Tetrahedron Vol 45, No 7, pp 2213 to 2222, 1989
Printed in Great Britain

0040-4020/89 $3.00+.00

TEMPLATE EFFECTS. 8.[1] THE TEMPLATE EFFECT OF TWO ALKALI METAL IONS IN THE FORMATION OF CROWN ETHERS

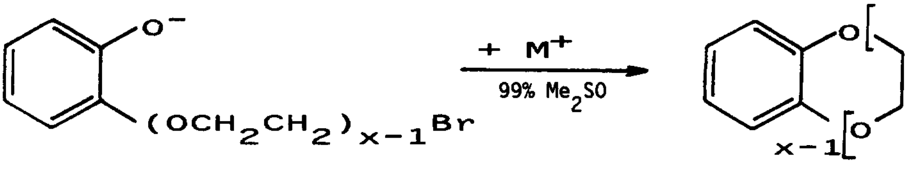
Chiara Antonini Vitali and Bernardo Masci*

Dipartimento di Chimica and Centro C.N.R. di Studio sui Meccanismi di Reazione,
Università di Roma "La Sapienza", P.le Aldo Moro 2, 00185 Roma, Italy.

(*Received in UK* 26 *January* 1989)

Abstract - In the search for evidence supporting a template effect of two alkali metal ions in the formation of coronands, the formation of 21- to 30-membered benzo-crown ethers has been investigated kinetically at varying $KClO_4$ concentrations in a mixed solvent (dioxane/99% Me_2SO 2:1). Besides the clean-cut appearance of two catalytic waves in the formation of benzo[30]crown-10, evidence is reported for the involvment of a second K^+ ion also in the formation of benzo[27]crown-9. Other evidence has been obtained from the analysis of the yields in preparative conditions of unsubstituted crown ethers from polyethylene glycols and p-toluenesulfonyl chloride in the presence of NaOH, KOH, and CsOH. The overall picture is apparently consistent with the operation of a template effect of two cations which depends on spatial fit requirements and favours the formation of [27]crown-9 and [30]crown-10 in the presence of K^+, and of [24]crown-8 in the presence of Na^+. Caution should be used in the interpretation of the results in the lack of a direct kinetic support.

Much evidence supports the operation of template effects in the formation of coronands:[2] in particular, we carried out a thorough kinetic investigation to rationalize and quantitatively assess the template effect of alkali metal ions in the formation of benzo-crown ethers (B3xCx, with x = 4, 5, 6, 7, 10, and 16) according to eq 1.[3,4] All the observed profiles of rate versus cation concentration could be accounted for by the simultaneous reaction of the free substrate and of the substrate associated with the cation, apart from the case of the formation of B30C10 in the presence of K^+ which was quite anomalous.[4] In order to explain the kinetic behaviour observed in the latter case, we suggested that a second K^+ ion should enter the cavity of the cyclic transition state, and developed the quantitative



1)

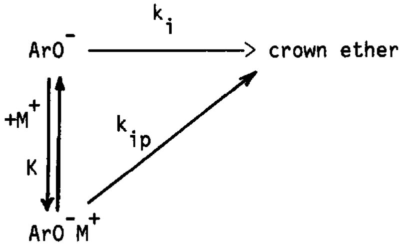
1   2

treatment of the phenomenon. No other direct evidence has been reported so far for the operation of such a peculiar type of catalysis. Actually, the fact that the yields of coronands in preparative work are still good for the formation of very large rings, suggests that some catalytic route other than 1:1 complexation can work,[1,5] but purely preparative investigations can hardly lead to safe mechanistic conclusions in this field, owing to the complexity of the reacting systems and to the difficulty of carrying out precise determinations in a systematic manner.

