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DIAZA-CROWN ETHERS. VIII. ALKALI METAL ION PROMOTED FORMATION OF 4,7,13,16,21,24-HEXAOXA-1,10-DIAZABICYCLO-[8,8,8]-HEXACOSANE

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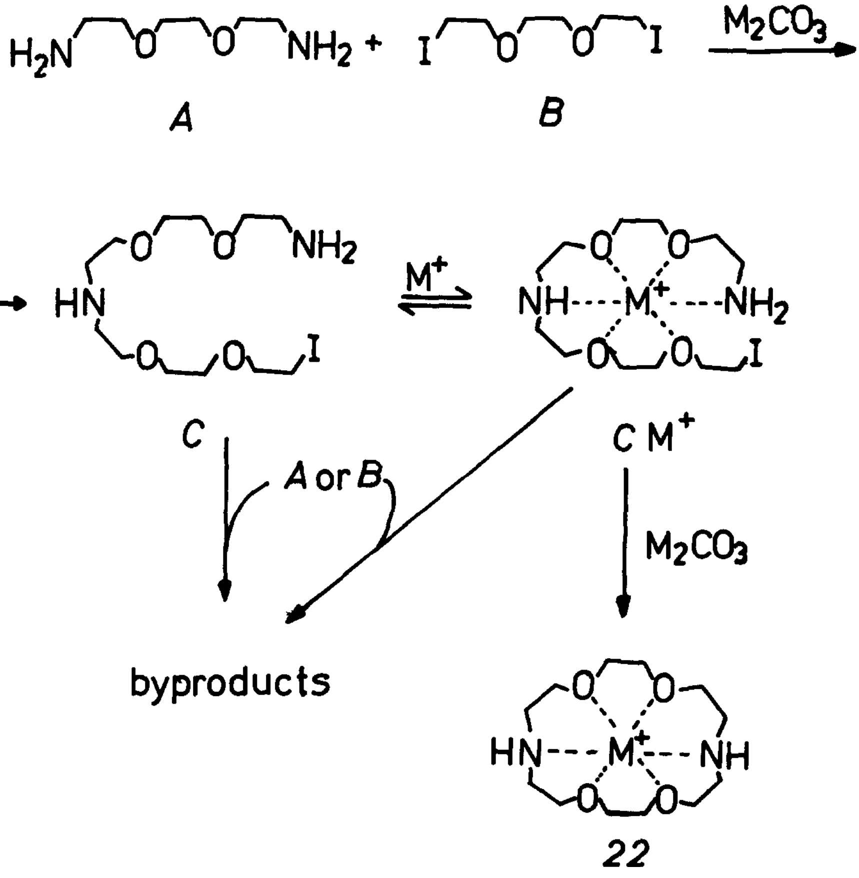
A direct synthesis of a bicyclic diazaoligoether without using high dilution technique, but instead based upon the template effect, is reported, and the mechanism is briefly discussed.

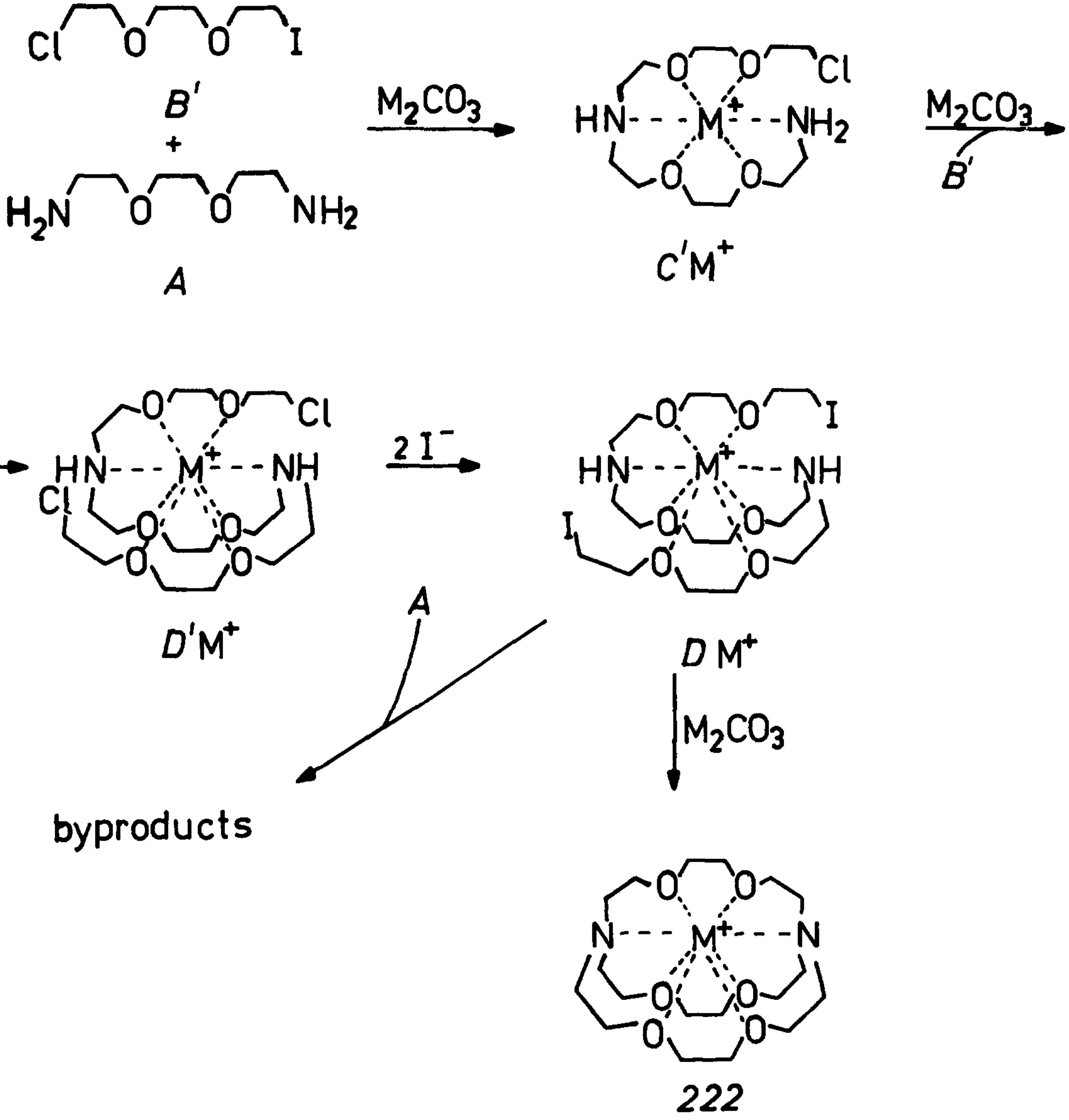
Macrobicyclic diazaoligoethers (cryptands) have previously been prepared by Lehn et al. using high dilution techniques.[1] We have recently developed a



