Synthesis and Cation Complexing of *N*,*N*′-Bridged Bis-(1,4,7-Trioxa-10-azacyclododecanes)

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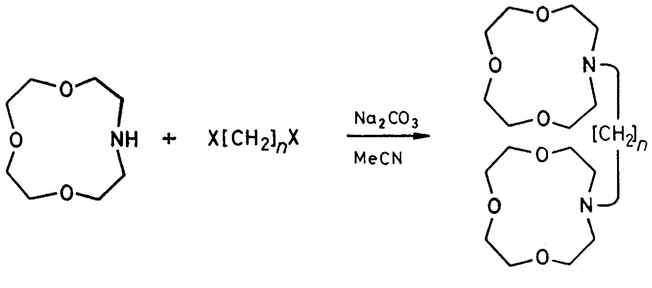
Summary Two molecules of monoaza-12-crown-4 can be linked through nitrogen in one step by direct double alkylation; the resulting bis-crown aminoethers give intramolecular alkali cation sandwich complexes which are particularly strong when the bridge is $-CH_2CH_2-$ and the cation is sodium.

A VARIETY of organic macrocyclic ligands have been reported consisting of two crown-ether or -aminoether moieties covalently linked together by a single chain, between either carbon[1–5] or nitrogen bridgeheads.[2,6] However, these bridges were all rather long and often structurally complicated, and hardly the correct choice if it is desired to bring the two crowns together without conformational problems to form an intramolecular sandwich with a single cation.

The geometric details of crystal structures of 12-crown-4 sandwich complexes with NaCl[7] and NaOH[8] suggest very strongly that the ideal bridge between such crowns should link, not carbon atoms, but donor atoms, and should consist of just two CH_2 groups. Thereby, the 1,4-relationship between donor atoms, known to be by far the most favourable for alkali and alkaline earth cation complexing in monocyclic crown ethers and aminoethers, would also be extended in the third dimension in bis-crown-aminoethers. Furthermore, the ease of nitrogen inversion obviates stereochemical complications at the bridgeheads.



(1) (2) $n = 2$; X = p-$MeC_6H_4SO_3$ (4) $n = 2$

(3) $n = 3$; X = I (5) $n = 3$

As starting material for the synthesis of such bridged ligands the hitherto unknown 1,4,7-trioxa-10-azacyclododecane (**1**) was needed. We found[9] that the reaction of 1,11-di-iodo-3,6,9-trioxaundecane with primary amines in acetonitrile in the presence of dispersed Na_2CO_3 gives *N*-substituted 12-membered ring monoaza-crown ethers in good yields and as the only distillable or sublimable product. The unsubstituted macrocycle (**1**) was obtained by hydrogenolysis of the *N*-benzyl derivative on Pd–C (m.p. 60 °C, 85%). Reaction with oxalyl chloride in dichloromethane containing an excess of triethylamine, followed by $LiAlH_4$ reduction of the dicarboxamide in tetrahydrofuran, gave the bis-crown-aminoether (**4**) (overall yield 85%). More simply, reaction with ethylene bistoluene-*p*-sulphonate in acetonitrile in the presence of suspended Na_2CO_3 gave (**4**) directly as a crystalline 1 : 1 complex with sodium toluene-*p*-sulphonate. The free ligand was distilled from the complex as a viscous oil solidifying on storage at 0 °C (yield 84%). For comparison the bis-crown (**5**) was also prepared using 1,3-di-iodopropane. The free aminoether was extracted with $CHCl_3$ from an aqueous solution of its NaI complex and distilled as an oil (yield 84%).

The ligand (**4**) gave very stable complexes with alkali salts, in particular with sodium salts, which can be extracted quantitatively from water into chloroform. The complexation is most clearly demonstrated in the ^{13}C n.m.r. spectrum of an acetonitrile solution of (**4**) at room temperature on portionwise addition of the dry salt. Ligand exchange is slow on the n.m.r. time-scale for NaSCN, and lines for free and complexed ligand are seen separately. For $LiClO_4$ and KSCN the exchange is fast, but titration curves in methanol show breaks in both cases which are much sharper than with *N*-methyl-1,4,7-trioxa-10-azacyclododecane as a ligand,[9] and sharp enough to suggest[10] a complexation constant of 10^3 or higher. The stoicheiometry is in all cases strictly 1 : 1 (intramolecular sandwich) even for the Li cation.