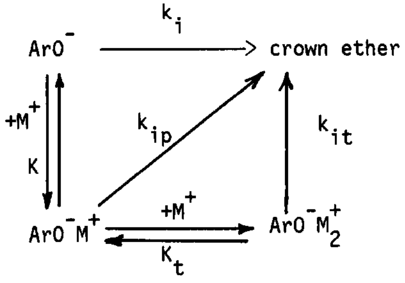
We report in this paper on the role of the catalysis by two cations in the formation of coronands with up to 30 members in the ring: we carried out both kinetic investigations and a systematic analysis of the yields in preparative conditions.

RESULTS AND DISCUSSION

In order to ascertain the scope of the phenomenon previously observed in the formation of B30C10,[4] the phenolic precursor of compound 1, x = 9 was synthesized and the effect of added $KClO_4$ on the rate of its conversion to 2, x = 9 was determined in the same conditions and with the same techniques as reported for previous investigations:[3,4] $KClO_4$ and KBr showed the same behaviour in this kind of reactions.[3] No anomalous template effect is apparent: relative rates fit eq 2 which is derived from the simple Scheme I and yield a sigmoid shaped profile in the log-log plot (Fig. 1) similar to those obtained for the smaller homologues. The analysis of the data with the usual procedure gave the following parameters: $k_{ip} = 1.15 \times 10^{-2}\ s^{-1}$, $K = 382\ \underline{M}^{-1}$. The profile relative to B21C7 is reported



SCHEME I



SCHEME II

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

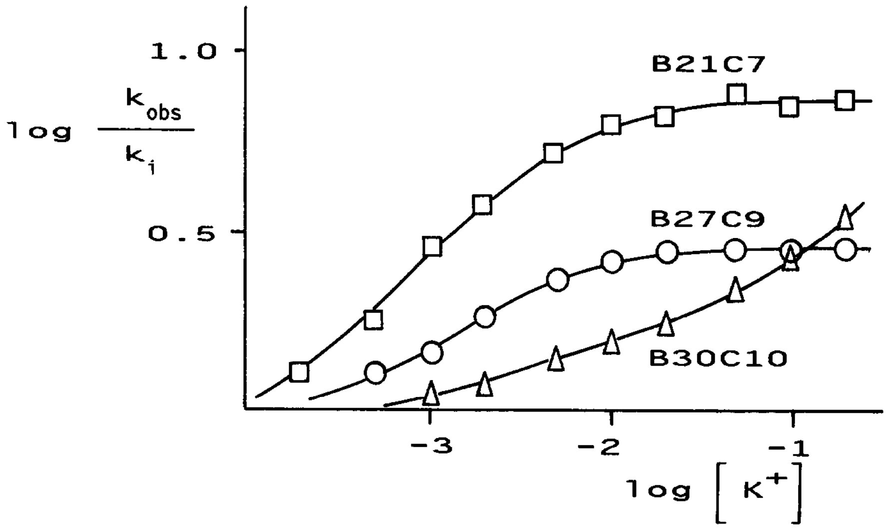


Fig. 1. Effect of added potassium salts on the rate of formation of compounds 2, x = 7, 9, and 10 in 99% Me_2SO at 25.0 °C.

for comparison in Fig. 1, together with the anomalous profile that had been obtained for the formation of B30C10:[4] the reaction paths which can be thought to be relevant when a second metal ion enters the transition state are reported in Scheme II.

Although 99% Me_2SO has several merits as a solvent for a strictly quantitative kinetic investigation,[3] it binds strongly alkali metal ions and the association constants for their complexes with polyoxygenated ligands are fairly low. We then resorted to change the solvent in order to allow weak association phenomena to emerge. The solvent obtained by mixing 2 volumes of dioxane and 1 volume of 99% Me_2SO was employed: it still allowed $KClO_4$ to be dissolved up to 0.2 M concentration and the techniques well-tested in 99% Me_2SO to be used.[3,4] The results for the formation of B30C10 in the mixed solvent are reported in Fig.2. From the comparison with the results obtained in 99% Me_2SO[4] two features emerge: i) the catalytic action is significantly higher in the whole concentration range when dioxane is added; ii) the two catalytic waves, corresponding to the template action of one and two K^+ ions, which were hardly distinguishable in 99% Me_2SO, are neatly separated when dioxane is added. At low salt concentrations the added K^+ ion is largely associated with the substrate (2.0×10^{-4} M) and the obtained profile should be unreliable: the dashed line simply indicates the expected continuation of the profile of the rate versus free ion concentration.

