# Complexation of the Macrocyclic Hexa-amine Ligand 1,4,7,10,13,16-Hexa-azacyclo-octadecane (' 18-Azacrown-6 ')

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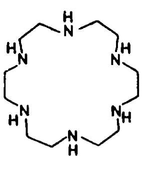
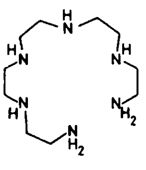
Complexation constants in aqueous solutions of the title compound with various metal ions are presented, together with $\Delta H$ and $\Delta S$ parameters. Unlike lower polyamine macrocyclic homologues, it has appreciable affinity to non-polarizable cations.

COMPLEXATION constants of saturated macrocyclic polyamine homologues with varying numbers of *N*-donor atoms (from $N_3$ to $N_4$ and $N_5$) and ring sizes (9- to 17-membered) have been extensively studied.[1] An increase in the number of donor atoms, provided that they are in appropriate ring sizes, enhances the metal-encapsulating abilities. It is of interest to see whether this trend continues up to hexa-amine incorporated into a larger 18-membered ring $L^1$. The hexa-amine is of further interest due to its sexidentate nature to saturate the primary co-ordinate bondings which may provide unparalleled sequestering properties.



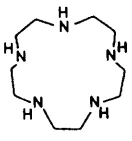
$L^1$

1,4,7,10,13,16-hexa-azacyclo-octadecane



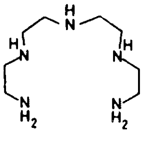
$L^2$

3,6,9,12-tetra-azatetradecane-1,14-diamine



$L^3$

1,4,7,10,13-penta-azacyclo-pentadecane



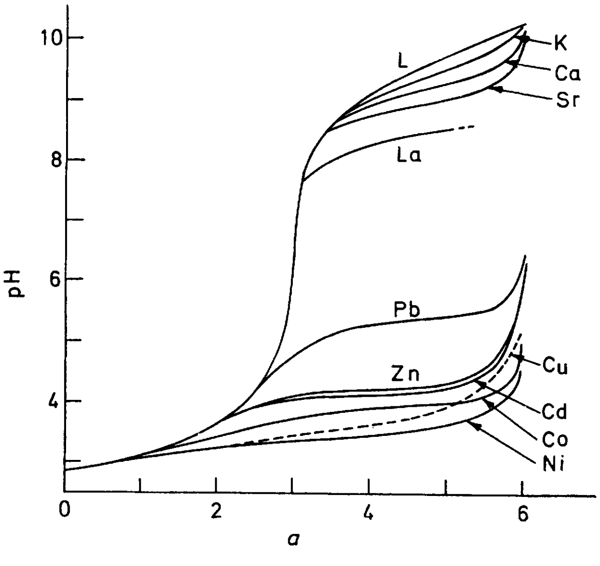
$L^4$

3,6,9-triaza-undecane-1,11-diamine

## EXPERIMENTAL AND CALCULATION

The macrocyclic hexa-amine $L^1$ as its 6 HCl adduct was synthesized by the method of Richman and Atkins.[2] Stock solutions of metal ions $Co^{2+}$,[3] $Cu^{2+}$, $Zn^{2+}$, $Cd^{2+}$, and $Pb^{2+}$ were prepared as described before.[1] For other metal ions, $Ni[NO_3]_2$, $K[NO_3]$, $CaCl_2$, $Sr[NO_3]_2$, and $La[NO_3]_3$ (all analytical grade) were used. Complexation with $Hg^{2+}$ was determined polarographically in an identical fashion to that applied to the lower polyamines.[1,4] All the other equilibrium measurements including protonation were conducted potentiometrically as before.[1] Three titrations were performed for each system. Typically, solutions (50 cm³) of ligand-to-metal ion ratio 1 : 10, 1 : 50 (with $Sr^{2+}$ and $Ca^{2+}$), or 1 : 200 (with $K^+$) (ligand concentration $10^{-3}$ mol dm$^{-3}$) were titrated with aqueous solutions of Na[OH] or $[NEt_4][OH]$ (both gave identical results) at 25.0 °C (or 35.0 °C for $Co^{2+}$, $Ni^{2+}$, and $Sr^{2+}$) and $I = 0.2$ mol dm$^{-3}$ ($Na[ClO_4]$ or $[NEt_4][ClO_4]$). As is usual in complexation reactions of macrocycles (with transition-metal ions and heavy-metal ions),[1] considerable time (*ca.* 1 min) was required at 25 °C for equilibration after each addition of the alkali titrant. This is especially true with $Ni^{2+}$ and $Co^{2+}$, so that a temperature of 35 °C was used to shorten the equilibration time to *ca.* 15 min. To prevent precipitation, the strontium(II) solution was measured at 35 °C. Values of $-\log [H^+]$ were read directly from the pH readings. The pH range covered in the titration was relatively high (see Figure) (for $K^+$, $Ca^{2+}$, $Sr^{2+}$, and $La^{3+}$), but in view of the small $K^{OH}$ $\{= [M(OH)^+]/[M^{2+}][OH^-]\}$ values, $10^{0.86}$ ($Ca^{2+}$) and $10^{0.32}$ dm³ mol$^{-1}$ ($Sr^{2+}$), except for the $La^{3+}$ system,[5] the formation of $[M(OH)]^+$ was neglected. For other metal ions the buffer pH ranges were very low and hence the metal hydrolysis was ignored, as in the $N_5$ system.[1]