The relative strengths of these complexes can be assessed from a study of the ligand exchange kinetics by dynamic ^{13}C n.m.r. spectroscopy using a ratio of ligand to salt of 2 : 1, and assuming that a high dissociation barrier parallels strong complexation, as found for cryptates.[11–13] For NaSCN the dissociation barriers in acetonitrile, methanol, and water were found to be > 18, *ca.* 17, and *ca.* 13 kcal/mol† respectively. For $LiClO_4$ and KSCN in acetonitrile the barrier is below 13 kcal/mol, suggesting that the free energy of formation for the NaSCN complex may be larger by > 4 kcal/mol.

From a study by dynamic ^1H n.m.r. spectroscopy of geminal proton site exchange within the NaSCN complex in CD_3CN a similar activation energy $\Delta G^{\ddagger}$ of 18—19 kcal/mol was obtained (T_c *ca.* 64 °C at 100 MHz), while this conformational exchange is fast at room temperature in the other complexes. Also on this basis we conclude that Na is complexed much more strongly than K and Li.

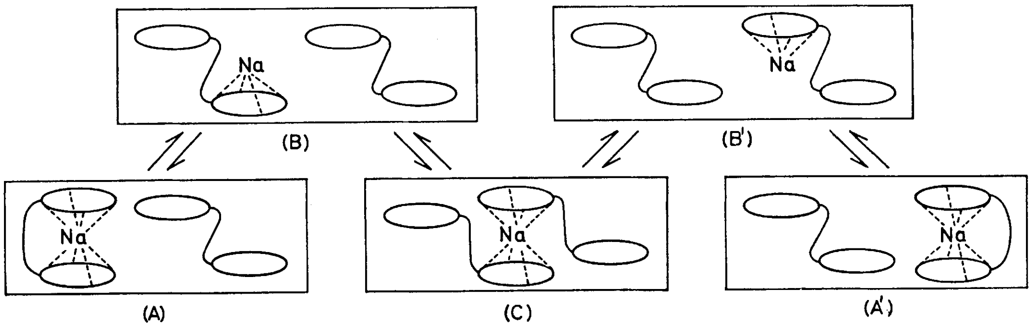


FIGURE. Proposed steps for exchange of the bis-crown ligand of the intramolecular sandwich complex of alkali cation with excess of free ligand.

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† 1 cal = 4·184 J.

We further conclude that both processes have most probably a common critical barrier,‡ and interpret this as the first step (A) $\rightleftharpoons$ (B) shown in the Figure, involving a detachment of one ring from the cation of the 1:1 intramolecular sandwich in (A). To effect geminal ring proton exchange, the detached ring of the half-complex in (B) can undergo the necessary conformational changes, including nitrogen inversion, over low barriers and revert to (A) over the same critical barrier, whereafter the same process is repeated with the other ring. To effect ligand exchange, a second molecule participates in forming a 2:1 intermolecular sandwich (C) (not populated), whereafter the process is reversed *via* (B′) to the exchanged situation (A′). Completion of the co-ordination sphere around sodium in (B) (and B′) with solvent molecules explains the observed higher exchange rates in methanol and water.

The ligand (**5**), although also a stronger complexer than *N*-methyl-1,4,7-trioxa-10-azacyclododecane for NaSCN, is much weaker than (**4**). Thus, at room temperature the 15 MHz ^{13}C n.m.r. spectrum of an acetonitrile solution of (**5**) and NaSCN (2:1) has one averaged set of lines, which splits into two sets only on cooling below 0 °C ($\Delta G^{\ddagger}$ *ca.* 13·5 kcal/mol).

Our results show not only that bridging the two monoazacrowns in itself increases the strength of sandwich complexation of alkali cations, but also that it is even more important that the bridge should contain just two methylene groups. In particular the optimal fit of the Na cation in the cavity of the ligand (**4**), as predicted from examination of a Corey–Pauling–Koltun model, appears to result in a cryptate-like selectivity.

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‡ This is in contrast with the sandwich complex of 12-crown-4 with NaSCN where high conformational mobility within the complex is observed.[14]

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