It was hoped that the solvent dioxane/99% Me_2SO 2:1 could show a second catalytic wave

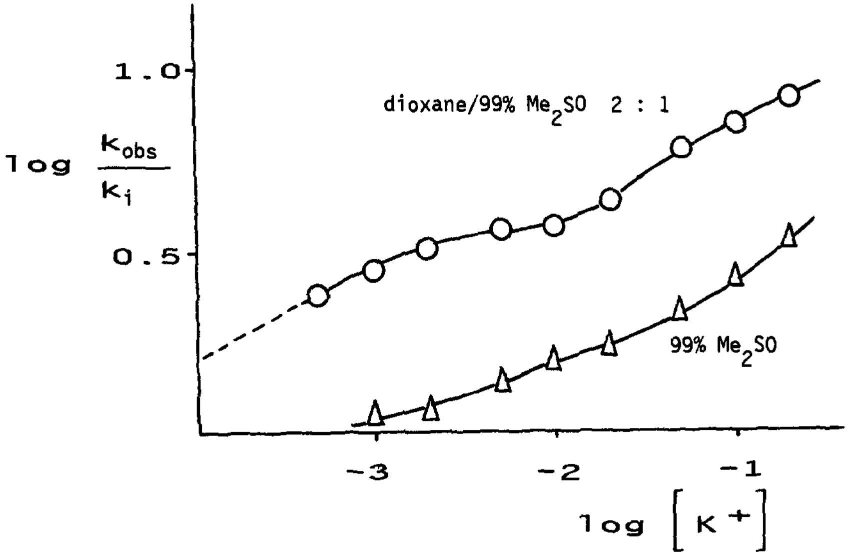


Fig. 2. Effect of potassium salts on the rate of formation of B30C10 in 99% Me_2SO and in the mixed solvent dioxane/99% Me_2SO 2:1, at 25.0 °C.

also for the formation of B27C9: at first sight the results are disappointing (Fig. 3) as a large plateau extending from 1×10^{-3} up to 0.2 M $KClO_4$ concentration is observed instead of the further increase in the rates observed in the case of B30C10. However, in spite of the plateau, some special effect is most likely taking place, namely, in the formation of the smaller crown ethers, for which the presence of two cations in the cavity of the cyclic transition state is unlikely, a rate decrease at high $KClO_4$ concentration is observed. The profiles for the formation of B21C7 and B24C8 are shown for comparison. Downward drifts at high salt concentration have been reported to occur in the reaction of ion paired nucleophiles even in 99% Me_2SO,[3] but are more easily detected in solvents with lower dielectric constant: they have been attributed to the formation of ion triplets or higher aggregates less reactive than the ion pair.[6] In a check experiment we determined the rate of formation of B21C7, B27C9, and B30C10 at 2×10^{-3} M $KClO_4$ concentration in the presence and in the absence of 0.2 M $Me_4N^+ClO_4^-$. The same rates were observed in the two cases,[7] so that, both the downward drifts in the formation of the smaller rings and the rate increase in the formation of B30C10, that were observed at high $KClO_4$ concentration, can be attributed to the formation of cationic triplets rather than to triplets of the type $ArO^-M^+ClO_4^-$.