Assuming the formation of the complex species $[M(HL)]^{3+}$ and $[ML]^{2+}$ during the titrations, equation (1) can be derived from a modification of equation (10) of ref. 1 (the



Titration curves of $[H_6L^1]^{6+}$ in the presence of metal ions. For experimental conditions and definition of *a*, see Experimental section formula applied to the macrocyclic penta-amine system). For definitions of the symbols used hereafter, see ref. 1.

$$\frac{\alpha(\alpha_H)_L - \beta_H c_L}{[M^{2+}][H^+](5c_L - \alpha)} = K_{ML}\frac{(6c_L - \alpha)}{[H^+](5c_L - \alpha)} + K_{ML}K^H \quad (1)$$

This relation fits to Co (in the titration range $3.5 < a < 5$), Ni ($3.8 < a < 5.1$), and Pb ($2.8 < a < 5$) where $a$ indicates the number of moles of base added per mole of ligand present.

Equation (1) simplifies to equation (2) when $[ML]^{2+}$ alone

$$\alpha(\alpha_H)_L - \beta_H c_L = K_{ML}(6c_L - \alpha)[M^{2+}] \quad (2)$$

is formed; *i.e.* $K^H = 0$. This is the formula applied to Zn ($2.8 < a < 5$), Cd ($2.8 < a < 5$), Ca ($4 < a < 5.5$), Sr ($4 < a < 5.5$), and K ($4.5 < a < 5.5$). The $K_{ML}$ values were determined from the gradient of the linear plots of $[\alpha(\alpha_H)_L - \beta_H c_L]$ against $(6c_L - \alpha)$.

Equilibrium constants and their confidence limits for polyamine complexation at $I = 0.2$ mol dm$^{-3}$ and 25 °C unless otherwise noted (1 cal = 4.184 J)

| | $L^1$ | | | $L^2$ | $L^3$ | $L^4$ |
|---|---|---|---|---|---|---|
| Metal ion | log $K_{ML}$ (log $K_{MHL}$) [a] | $-\Delta H$/kcal mol$^{-1}$ | $\Delta S$/cal K$^{-1}$ mol$^{-1}$ | log $K_{ML}$ | log $K_{ML}$ | log $K_{ML}$ |
| $Co^{2+}$ | $18.9 \pm 0.2$ [b]<br>$(11.8 \pm 0.3)$ | | | | 16.8 [b,c] | 13.7 [c] |
| $Ni^{2+}$ | $19.6 \pm 0.2$ [b]<br>$(13.9 \pm 0.3)$ | | | | 18.1 [b,d] | 17.4 [d] |
| $Zn^{2+}$ | $17.8 \pm 0.1$ | $12.4 \pm 0.3$ | $40 \pm 1$ | | 19.1 [e] | 15.1 [e] |
| $Cu^{2+}$ | $(21.6 \pm 0.2)$<br>$[16.1 \pm 0.2]$ [f] | $(22.9 \pm 0.3)$ | $(22 \pm 1)$ | 25.1 [g] | 28.3 [e] | 22.8 [e] |
| $Cd^{2+}$ | $17.9 \pm 0.1$ | $14.1 \pm 0.3$ | $34 \pm 1$ | 19 [h] | 19.2 [e] | 14.1 [e] |
| $Hg^{2+}$ | $29.1 \pm 0.2$ | $42.1 \pm 0.9$ | $-4 \pm 4$ | | 28.5 [e] | 24.8 [e] |
| $Pb^{2+}$ | $14.1 \pm 0.1$ | $13.3 \pm 0.3$ | $20 \pm 1$ | 11.0 [h] | 17.3 [e] | 9.9 [e] |
| $Ca^{2+}$ | $2.5 \pm 0.2$ [b] | $6.9 \pm 0.9$ | $-12 \pm 4$ | | | |
| $Sr^{2+}$ | $3.2 \pm 0.2$ | | | | | |
| $La^{3+}$ | $5.7 \pm 0.3$ | | | | | |
| $K^+$ | *ca.* 0.8 | | | | | |

