pairs was possible, thus providing for the first time a quantitative determination of the template effect on the formation of a macrocyclic ligand (ref. 5). At 25°C the ratio k_ip/k_i is 60.7 for Na⁺, 199 for K⁺, 48.7 for Rb⁺, 17.1 for Cs⁺, 51.6 for Ca⁺⁺, 1190 for Sr⁺⁺, and 334 for Ba⁺⁺ (ref. 6). In the case of Li⁺, no significant effect on the cyclisation rate was observed.

In a qualitative description of the phenomenon, the template effect is believed to arise from a greater proximity of chain ends in the metal ion associated reactant than in the unassociated one. Superimposed to the proximity effect there is an adverse chemical effect due to reduction of the inherent nucleophilicity of the nucleophilic end of ArO⁻ upon cation pairing (ref. 5).

In order to provide a sound basis for a more quantitative analysis of the template effect, we have obtained from equilibrium measurements (ref. 7) log K data for associations of the metal ions with the three polyether ligands involved in the reaction, namely, ArOH, ArO⁻, and B18C6 (Scheme 3). These are all sexadentate oxygen ligands, but belong to different structural types. Both ArOH and ArO⁻ are open chained, but a negative charge is present on the latter. Coulombic interaction of the negative charge with the positive charge(s) of the cations is expected to provide an additional driving force for association. Similarly, B18C6 is predicted to bind cations more strongly that its acyclic counterpart ArOH, in view of well established properties of multidentate ligands (macrocyclic effect, see ref. 1 and 8). The log K data plotted in Fig. 1, are consistent with expectations and provide a quantitative evaluation of the negative charge effect and of the macrocyclic effect. The stabilising effect of the negative charge amounts to 1 order of magnitude with the singly charged cations, but increases to 4—5 powers of ten with the doubly charged ones. The 18-membered macrocycle binds cations 2 to 3 orders of magnitude more strongly that its acyclic counterpart.

Scheme 3

![Scheme 3](image)

Distribution scheme involving fully coordinated structures.
Let us now consider the ligation properties of the transition state $T^\#$. The log $K_{T^\#}$ values, calculated by means of eq. (6) from the known $k/k_1$ and $K_{T^\#}$ values, are plotted in Fig. 1. One first notes that the transition state $T^\#$ is the best ligand out of the four species $\text{ArOH}$, $\text{ArO}^-$, $T^\#$, and $\text{B}18\text{C}6$ for all of the given metal ions. This is clearly consistent with a fully coordinated structure for the cation-paired transition state, as shown in Scheme 4. It is remarkable that the effect of the variation of cation on the stability of the $T^\#$ pairs roughly parallels the effect of the variation of cation on the stability of the $\text{B}18\text{C}6$·$\text{M}^{2+}$ pairs. Furthermore, cation interactions with $T^\#$ are stronger than with $\text{B}18\text{C}6$ because the former is negatively charged. We note, however, that the stabilizing effect of the negative charge tends to be stronger with the open chain ligands than with the cyclic ones. This is written as eq. (7), in which $P$ is 0.62±0.06 for $\text{K}^+$, $\text{Rb}^+$, $\text{Cs}^+$, $\text{Ca}^{2+}$, and $\text{Sr}^{2+}$, it is 0.25 for $\text{Na}^+$ and negligibly small for $\text{Sr}^{2+}$. If $\text{B}18\text{C}6$ and $\text{ArOH}$ properly mimic hypothetical neutral ligands having the same structure and geometry of $T^\#$ and $\text{ArO}^-$, respectively, the quantity $P$ is easily interpreted as due to the loss of cation-anion interaction on going from initial to transition state because of dispersal of the negative charge of the latter on a three-atom-system. Equation (7) may be rewritten as eq. (8), which shows that the template effect can be viewed as a manifestation of the macrocyclic effect due to the fact that $T^\#$ is cyclic whereas $\text{ArO}^-$ is open.

$$\log(K_{\text{ArO}^-}/K_{\text{ArOH}}) = \log(K_{T^\#}/K_{\text{B}18\text{C}6}) + P$$

(7)

$$\log(k_{iP}/k_i) = \log(K_{\text{B}18\text{C}6}/K_{\text{ArOH}}) - P$$

(8)
Fig. 2. Effect of tetraethylammonium and alkali metal bromides on the rate of the B18C6 forming reaction in 99% Me₂SO at 25°C. The horizontal line represents log k. (Reproduced with permission from ref. 9).

Fig. 3. Effect of tetraethylammonium and alkali metal bromides on the rate of the B18C6 forming reaction in 99% Me₂SO at 25°C. (Reproduced with permission from ref. 7).

chained, allowance being made for the dispersal of the negative charge on going from ArO⁻ to T⁻. A plot of log(k₁/k₁) against log(K₁B18C6/K₁ArOH) is shown in Fig. 2. The full line with unit slope and zero intercept represents the extent of catalysis for hypothetical templated reactions in which the sole effect of the metal ion is to gather the reactive ends together. Thus, within the precision of the extrathermodynamic analysis on which eq.(8) is based, the macrocyclic effect K₁B18C6/K₁ArOH provides an estimate for the proximity effect. Figure 2 shows that, apart from some deviant values, the experimental data fall below the full line by a factor of about 4, which provides a measure for the nucleophilicity decrease of the aryloxide end of ArO⁻ upon cation pairing.