A possible qualitative description could be as follows: at high salt concentration a

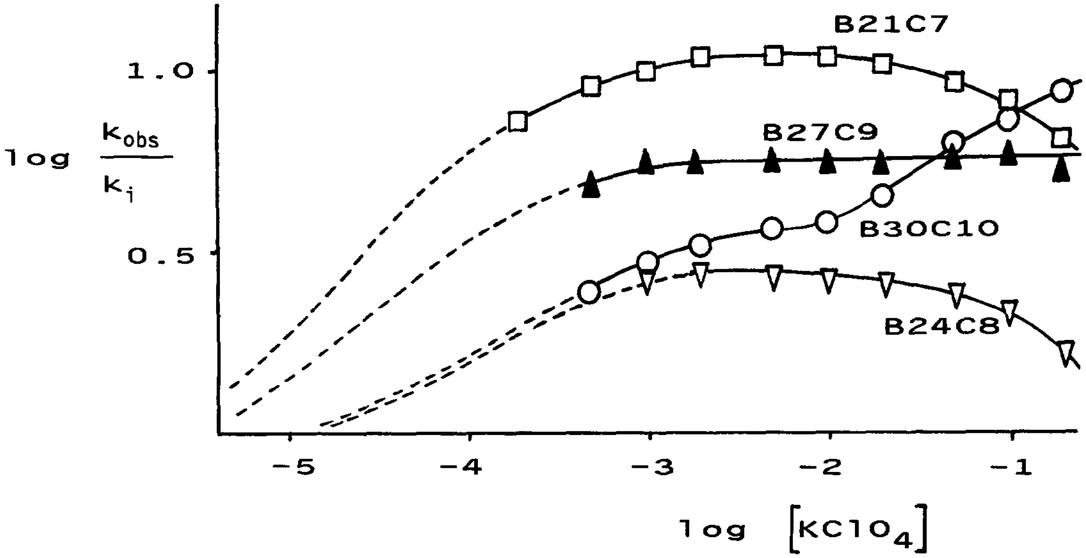
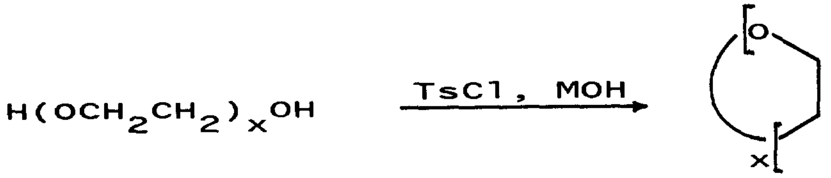


Fig. 3. Effect of $KClO_4$ on the rate of formation of compounds 2, x = 7, 8, 9, and 10 in the mixed solvent dioxane/99% Me_2SO 2:1 at 25.0 °C.

cationic ion triplet $K^+Nu^-K^+$ can form; it is less reactive than the ion pair for most substrates, including compounds 1, x < 9; if the nucleophile is compound 1, x = 10 the ion triplet is more reactive than the ion pair and a further increase in reactivity is observed on increasing the salt concentration; if the nucleophile is compound 1, x = 9 the ion triplet[8] has about the same reactivity as the ion pair and the large plateau is observed. Clearly a quantitative analysis of the profiles in Fig. 3 is difficult in the lack of information on the extent of dissociation of $KClO_4$ and on the activity coefficients of ionic species. Whatever the cause of the downward drifts can be, the behaviour for 1, x = 9 is clearly intermediate between that for 1, x = 10 and that for 1, x < 9, and the factors producing the "normal" behaviour (downward drift) can be thought to be superposed to those causing the second catalytic wave (upward drift) for the higher homologue.

