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THE EFFECTS OF SIZE AND DONOR ATOMS OF MACROCYCLIC POLYAMINES BINDING TO Mg^{2+} AND Ca^{2+}

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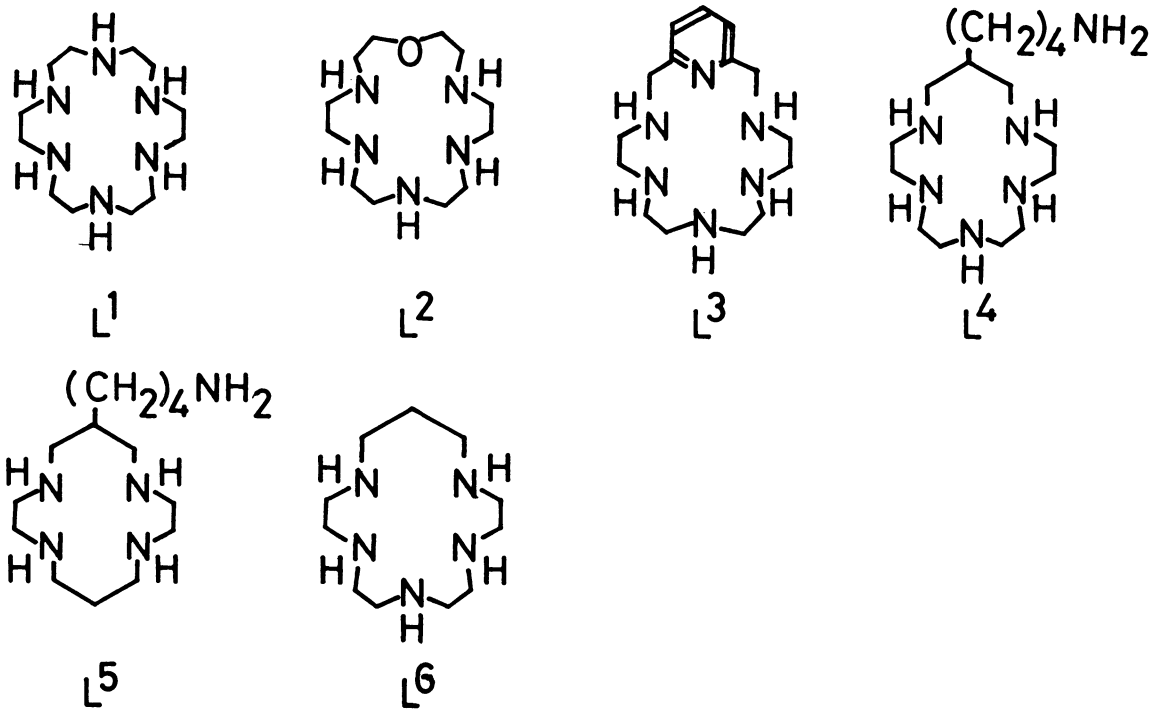
New macrocyclic polyamines L^2-L^5 have been synthesized to develop sequestering agents selective for Na^+, K^+, Mg^{2+} and Ca^{2+} ions in aqueous solutions. 18-membered hexadentate ligands L^2 and L^3 show specificity toward Ca^{2+}, whereas a 16-membered pentaamine with an amine branch (L^4) bind only to Mg^{2+}.

Currently we have been studying saturated polyamine macrocycles to reveal their versatile properties.[1] Among the properties physiologically useful is crown ether (polyether macrocycle)-like ligating ability: thus 18-membered hexaamine (L^1) can accomodate hard metal ions K^+ and Ca^{2+} in aqueous solutions.[2] In order to develop more selective and hence physiologically more practical chelating agents for Na^+, K^+, Mg^{2+} and Ca^{2+} we now have modified the basic structure of L^1 with various parameters such as donor atom and ring size, as shown by L^2-L^6.

A macrocyclic oxapentaamine L^2 and pentaamine L^6 as 5HBr salts were prepared by the method of Richman and Atkins.[3] Other polyamine derivatives (as 5HBr salts except for L^4 which is isolated in free form) were synthesized according to a slightly modified procedure by Tabushi et al.[4] All of the new compounds L^2-L^5 gave satisfactory elemental analysis, mass spectra and nmr data.

