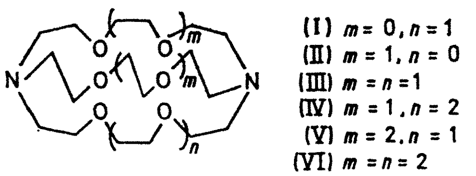
Cation and Cavity Selectivities of Alkali and Alkaline-earth "Cryptates"

By J. M. LEHN* and J. P. SAUVAGE

(*Institut de Chimie, 1 rue Blaise Pascal, Strasbourg-67, France*)

Summary The stability constants of alkali and alkaline-earth cryptates have been measured; they display strong cation and cavity selectivities.

SELECTIVE complexation of alkali and alkaline-earth cations by natural and by synthetic macrocyclic compounds has led to many biological and chemical studies.[1,2] The broad impact (from the theory of complexation to cation transport through membranes) of such studies makes the ability to control cationic selectivities *via* tactical structural changes in the complexing species of prime importance. Such a possibility is offered by macrocyclic polyethers[3] where modifying ring size is expected to alter the complexation selectivities.[2–4] Macrobicyclic substances should even be better suited, since changes in cavity size should drastically affect the relative stabilities of the complexes if the cations are included in the central molecular cavity. Such properties are displayed by the macroheterobicyclic systems (I)—(VI) which form strong inclusion complexes, the cryptates, with many metal cations.[5–7]



(I) $m = 0, n = 1$
(II) $m = 1, n = 0$
(III) $m = n = 1$
(IV) $m = 1, n = 2$
(V) $m = 2, n = 1$
(VI) $m = n = 2$

We describe here some results about cavity specific control of cationic selectivities *via* cryptate formation in a homogeneous series, (I)—(VI), prepared as described previously. The stability constants, K_s of the complexes formed in water between alkali or alkaline-earth cations and a ligand molecule according to equation (1),† have been obtained by the analysis of pH-metric titration curves[9] and, in some cases, with cation specific electrodes. The stabilities, $\log K_s$, are

$$[L]_{aq} + M^{n+},mH_2O \overset{K_s}{\rightleftharpoons} [L,M]^{n+}_{aq} + mH_2O \qquad (1)$$

listed in the Table.‡ In the cryptates the bicyclic system is probably in the *endo–endo* form [as found for complexes of (III)[10] by *X*-ray crystallography] since in this form all hetero-atoms may participate in complexation.

Stability constants for cryptate formation, log K_s[a]

Cation	Li+	Na+	K+	Rb+	Cs+	Mg2+	Ca2+	Sr2+	Ba2+
Ionic radius (Å)[b]	0·86	1·12	1·44	1·58	1·84	0·87	1·18	1·32	1·49
Co-ordination number[c] ..	4	6	8	8	10?	6	8	8	8
Bicyclic ligand (cavity size, in Å)[d]					$\log K_s$				
(I) (0·8)	4·30	2·80 2·55[e] 2·7[f]	<2·0 <1·0[g]	<2·0	<2·0	?[h]	2·80	<2·0	<2·0
(II) (1·15)	2·50	5·40 5·40[e] >9·0[f]	3·95 3·9[g]	2·55	<2·0	<2·0	6·95	7·35	6·30
(III) (1·4)	<2·0	3·90 3·70[e] >9·0[f]	5·40 >5·0[g]	4·35 4.8[g]	<2·0	<2·0	4·40	8·00	9·50
(IV) (1·8)	<2·0	<2·0 1·65[e] 4·80[f]	2·2 2·1[g]	2·05[g]	2·20 1·8[g]	<2·0	*ca.* 2·0	3·40	6·00
(V) (2·1)	<2·0	<2·0 2·80[f]	<2·0	⩽0·7[g]	<2·0	<2·0	<2·0	*ca.* 2·0	3·65
(VI) (2·4)	<2·0	<2·0	<2·0	⩽0·5[g]	<2·0	<2·0	<2·0	<2·0	?[h]