Analysis of the yields in preparative conditions. A further step towards conditions which should favour association can be made by the use of pure dioxane as a solvent. Although such a medium seems to be unsuitable for a strictly quantitative kinetic investigation , it is a typical solvent for crown ethers formation in preparative conditions. We carried out the analysis of the yields of the " monomeric" unsubstituted crown ethers produced according to equation 3, with x varying from 4 to 10 in the presence of heterogeneous sodium, potassium, and cesium hydroxide. Concentration, addition times, temperature and operating conditions were strictly the same in all cases: the procedures and the glc analytical technique were as reported in the preceding paper. As fairly small differences in the yields can be significant for the present purposes, a number of check experiments have been carried out: i) no significant loss of material occurs in the extraction of the crown ethers from the crude products with CH_2Cl_2; ii) quite similar yields were obtained either by reacting equimolar mixtures of hepta-, octa-, nona-, and deca-ethylene glycol, or by reacting the various polyethylene glycols separately; iii) the water content of the alkali metal hydroxide was found to influence the yields: higher yields were obtained in small scale experiments by adding small quantities of water, but we chose to work with no water added because the results were more reproducible.[9]



3)

The results are plotted in Fig. 4, those for K$^+$ are taken from the preceding paper (upper transversal line in Table 1). The yields of a given crown ether change with the alkali metal hydroxide employed and different orders for the three cations are observed for the various sizes of the formed ring. At least in part these orders can be influenced in our multistep heterogeneous reactions by the state of the surface of the powdered alkali metal hydroxide and by the water content of the base. On the other hand the yields of the various crown ethers with a given alkali metal hydroxide can be expected to give straightforward information, as they have been obtained in strictly the same conditions. For the Cs$^+$ template, yields increase regularly from 12C4 to 21C7, and then regularly decrease. This is the typical profile expected for the operation of the template effect by the large Cs$^+$ ion .[4] The principle of geometrical complementarity is strictly obeyed, namely the more different the size of the cavity in the formed product from that of the metal ion template, the lower the yield. The profile for potassium ion is a more complex one, namely the yields increase regularly up to 18C6 , which is known to be very well fitted to K$^+$ ion: then they decrease, as expected, for 21C7 and 24C8, but increase again

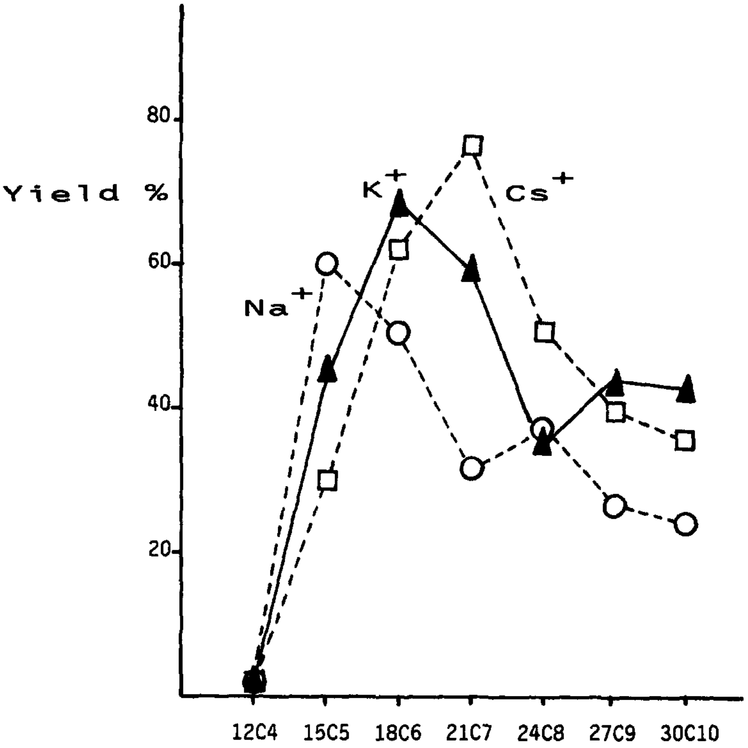


Fig. 4. Yields of unsubstituted crown ethers according to eq 3, in the presence of NaOH (○) , KOH (▲), and CsOH (☐).

for 27C9 and 30C10. The profile for Na$^+$ ion is also a complex one: as expected the highest yield is observed for 15C5, but after a decrease, a second maximum is observed for 24C8.

