

by adding Br₂ to 3,5-dimethylstyrene, followed by dehydrobromination. The colorless liquids were separated by preparative GC. **17**: $\delta(\text{CCl}_4)$ 2.3 (s, 6 H), 5.62 (d, 1 H, $J = 1$ Hz), 5.98 (d, 1 H, $J = 1$ Hz), 6.98 (s, 1 H), 7.1 (s, 2 H); MS M^+ , m/z 212/210 (35%), 131 (100). **18**: $\delta(\text{CCl}_4)$ 2.3 (s, 6 H), 6.63 (d, 1 H, $J = 14$ Hz), 6.84 (s, 3 H), 6.98 (d, 1 H, $J = 14$ Hz); MS M^+ , m/z 212/210 (40%), 131 (100).

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Template Effects. 3.¹ The Quantitative Determination of the Catalytic Effects of Alkali and Alkaline Earth Cations in the Formation of Benzo-18-crown-6 in Methanol Solution

Gianfranco Ercolani, Luigi Mandolini,* and Bernardo Masci*

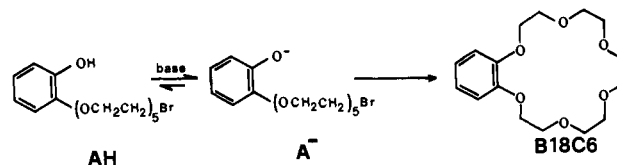
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Abstract: Cyclization of the conjugate base of *o*-hydroxyphenyl 3,6,9,12-tetraoxa-14-bromotetradecyl ether to benzo-18-crown-6 in methanol solution has been found to be strongly and specifically accelerated by added alkali and alkaline earth bromides. The observed accelerations range from 13.2 for Cs⁺ to a spectacular 540 for Sr²⁺. The reported data refer to conditions in which the rate is independent of cation concentration, thus providing for the first time a quantitative determination of the template effect of added cations in the formation of a macrocyclic polydentate ligand. The different catalytic abilities as observed for the different cations are tentatively discussed in terms of a combination between proximity of the reactive ends in the bifunctional precursor complexed around the metal ion, and chemical factors arising from the extent of interaction of the cation with the nucleophilic oxide ion.

The study of interactions between alkali and alkaline earth cations with a variety of ligands has developed rapidly in the past decade as a subject of interdisciplinary nature.² It is now increasingly appreciated that coordinative interactions of alkali and alkaline earth cations may have a deep influence on a variety of chemical phenomena, among which is the course of many organic reactions. Remarkable examples of these effects may be found in the findings that alkali and alkaline earth cations may strongly facilitate the ease of formation of crown ethers.^{1,3} The high yields obtained without high dilution led several authors to suggest that the metal ion acts as a template, i.e., organizes the crown's precursor around the metal ion itself in a conformation similar to that of the crown formed. Kinetic evidence of the template effect of some alkali and alkaline earth cations has been reported by us⁴ for the base-promoted cyclization of *o*-hydroxyphenyl 3,6,9,12-tetraoxa-14-bromotetradecyl ether (AH) to benzo-18-crown-6 (B18C6) in water solution (Scheme I). The observed effect was explained as due to the greater reactivity of A⁻M^{z+} as compared to that of free A⁻. The reactivities of the associated forms could not be determined because of the failure to observe saturation kinetics even at the highest attainable cation concentrations, which indicated that conversion of A⁻ to A⁻M^{z+} was far from being complete. Thus, the assessment of the catalytic effectiveness of the different cations was not possible in water solution. We have now obtained definite evidence that this goal

Scheme I



can be achieved working in methanol solution, where interactions of cations with polyether ligands are known to be much stronger than in water.⁵ The results of such an investigation are reported herein.

Results and Discussion

The kinetics of cyclization of AH were carried out spectrophotometrically⁴ on very dilute substrate ($\sim 3 \times 10^{-4}$ M) in order to suppress polymerization. MeOEt₄N was added as the base to generate the anion A⁻. Because of the low acidity of AH, excess MeOEt₄N was required to promote extensive dissociation. For instance, in the presence of 0.08 M base the degree of dissociation was 0.88 (Table I). The amount of base to obtain a given extent of dissociation was significantly lowered by the presence of 0.05–0.1 M sodium, potassium, and cesium bromides. A significantly greater acidity-enhancing effect was brought out by added 0.001–0.003 M calcium, strontium, and barium bromides, which permitted AH to be quantitatively neutralized by an equivalent amount of base. This observation is indicative of strong interactions of the A⁻M^{z+} type with the alkali cations and, even more so, with the alkaline earth cations.⁶

(1) Part 2: Mandolini, L.; Masci, B. *Synth. Commun.* **1979**, *9*, 851.

(2) Poonia, N. S.; Bajaj, A. V. *Chem. Rev.* **1979**, *79*, 389.