Metal complex formation of these macrocycles were studied using a pH-metric titration method. Aqueous solutions (50 ml) of ligand-to-metal ion ratio 1 (with L^2, concentration 5×10^{-4} M) : 66.6 ($CaCl_2$), or 1 (L^4 and L^5, concentration 10^{-3} M) : 33.3 ($CaCl_2$ and $Mg(ClO_4)_2$) were titrated three times with an aqueous



solution of NaOH or $[NEt_4][OH]$ (either gave an identical result) at 25°C and I = 0.1 M ($NaClO_4$). Typical titration curves are shown in Figures 1 and 2. The titration curves of pentaamines L^5 and L^6 in the presence of the metal ions did not show any pH depression to indicate no M-L interaction. The complexation data were analyzed using the formulae previously derived for pentaamines (n = 5, *e.g.* L^2 and L^3)[5] and hexaamines (n = 6, *e.g.* L^4)[2].

$$\alpha(\alpha_H)_L - \beta_H[L]_{total} = K_{ML}(n[L]_{total} - \alpha)[M^{2+}] \quad (1)$$

Here

$$\alpha = [H^+] + a[L]_{total}$$
$$= n[ML^{2+}] + n[L] + (n-1)[HL^+] + (n-2)[H_2L^{2+}] + \cdots + [H_{n-1}L^{(n-1)+}] \quad (2)$$

$$(\alpha_H)_L = [L]_{uncomplexed}/[L]$$
$$= 1 + [H^+]K_1 + [H^+]^2K_1K_2 + \cdots + [H^+]^nK_1K_2\cdots K_n \quad (3)$$

$$\beta_H = n + (n-1)[H^+]K_1 + (n-2)[H^+]^2K_1K_2 + \cdots + [H^+]^{(n-1)}K_1K_2\cdots K_{(n-1)} \quad (4)$$

$$[L]_{total} = [L]_{uncomplexed} + [ML^{2+}] \quad (5)$$

$$[L]_{uncomplexed} = [L] + [HL^{+}] + [H_2L^{2+}] + \cdots + [H_nL^{n+}] \quad (6)$$

a = the number of base added per mol of ligand

and K_{ML} is 1:1 complex formation constant

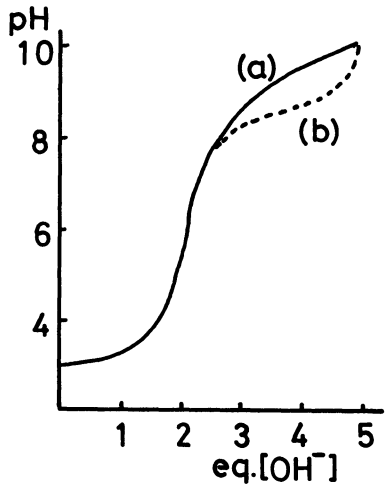


Fig.1

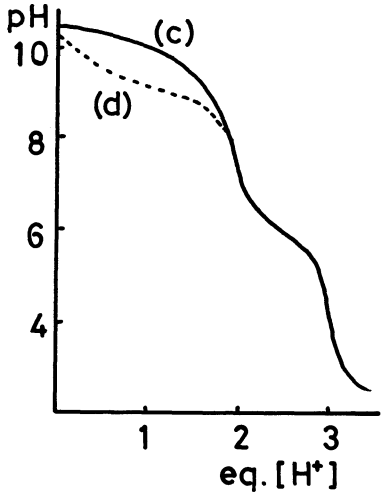


Fig.2

Fig. 1 Titration curves of $L^2 \cdot 5H^+$ without (a) and with Ca^{2+}(b) at $[L^2] = 0.5 \times 10^{-3}$ M and $[Ca^{2+}] = 33.3 \times 10^{-3}$ M at I = 0.1 M and 25°C

Fig. 2 Titration curves of L^4 without (c) and with Mg^{2+}(d) at $[L^4] = 1.0 \times 10^{-3}$ M and $[Mg^{2+}] = 33.3 \times 10^{-3}$ M at I = 0.1 M and 25°C

The (mixed-mode) protonation constants K_i were determined potentiometrically under the same conditions: 9.48, 9.29, 7.74, 3.65, 1.0 (L^2); 9.63, 9.05, 7.56 (L^3); and 10.64, 9.37, 2.0 (L^4). Other relevant data were previously reported.[2,5]

The results (Table) show that the macrocyclic hexaamine derivatives L^2, L^3 and L^4 have a distinct trend to bind to the alkaline earth metal ions. The most interesting of all is the 16-membered macrocycle with a n-butyl amine branch L^4, which specifically sequester Mg^{2+}ion. This selective recognition of Mg^{2+} over Ca^{2+} is not known with other previous chelating agents and would be extremely useful in biological applications. Another fact that either of 18-membered hexaamine L^1,

Table. 1:1 Complex Formation Constants log K_{ML} at I=0.2 M and 25°C.

Metal ions	ligand						
	L^1 [a]	L^2	L^3	L^4	L^5	L^6	[18]-crown-6 [c]
Na^+	no	no	no	no	no	no	0.8
K^+	ca. 0.8	no	no	no	no	no	2.03
Mg^{2+}	no	no	no	2.5	no	no	no
Ca^{2+}	2.5[b]	2.30	2.70	no	no	no	0.5

[a] Reference 2. [b] at 35°C. [c] Reference 6.

14-membered tetraamine homologue L^5, or 16-membered skeleton macrocycle without the amine branch L^6 negligibly interacts with Mg^{2+} ion is very instructive in designing new Mg^{2+}-selective chelating agents which demands proper ring size, donor atom numbers and an amine branch.

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