In our previous work on template effects the catalytic efficiencies of alkali metal ions were found to parallel the strength of interaction with the reaction product[4] and this interaction is well known to be affected by spatial fit requirements.[10] It seems reasonable that these relations hold also for the formation of large crown ethers, although we actually lack information on the structure and the stability constants of the complexes of the crown ethers formed in the present conditions. Clearly the situation for a good spatial fit must be different from a nearly planar arrangement of oxygen atoms encircling one cation: two possible arrangements can in principle be suggested, coiled structures with 1:1 stoichiometry and binuclear complexes.[11] Both molecular models of the highly mobile large macrocycles and analysis of the yields in preparative conditions can hardly discriminate between these two possibilities, but kinetic investigation can do it easily because the observed picture should conform either to Scheme I or to Scheme II: downward drifts in our actual systems complicate the kinetic picture, but do not prevent the fundamental features from being displayed.

Deviations from the trends expected for the simple 1:1 template effect of an alkali metal ion have been observed both in the kinetic measurements and in the reactions carried out in preparative conditions: these special effects conform to a consistent pattern in spite of the complexity of the preparative system and the differences in the solvent and in the structure of the crown ethers. In both cases the formation of 27- and 30-membered crown ethers in the presence of K^+ is easier than expected. The kinetic measurements indicate that at high salt concentration a new mechanism of catalysis occurs, which involves the participation of two cations, and with the support of the kinetic measurements also the high yields of 27C9 and 30C10 can be interpreted as due to the inclusion of two K^+ ions in the cavity of the transition state: by the same token the inclusion of two Na^+ ions should account for the increased yield of 24C8 with respect to 21C7, but in the lack of a direct kinetic support also a favourable coiled conformation around one Na^+ ion can be held responsible for the latter increase in the yields. That "conformational" factors are to be reckoned with, can also be seen in Fig. 3. Actually , even in the absence of 1:2 complexation, K^+ favours the formation of B27C9 (and possibly also of B30C10) more than that of B24C8, namely the order of the k_{obs}/k_i values at 2×10^{-3} $\underline{M}$ $KClO_4$ concentration is [12] B21C7 > B27C9 > B30C10 > B24C8. The template effect of two cations makes this advantage stronger and stronger on increasing $KClO_4$ concentration.

As to the structure of binuclear complexes in the transition state, the two cations in the same cyclic structure are expected to repel each other: they can possibly reduce this unfavourable interaction by slight shifting to opposite faces of the ring, moreover the fraction of negative charge on nucleophilic oxygen should reduce the repulsion with respect to that expected in the complex with the final product. Evidence supporting the formation of binuclear complexes of crown ethers with alkali metal ions in solution are quite scanty,[13,14] but a few x-ray structures are available for complexes in the solid state.[15] Although the usual caution must be used in extending structural features observed in the crystal to the solution state, and although no systematic trend is apparent from the available x-ray data, the following points can be valuable for our discussion: i) binuclear complexes of

24- to 30-membered crown ethers with two Na^+ or two K^+ ions can actually form; ii) the distance between the two cations can be only a bit larger than the sum of their radii; iii) two oxygen atoms of the ring usually bridge the pair of cations.

A criterion of optimum spatial fit apparently accounts for the observed trends in the template effect of two cations as well as in that of one cation. With the support of the crystallographic information on complexes of crown ethers and of molecular models, the following tentative conclusion can be drawn from our results: two Cs^+ ions are too large even for the cavity of a 30-membered cyclic transition state, but two K^+ ions fit well this cavity and can still be accommodated within a 27-membered cyclic transition state; two Na^+ ions on the other hand possibly fit the cavity of the smaller 24-membered cyclic transition state better than the larger ones.