(3) Gokel, G. W.; Durst, H. D. *Synthesis* **1976**, 168, and references cited there. For more recent examples see ref 1 and Ping-Lin, K.; Miki, M.; Okahara, M. *J. Chem. Soc., Chem. Commun.* **1978**, 504; van Keulen, B. J.; Kellogg, R. M.; Piepers, O. *Ibid.* **1979**, 285.

(4) Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1977**, *99*, 7709.

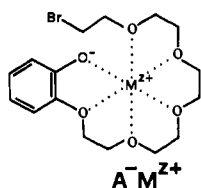
(5) Pedersen, C. J.; Frensdorff, H. K. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 16.

Table I. Effect of Added Alkali and Alkaline Earth Cations on the Cyclization Rate of A⁻ to B18C6 in MeOH at 50.0 °C

[MeOEt ₄ N], M	added cation (M ^a)	<i>k</i> _{obsd} , s ⁻¹	α ^b	γ, % ^c	<i>k</i> , s ⁻¹	<i>k</i> _{rel}
0.080	none	1.22 × 10 ⁻⁵	0.88	63	8.73 × 10 ⁻⁶	1.00
0.080	none	1.22 × 10 ⁻⁵	0.88	66	8.98 × 10 ⁻⁶	
0.025	Na ⁺ (0.080)	3.74 × 10 ⁻⁴	0.91	93	3.83 × 10 ⁻⁴	43.5
0.025	Na ⁺ (0.142)	3.74 × 10 ⁻⁴	0.91	95	3.87 × 10 ⁻⁴	
0.020	K ⁺ (0.066)	1.08 × 10 ⁻³	0.91	91	1.08 × 10 ⁻³	124
0.020	K ⁺ (0.132)	1.12 × 10 ⁻³	0.91	90.5	1.11 × 10 ⁻³	
0.020	Rb ⁺ (0.047)	3.39 × 10 ⁻⁴	0.92	90	3.32 × 10 ⁻⁴	37.2
0.020	Rb ⁺ (0.094)	3.28 × 10 ⁻⁴	0.93	92	3.26 × 10 ⁻⁴	
0.020	Cs ⁺ (0.045)	1.22 × 10 ⁻⁴	0.93	91	1.19 × 10 ⁻⁴	13.2
0.020	Cs ⁺ (0.070)	1.20 × 10 ⁻⁴	0.94	90	1.15 × 10 ⁻⁴	
0.0012	Ca ²⁺ (0.0016)	3.25 × 10 ⁻⁴	1.00	90	2.93 × 10 ⁻⁴	33.2
0.0012	Ca ²⁺ (0.0036)	3.23 × 10 ⁻⁴	1.00	91	2.95 × 10 ⁻⁴	
0.0012	Sr ²⁺ (0.0015)	5.08 × 10 ⁻³	1.00	93	4.72 × 10 ⁻³	540
0.0012	Sr ²⁺ (0.0030)	5.20 × 10 ⁻³	1.00	93	4.85 × 10 ⁻³	
0.0012	Ba ²⁺ (0.0014)	1.71 × 10 ⁻³	1.00	92.5	1.58 × 10 ⁻³	175
0.0012	Ba ²⁺ (0.0029)	1.65 × 10 ⁻³	1.00	92	1.52 × 10 ⁻³	

^a As the bromide salt. ^b Dissociation degree of AH as based on a model compound.⁶ ^c Yield of B18C6 as estimated spectrophotometrically.

It is worth noting that the apparent acidity of guaiacol was not appreciably affected by the presence of any of the alkali cations, and that the alkaline earth cations caused but a small acidity-enhancing effect. It seems therefore reasonable to conclude that electrostatic interaction between ions of opposite charge is not the sole driving force for the formation of A⁻M^{z+}, and that coordinative interaction of the metal with the ether oxygens also has a significant role, as schematically depicted.



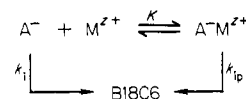
The progress of the reaction was followed by monitoring at 296 nm the disappearance of the phenoxide ion absorption, which in all cases was found to strictly exhibit first-order decay up to high conversions. The results of the kinetic experiments are listed in Table I. In all cases the infinity spectra showed residual phenoxide absorption, most likely due to concurrent methanolysis of the CH₂Br end of the bifunctional reactant. Yields reported in Table I were calculated assuming that the fraction of phenoxide consumed corresponds to quantitative formation of B18C6. The reliability of the above estimates was checked by VPC analysis in one typical case, as shown in the Experimental Section. Rate constants of cyclization of A⁻ to B18C6 (*k*) were obtained from the observed first-order rate constants (*k*_{obsd}) by means of the equation $k = k_{\text{obsd}}\gamma/100\alpha$, where γ is the yield of B18C6 and α is the dissociation degree of AH in the reaction medium. The latter was calculated from the zero time spectra, assuming that the extinction coefficient of A⁻ is equal to that of the anionic form of a model compound.⁶ The correction was significant only for the reaction carried out in the presence of the tetraalkylammonium ion as the sole counterion, and was relatively unimportant in all the other cases.