**TEMPLATE EFFECT IN 99% Me₂SO SOLUTION**

The crown-ether forming reactions are faster by about 4 orders of magnitude in the nearly aprotic 99% Me₂SO than in the protic MeOH. In the former, cyclisations proceed at rates convenient for extensive kinetic measurements. Fig. 3 shows the effect of added tetraethylammonium and alkali metal bromides on the rate of cyclisation of 1.5x10⁻⁴ M ArO⁻Me₄N⁺ to B18C6 in 99% Me₂SO at 25°C (ref. 9). The close adherence of the reactions to the mechanism of Scheme 1 (or Scheme 2) is shown by the full lines calculated by means of eq.3 (or eq.5). Whereas the rate of formation of B18C6 is depressed by Li⁺(k₁/k₁<0.01) the effect of the other alkali cations is rate enhancing, the catalytic effect k₁/k₁ being 100 with K⁺, 43 with Rb⁺, 19 with Cs⁺, and 6.1 with Na⁺.

Interestingly, the K₁ArO⁻ values were obtained in this case directly from the kinetics. Independent Ar⁻ equilibrium measurements gave a K₁ArO⁻ value for association with K⁺ coincident with that derived from the kinetics within experimental errors (ref. 9).
Considerable insight into the transition state structure is provided by comparison of the log K values for the associations of the metal ions with reactant, transition state, and reaction product (Fig. 4). Again we note that the transition state binds the alkali metal ions much more strongly than either the open chain reactant or the reaction product. Whereas ArO exhibits poor selectivity among cations, associations with both TÉ and B18C6 are markedly cation dependent and exhibit similarly structured patterns. These findings reinforce the conclusions that the geometry of TÉ closely resembles that of B18C6 and that fully coordinated structures are involved in the cation-paired transition states.

It is unfortunate that the KArOH values are not available in 99% Me₂SO, since we found no evidence for association with ArOH in this medium. However, if one makes the admittedly rough assumption that the magnitude of the macrocyclic effect $K_{B18C6}/K_{ArOH}$ does not vary in going from MeOH to 99% Me₂SO, on the basis of the known values in the former solvent the KArOH values in 99% Me₂SO are estimated to be nearly cation independent and in the neighborhood of 1 M⁻¹. Therefore within the limits of the above approximation eq.(8) reduces to the form of eq.(9), which is consistent with the free energy relationship shown in Fig. 5 for the B18C6 case. The negative values of the intercept (P= - 0.90) is highly significant, since it indicates a substantial decrease of nucleophilicity due to cation pairing, although the absolute value cannot be taken too seriously.

It was possible to provide an independent and more reliable estimate of the nucleophilicity decrease upon cation pairing. This was done by reference to the intermolecular alkylation of $\text{O-C}_6\text{H}_4(\text{OCH}_2\text{CH}_2)_4\text{OCH}_3$ with butyl bromide.
under the same conditions. It was found that the rate of this model reaction was indeed depressed by all alkali cations, the $k_{ip}/k_i$ value being 0.07 with K$^+$, Rb$^+$, and Cs$^+$, 0.035 with Na$^+$, and less than 0.01 with Li$^+$. These values permitted the rate-enhancing factors due to proximity alone to be evaluated by correcting the observed catalytic factors for the nucleophilicity decrease, as shown in eq. (10), in which intra and inter refer to the B18C6 forming reaction and to the intermolecular model reaction, respectively.

\[
\text{proximity effect} = \frac{(k_{ip}/k_i)_{\text{intra}}}{(k_{ip}/k_i)_{\text{inter}}}
\]

Introduction of the appropriate $k_{ip}/k_i$ values into eq. (10) yields values of $10^{2.2}$ for Na$^+$, $10^{3.2}$ for K$^+$, $10^{2.8}$ for Rb$^+$, and $10^{2.4}$ for Cs$^+$.

**Template effect and ring size**

Since associations between alkali metal ions and crown ethers are known to be highly dependent upon the ring size of the crown ether (ref. 2), changes in the chain length $x$ of the precursor ArO are predicted to exhibit a large variety of patterns, depending on the cation–substrate pair. An extensive study of the effect of alkali metal ions on the rate of formation of B$_{3x}$Cx ethers with $x = 4, 5, 7, 10,$ and 16 has been carried out in 99% Me$_2$SO (ref. 10) as an extension of that previously reported for the formation of B18C6. The rate data are plotted in Fig. 6, which indeed shows that each metal ion gives rise to a differently structured profile which is highly dependent on the size of the ring to be formed. Whenever possible, log $K_{B_{3x}Cx}$ data in 99% Me$_2$SO have been obtained (Fig. 7). Comparison with Fig. 6 indicates that there is a close similarity between structure effects on rates and structure effects on associations with the crown ether products. This is well shown by a plot of $\log(k_{ip}/k_i)$ vs. $\log K_{B_{3x}Cx}$ for all cation–substrate pairs for which data are available (Fig. 5). According to the simple model
which assigns to the M⁺-paired transition states the geometries of the corresponding M⁺-crown ether complexes, all the points in the plot of Fig. 5 should lie on the same line. This is clearly not the case, but an unmistakable trend is present, showing that a metal ion which associates strongly with a crown ether is also a good catalyst for the formation of that crown ether, and that the magnitude of the template effect is basically related to those factors which govern the strength of association with the reaction product.

REFERENCES