In summary, although some of the experimental evidence supporting the template effect of two cations cannot be regarded as unambiguous, the effect is not merely a suggestive hypothesis but a well established reaction path. We think it remarkable that the concerted action of two non covalently bonded catalytic entities has been ascertained to occur and that chains with a large number of rotors can be organized in solution by such a simple catalytic system. We plan to get further evidence on this topic, in particular on the template effect of two different alkali metal ions.

EXPERIMENTAL

Most techniques and apparatuses were as previously reported.[1,3,4] NaOH (Erba) and CsOH (Aldrich) were powdered in a mortar and used in the same molar ratios as previously described for KOH:[1] their water content after powdering was not tested.

Compounds **1**, x = 8 and 9 were synthesized by extending previously reported procedures[16] and gave the expected ^1H NMR spectra: their purity was also checked to be >95% by glc. Dioxane was distilled from Na and mixed with 99% Me_2SO: the small acidity content of the solvent was neutralized with $Me_4N^+OH^-$ (added as a 2.8×10^{-2} <u>M</u> solution in Me_2SO), then compounds **1** and the stoichiometric amount of the base were added. In dioxane/ 99% Me_2SO 2:1 the following k_1 values (s^{-1}) were observed: **1**, x = 7: 3.89×10^{-3} ; **1**, x = 8: 2.77×10^{-3} ; **1**, x = 9: 1.95×10^{-3}; **1**, x = 10: 1.91×10^{-3}. In 99% Me_2SO k_1 for **1**, x = 9 was 4.00×10^{-3} s^{-1}.

Acknowledgment - Financial support by the Ministero della Pubblica Istruzione is acknowledged. Thanks are due to Prof. L. Mandolini for critically reading the manuscript.

REFERENCES AND NOTES

1) For part 7 see preceding paper.
2) Gokel, G. W.; Korzeniowski, S. H. "*Macrocyclic Polyether Syntheses*"; Springer-Verlag: Berlin, **1982**.
3) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1983**, *105*, 555-563.
4) Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1984**, *106*, 168-174. See also *ibid*., p. 3706.
5) Chenevert, R.; D'Astous, L. *J. Heterocycl. Chem*., **1986**, *23*, 1785-1787.
6) Crescenzi, M.; Galli, C.: Mandolini, L. *J. Chem. Soc. Chem. Commun*., **1986**, 551-553.
7) The rate in the presence of the sole 0.2 *M* Me_4NClO_4 was found to be the same as in the absence of any added salt.
8) Actually, the structure of the ion triplet is a very peculiar one in this case, as the two cations are inside the cavity, but the same kinetic law must hold for the various arrangements with the same composition.
9) Some of the yields can be compared with those reported in apparently similar conditions (Kuo, P. L.; Kawamura, N.; Miki, M.; Okahara, M. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 1689-1693.): in general the values reported in Fig. 4 are lower.
10) Lamb. J. D.; Izatt, R. M.; Swain, C.S.; Christensen, J. J. *J. Am. Chem. Soc*. **1980**, *102*, 475-479.
11) Poonia. N. S. in "*Progress in Macrocyclic Chemistry*", Izatt, R. M.; Christensen, J. J., Eds., Wiley, New York, Vol. 1, **1981**, p. 115-155.
12) The k_{obs}/k_i values at this concentration are apparently quite close to the k_{ip}/k_i values.
13) Shamsipur. M.; Popov, A. I. *J. Am. Chem. Soc*. **1979**, *101*, 4051-4055.
14) Stöver, H. D. H.; Maurice, L. J.; Delville, A.; Detellier, C. *Polyhedron* **1985**, *4*, 1091-1094.
15) (a) Mercer, M.; Truter, M. R. *J. Chem. Soc. Dalton Trans*., **1973**, 2469-2473.
    (b) Hughes, D. L. *J. Chem. Soc. Dalton Trans*. **1975**, 2374-2378.
    (c) Owen. J. D.; Truter, M. R. *J. Chem. Soc. Dalton Trans*., **1979**, 1831-1835.
16) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc*. **1981**, *103*, 4142-4145.