[a] Values of $\log K_s$ for water solutions (*ca.* 10^{-3}M in ligand) from pH-metric titration unless otherwise stated. The salts (2—10 10^{-3}M) were chlorides, but no halogen anion effect has been found. Supporting electrolyte (4—8 10^{-2}M): NMe_4Br for (I)—(III); LiCl for (IV—(VI). [b] M. F. C. Ladd, *Theor. Chim. Acta*, 1968, **12**, 333. [c] See ref. 1. [d] Estimated cavity size measured by the radius of the sphere which may be included without distorting the ligand, into the molecular cavity of space filling models of compounds (I)—(VI) in the *endo-endo* form. [e] Values obtained for water solutions using a selective sodium cation electrode; see Z. Stefanac and W. Simon, *Analyt. Letters*, 1967, **1**, 1. [f] Values obtained for methanol solutions using a selective sodium cation electrode. [g] Values obtained for water solutions using a selective monovalent cation electrode. [h] In these cases, the determination of K_s is complicated by other processes.

The following points follow from consideration of the data in the Table.

(i) The optimal stability for a given cation is very high, considering that the ligand is uncharged and that the values are for water solutions.

(ii) Along a row in the Table, ligands (I)—(III) display remarkable cation selectivity. The selectivities are much lower for (IV)—(VI).

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† Only the overall stabilities of the complexes are discussed here. Because of the possible existence of the macrocyclic ligands in *exo–exo*, *exo–endo*, and *endo–endo* forms[5,6,8] the mechanism of the complexation reaction may be very intricate. It will be discussed in detail in the full account of this work.

‡ The stabilities of the cryptates of some other cations (for instance Ag^+, Tl^+, Pb^{2+}) have also been determined; *e.g.* for (III): Ag^+ ($\log K_s = 9{\cdot}60$), Tl^+ (6·30) Pb^{2+}(12); for (II): Ag^+ (10·6).

(iii) Down a column in the Table, the data indicate high cavity selectivity. The peak stability for a given cation depends to a great extent on the nature of the ligand; *e.g.* among the alkali cations, it shifts from Li^+ to Na^+, to K^+ on going from (I) to (II), to (III).

(iv) Properties (i)—(iii) result to a great extent from the three-dimensional nature of the cation discrimination process in bicyclic compounds, as compared to the overall two-dimensional discrimination of monocyclic ligands (except in cases where the monocyclic system is wrapped around the cation).

(v) The data in the Table show that, especially for (I)—(III), there is a correspondence between approximate cavity size and cation radius. The success of the operational "cavity size" criterion for relative stabilities incorporates several contributions; among them one may count the radius-ratio effects of cation and ligand atom, van der Waals' attractions and repulsions, and conformational effects introduced by more or less important changes in ligand conformation. In addition to these energy contributions, there is probably also an important entropy effect on stabilities.§

(vi) Changing to organic solvents markedly increases the stabilities of the cryptates, as shown by the results for Na^+ in MeOH. Thus, complexes which are unstable in water may be obtained in other solvents [*e.g.*, the Cs^+ complex of (III) may be isolated from chloroform solutions].

(vii) The present data also point to the fact that within certain limits it should be possible to design "*sur mesure*" a bicyclic ligand for selectively complexing a given cation, by monitoring cavity size, number of ligand sites, and nature of the hetero-atoms.[11] Numerous applications in chemistry and biology are possible.[12]

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§ This seems to be confirmed by preliminary calorimetric measurements: (II) + Na^+: $\Delta H^\circ = -3{\cdot}2$ kcal mol^{-1}, $\Delta S^\circ = +14$ e.u.; (II) + Ca^{2+}: $\Delta H^\circ = -1{\cdot}7$ kcal mol^{-1} $\Delta S^\circ = +26$ e.u. It is necessary to separate entropy and enthalpy effects to discuss the quantitative data in more detail.

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