Table I shows that the reaction was strongly and specifically accelerated by added alkali⁷ (Na, K, Rb, and Cs) and alkaline earth (Ca, Sr, and Ba) bromides, the observed rate enhancements ranging from 13.2 for Cs⁺ to 540 for Sr²⁺. The results may be

(6) Work in progress has shown that the equilibrium constants of interaction of the anion derived from the model compound *o*-HOC₆H₄-(OCH₂CH₂)₄OCH₃ with the alkali (Na, K, Rb, and Cs) cations are in the order of 10³ M⁻¹, and those with the alkaline earth (Ca, Sr, and Ba) cations are some three powers of ten higher. Also the parent neutral compound complexes the given cations, but the association constants are lower than those of the anionic form. No acidity-enhancing effect was brought out by Li⁺ and Et₄N⁺ cations at concentrations up to 0.1 M.

(7) Neither the cyclization rate nor the apparent acidity of AH was affected to a significant extent by added 0.1 M Li⁺ ion (see ref 6).

Scheme II



easily rationalized in terms of a simple distribution model (Scheme II), in which independent contributions to the overall reaction rate result from the associated and unassociated forms of the crown's precursor. Because any significant association of A⁻ with Et₄N⁺ cation can be ruled out,⁶ *k*_i may be identified with the specific rate of reaction in the presence of Et₄N⁺ as the sole counterion. On the other hand, the estimated approximate values of the association constants *K* for the alkali and alkaline earth cations⁶ are such that at the salt concentrations used in the kinetic runs the fraction of free A⁻ in equilibrium with A⁻M^{z+} should be very small. Hence, the specific rate for reaction in the presence of a given alkali and alkaline earth cation should practically coincide with the *k*_{ip} value of the associated species A⁻M^{z+}. This is consistent with the observation that the rate is independent of salt concentration, as shown in Table I. First-order rate constants relative to that of the tetraalkylammonium ion (*k*_{rel} values, Table I) may be therefore interpreted as the *k*_{ip}/*k*_i ratios. Such quantities provide a measure of the catalytic efficiencies of the given cations, which, referring to saturation kinetics, are independent of the varying association constants *K*.

Attempts at interpreting the nature of the phenomenon must take into account a combination of chemical and proximity effects. A major contribution to the former effect is expected to arise from a reduced nucleophilicity of the oxide ion due to interaction with the metal cation, but the magnitude of the effect cannot, at present, be estimated.⁸ As to the latter effect, one must consider that a significant portion of the free energy barrier to be overcome in a macrocyclization process is a substantial loss of the conformational entropy due to internal rotations around the single bonds. For instance, it has been reported⁹ that in the formation of catechol polymethylene ethers by intramolecular nucleophilic substitution the entropy of activation for the formation of the 16-membered ring is more negative than that for the formation of the 6-membered one by as large a quantity as 26 eu. There is no doubt that part of the conformational entropy is lost upon complexation around the metal cation and, therefore, that the associated species can reach the transition state with a lesser entropic penalty as compared to the unassociated one. In this respect, the metal ion

(8) It has been recently reported that alkali metal-ethoxide pairs in EtOH solution show no appreciable reactivity in the S_N2 reaction with ethyl iodide (Jones, P.; Harrison, R.; Wynne-Jones, L. *J. Chem. Soc., Perkin Trans. 2* 1979, 1679).

(9) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* 1977, 99, 6308.

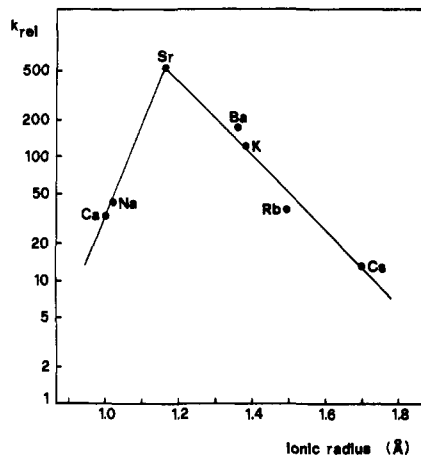


Figure 1. Template effect of alkali and alkaline earth cations in the formation of B18C6 in methanol solution.

template behaves much in the same way as an enzyme analogue¹⁰ since part of the entropy barrier to be overcome for the reaction to occur is compensated by means of favorable interactions with the chain donor sites. The situation may be stated in simple form by saying that the proximity of the chain ends is greater in the complexed chain than in the uncomplexed one. The rate-enhancing factors due to proximity cannot be estimated with confidence.¹¹ What can be said is that the proximity effect must be large enough so as to more than offset the adverse chemical factors for any of the given cations.