Scheme 1

method of synthesizing diaza-crown ethers like 22 in the normal concentration range using alkali metal ions as promotors.[2] The mechanism for the ring formation is shown in Scheme 1.[3]

In acetonitrile the ring precursor intermediate $\underline{C}M^+$ is completely associated if M = Na or K, and thus the competition between the ring-closure reaction of $\underline{C}M^+$ and/or its side-reactions with A and B determines the yield of 22. If $\underline{B}$



Scheme 2

would be replaced by $Cl(C_2H_4O)_2C_2H_4I$ (B')[4] with the much less reactive chloro substituent as one of the leaving groups, the ring-closure reaction of C'M$^+$ would be inhibited in favour of the formation of an intermediate D'M$^+$ as is shown in Scheme 2.

This complex would be a suitable precursor for the cryptate 222 M$^+$, if its conformation is favourable and the leaving groups are reactive enough. Since I$^-$ is formed in the reaction, substitution of Cl for I takes place, which gives a complex (DM$^+$) of much better reactivity than D'M$^+$.

In order to test this idea, a solution of A (20 mmol) and B' (40 mmol) in 50 ml of acetonitrile over finely ground sodium carbonate (200 mmol) was refluxed for 3 days and then filtered. The filtrate was analyzed by GLC, and 22 was not detected. This indicates that a major part of the complex C'M has reacted to D'M$^+$ and not with I$^-$ to CM$^+$, which then to a large extent would react further to 22.[3]

The filtrate was evaporated and the residue was treated with acetone, upon which the product precipitated as white crystals, which were filtered off. Again the filtrate was evaporated, and the procedure was repeated until no more crystals were obtained. This gave 2.2 g (21 %) of a compound, which analyzed as the NaI complex of 222.[5,6] By passing an acidic aqueous solution of this complex through first a cation and then an anion exchange resin, the cryptand 222 was obtained with physical data that agreed with those in the literature.[1]

When potassium carbonate was used instead of sodium carbonate, no 22 could be detected by GLC. No crystals were obtained by the treatment with acetone, and the NMR spectrum in $CDCl_3$ showed no signals at δ 2.58, where the CH_2-N triplet of the KI complex of 222 should appear.[6] This shows that no significant amount of the cryptate was formed in the reaction.

The yield of bicyclic product is thus dependent on the metal ion. Since no monocyclic product is found, the most probable reaction pathway to byproducts originates from the intermediate DM$^+$. Analogously to what has previously been found for the formation of 22,[3] this complex probably is completely associated in acetonitrile. Thus the conformation of this complex determines whether the ring-closure reaction can compete with the formation of byproducts.[7,8]

This method might be useful for the synthesis of other bicyclic diazaoligoethers. Unfortunately it is not possible to predict the best solvent or the best promoting ion for the reaction.

References and Notes

1. B. Dietrich, J. M. Lehn, J. P. Sauvage and J. Blanzat, *Tetrahedron* **29**, 1629 (1973).
2. S. Kulstad and L. Å. Malmsten, *Acta Chem. Scand*. **B 33**, 469 (1979).
3. S. Kulstad and L. Å. Malmsten, *To be published*.
4. *B'* was prepared by refluxing a mixture of *bis-(2-chloroethyl)ether* (100 g) and sodium iodide (200 g) in 400 ml of acetone for 5 h. The mixture was filtered and evaporated, and the residue was washed with an aqueous solution of sodium thiosulfate and then distilled. This gave *B'*, yield 44 g (30 %), bp 89-90 °C/0.8 mm Hg. NMR ($CDCl_3$): δ 3.8, 3.67 (10 H, m + s), 3.2 (2 H, m).
5. Elemental analyses agreed within ± 0.6 % units with the calculated values. NMR ($CDCl_3$): δ 3.67, 3.62 (24 H, s + t), 2.69 (12 H, t).
6. B. Dietrich, J. M. Lehn and J. P. Sauvage, *Tetrahedron Lett*. 2885 (1969).
7. The cryptand *222* is probably not formed directly from *DM*$^+$ but *via* a monocyclic intermediate not shown in the simplified Scheme 2.
8. The importance of the *gauche* conformation about the C-C bond has recently been discussed (J.F. Stoddart, *Chem. Soc. Rev*. **8**, 85 (1979)). Considering this and assuming the same conformation of the $(C_2H_4O)_2C_2H_4$ units that has been observed in crystallographic investigations of cryptates, we constructed a molecular model of the intermediate *D*. This shows that the larger K^+ may hinder the ring-closure reaction, while the smaller Na^+ does not.

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