Cryptates: Control over Bivalent/Monovalent Cation Selectivity

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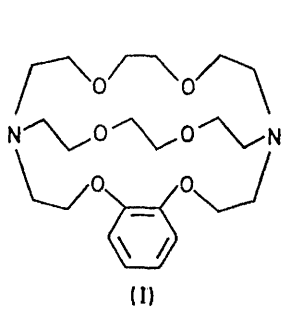
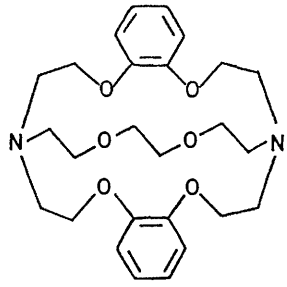
Summary Macrobicyclic ligands are described which demonstrate how the alkaline-earth/alkali cation complexation selectivity may be controlled in designing synthetic ligands.

SYNTHETIC macrocyclic[1] and macrobicyclic ligands[2] form more stable complexes with alkaline-earth cations than with alkali cations of about the same size (*e.g.*, Ba^{2+} and K^+, respectively). On the other hand, the natural macrocyclic antibiotics show opposite properties, discriminating in favour of K^+ as compared with Ba^{2+} (see ref. 3 and references therein). The control over alkaline-earth *versus* alkali cation complexation selectivity in synthetic ligands is important in at least two respects: the understanding of complexation selectivity and the design of cation selective ligands for specific applications. In particular, since the cation transport processes of potassium and sodium are of special interest because of their biological implications, it is important to understand how poisoning of a carrier by alkaline-earth cations may be avoided. We report here our studies on this problem.

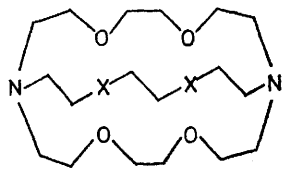
We measured the stability constants (log K_s) of the cryptate-type[4] inclusion complexes formed by the macrobicyclic ligands (I), (II), and (III) and by the macrocyclic ligand (V) (see Table). The properties of (IV) and of the natural macrolide antibiotic nonactin serve as reference values. Compounds (I)—(III) were synthesized by previously described methods.[4]



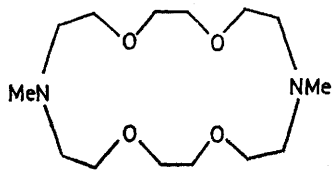
(I)



(II)



(III) X = CH_2
(IV) X = O



(V)

The M^{2+}/M^+ selectivity of macrocyclic and macrobicyclic ligands is sensitive to several ligand features (for a recent analysis of structural effects see ref. 3). We have made use of two controlling factors: the thickness s of the organic ligand layer separating the complexed cation from the

solvent and the number of binding sites built into the ligand. It is expected that increasing s will decrease the interaction of the complexed cation with a polar solvent (water, methanol) and thus destabilize the complex, the effect being much larger for bivalent than for monovalent cations.

The results show (Table), that addition of a first benzene ring to ligand (IV), as in (I) does not much affect the Ba^{2+}/K^+ selectivity, probably because solvent approach to one side of the bicyclic system remains unhindered. However, addition, because of their two charges, the complexes of alkaline-earth cations should be more destabilized than those of alkali cations. Indeed, (III) complexes K^+ much more strongly than Ba^{2+}, the Ba^{2+}/K^+ selectivity of (III) being even higher than in nonactin.[3] The selectivity change from (IV) to (III) amounts to more than a factor of 10^4.

Comparing the properties of (III) and (V), we note that the strong destabilization of the Ba^{2+} complex of (III) is due to its cryptate nature: the three bridges of the bicyclic

Stability constants for cryptate formation, log K_s[a]

Ligand	(I)[b]	(II)	(III)	(IV)	(V)	Nonactin[c]
Na^+	7·4	7·3	3·0	6·95	3·26	2·4
K^+	9·05	8·6	4·35	9·45	4·38	3·6
Ba^{2+}	11·05	8·5	<2·0	11·5	6·67	1·7
Ba^{2+}/K^+[d]	100	*ca.* 1	1/>200	110	200	1/80

[a] Values of log K_s for 95 : 5 methanol : water solutions determined by pH-metric titration. This solvent was chosen because of the very low solubility of (II) and (III) in water. [b] Values of log K_s in water: 4·0 (Na^+), 4·9 (K^+), 3·4 (Rb^+), 3·8 (Ca^{2+}), 6·9 (Sr^{2+}), 7·4 (Ba^{2+}). [c] Values in methanol; see ref. 3. [d] Selectivity K_s (Ba^{2+})/K_s (K^+).

the presence of two benzene rings as in (II) greatly reduces this ratio and the stabilities of the Ba^{2+} and K^+ cryptates become equal. The slight decrease in log K_s caused by the introduction of the benzene rings may be ascribed both to a decrease in oxygen basicity and in cavity size; this latter factor also explains the increase of the stability of the Na^+ cryptates.

On the other hand, ligands (III) and (IV) are expected to be about equally thick, shielding the cation from the environment to the same extent, but (III) contains two binding sites fewer than (IV). This explains why the stability of the cryptates of (III) is drastically reduced. In ligand shield the cation from the solvent much more efficiently than the macrocyclic ligand (V) where the approach of polar solvent molecules from the top and the bottom of the complex towards the cation is unhindered. Therefore in complexes with (V) the cations can complete their solvation shell using solvent molecules, thus yielding the same stability order $Ba^{2+} > K^+$ as with (IV).

Effects resembling those described here may occur when other macrobicyclic ligands[2,4] undergo similar structural modifications.

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[1] C. J. Pederson and H. K. Frensdorff, *Angew. Chem.*, 1972, **84**, 16.
[2] J. M. Lehn and J. P. Sauvage, *Chem. Comm.*, 1971, 440.
[3] W. E. Morf and W. Simon, *Helv. Chim. Acta*, 1971, **54**, 2683.
[4] B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Letters*, 1969, 2885, 2889.