Given that the template effect is the net result of two unknown and presumably large factors acting in opposite directions, no simple explanation of the different catalytic abilities observed for the different cations seems at present available. We may simply note that in each series the maximum catalytic effect occurs at an intermediate term of the series, K^+ for the alkali and Sr^{2+} for the alkaline earth cations. This is very likely related to the size of the cation¹² and to the problem of the fit of the latter into the cavity of the cyclic transition state which, apart from the presence of a negative charge, should resemble in geometry the reaction product, B18C6. Cyclic multidentate macromolecules with certain ring sizes are known to be much better ligands than their acyclic counterparts,² a phenomenon which is often referred to as the macrocyclic effect. Thus, the observed template effect of added

(10) Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 84.

(11) The assumption of a very rigid conformational situation for A^-M^{2+} leads to an estimate for the proximity factor. If the oxygen-metal bonds were very strong bonds holding the chain in a fixed position, then cyclization of A^-M^{2+} might be visualized as that of a short chain leading to a common ring. The entropy advantage over the cyclization of a long, freely rotating chain may then be estimated as about 26 eu from the entropy of activation of 6- vs. 16-membered ring formation.⁹ This would lead to a value of $\exp(26/R)$ or $10^{5.7}$ as an upper limit for the magnitude of the proximity effect.

(12) Lamb, J. D.; Izatt, R. M.; Swain, C. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 475.

alkali and alkaline earth cations may be viewed as a sort of macrocyclic effect, i.e., the one in which the macrocyclic ligand is a transition state.

Figure 1 shows that the catalytic factors observed for the different cations are undeniably related to the cation radii from crystallographic data¹³ by means of an inverted V-type relationship, with a maximum value of 540 for the Sr^{2+} cation. What seems rather surprising is that a single correlation appears to hold in spite of the basically different nature of singly charged vs. doubly charged cations, and of the presumably different weights of the M^{2+} -anion interactions in the M^{2+} -ligand interactions. Since a better understanding of the coordinative principles of M^{2+} with the different multidentate ligands (open chain vs. cyclic and electrically neutral vs. negatively charged) would provide a basis for the interpretation of the template effect, we are now determining⁶ the stability constants of interaction of M^{2+} with AH, A^- , and B18C6. The results of such an investigation will be published in due course.

Experimental Section

Materials. *o*-Hydroxyphenyl 3,6,9,12-tetraoxa-14-bromotetradecyl ether (AH) was available from a previous investigation.⁴ Tetraethylammonium hydroxide, 25% in methanol, was from Fluka. MeOH (Erba RP) was fractionally distilled over magnesium methoxide. NaBr (Erba RP) and KBr (Erba RP) were crystallized from water and dried under vacuum at 200 °C. RbBr (Merck Suprapur), CsBr (Merck Suprapur), and LiBr (Riedel De Haën) were dried under vacuum at 200 °C. $CaBr_2 \cdot 2H_2O$ (Ciba purissimum), $SrBr_2 \cdot 2H_2O$ (Erba RP), and $BaBr_2 \cdot 2H_2O$ (Riedel De Haën) were used as such, since attempted drying was unsuccessful. The bromide content of the methanolic solutions was checked by argentometric titration.

Rate measurements were carried out on a Beckman DB-GT spectrophotometer fitted with a cell holder thermostated at 50.0 ± 0.1 °C. The kinetic runs were started by rapidly adding with a microsyringe a calculated amount of base to a methanolic solution of the reactant and added salt contained in a 10-mm all-quartz cuvette.

Product Analysis. A 5.2×10^{-4} M solution of AH in methanol was treated with excess of base ($MeOEt_4N$, 6.4×10^{-2} M) and heated at 50 °C over 2 weeks to ensure complete reaction. From the absorbance of the solution at the beginning and at the end of reaction a 68% conversion to B18C6 was calculated. VPC analysis of the reaction mixture was carried out as follows. After the addition of a calculated amount of 2,3-benzo-1,4-dioxacyclotetraicosane⁹ as the internal standard, the mixture was neutralized with dilute hydrobromic acid. The solvent was distilled off and the residue was treated with ether to dissolve any organic material. After concentration to a small volume, the solution was analyzed on a "Erba Mod. G1" instrument, fitted with a 2% SE30 plus 0.4% FFAP on Chromosorb W 60-80 column, operating at 200-230 °C. The chromatogram consisted of only two peaks, i.e., the ones of B18C6 and of the standard. By comparison of relative peak areas with those obtained from standard solutions, the yield of B18C6 was 70%, in good agreement with the spectrophotometric estimate.

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(13) Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr., Sect. B* **1969**, *25*, 925.