[a] $K_{MHL} = [MHL^{3+}]/[M^{2+}][HL^+] = K_{ML}K^H/K_1$. [b] At 35 °C. [c] Ref. 10. [d] Ref. 11. [e] Ref. 1. [f] Log $K_{MH_2L}$ where $K_{MH_2L} = [MH_2L^{4+}]/[M^{2+}][H_2L^{2+}] = K_{MHL}K^{H'}/K_2$. [g] H. B. Jonassen, J. A. Bertrand, F. R. Groves, jun., and R. I. Stearns, *J. Amer. Chem. Soc.*, 1957, **79**, 4279. [h] E. Jacobsen and K. Schroder, *Acta Chem. Scand.*, 1961, **16**, 1393.

For complexation of $La^{3+}$, equimolar L : M solutions were titrated to avoid precipitation of $La[OH]_3$ (although precipitation starts to occur at $a = 5$). The data ($3.5 < a < 4.8$) obey equation (3) derived in a similar way to equation (15) of ref. 6, where $c_M = c_L$, $N_4$ terms are replaced by $N_6$ terms, and double deprotonation terms are eliminated.

$$K_{ML}\frac{(6c_L - \alpha)^2(\alpha_H)_L}{(1 + K^{OH}[OH^-])} = [(6 - R)(\alpha_H)_L - \beta_H][(\alpha - Rc_L)(\alpha_H)_L - c_L\beta_H] \quad (3)$$

The $K^{OH}$ value used for calculation was $10^{3.7}$ dm$^3$ mol$^{-1}$ (corrected to $I = 0.2$ mol dm$^{-3}$).[5]

For $Cu^{2+}$, the titration data at $2.8 < a < 3.7$ fit to equation (10) of ref. 1, indicating penta-amine $HL^+$ complexation to $[Cu(HL)]^{3+}$ ($\rightleftharpoons Cu^{2+} + HL^+$, $K_{CuHL}$) and $[Cu(H_2L)]^{4+}$ $\{\rightleftharpoons [Cu(HL)]^{3+} + H^+, K^{H'}\}$. Above $a = 5$, the formation of $CuL^{2+}$ is presumed likely, although the data could not be resolved.

Whenever possible, the complexation constants were determined at 15, 25, and 35 °C to permit estimation of the thermodynamic parameters $\Delta H$ and $\Delta S$. All the results are summarized in the Table along with the data for hexa- ($L^2$) and penta-amines ($L^3$ and $L^4$) previously reported, for reference. Mixed protonation constants log $K_i$ were 10.46, 9.51, 9.01, 4.30, *ca.* 2, and *ca.* 1 at 15 °C; 10.19, 9.23, 8.73, 4.09, *ca.* 2, and *ca.* 1 at 25 °C; and 9.92, 8.96, 8.45, 3.89, *ca.* 2, and *ca.* 1 at 35 °C.

## DISCUSSION

Most remarkable with $L^1$ is its sequestering ability in aqueous solutions for non-polarizable metal ions such as $K^+$, $Ca^{2+}$, $Sr^{2+}$, or $La^{3+}$, a property hitherto unknown with polyamine macrocyclic systems[7] or with linear polyamines.[8] Cyclic hexa-amine donors capable of filling the inner co-ordination sphere and occupying some of the lipophilic outer sphere may render, otherwise unfavourable, amine chelation favourable to the hydrated alkali, alkaline earth, or lanthanoid cations. Ligand $L^1$ thus shares properties of the ' hard ' ligand, ' 18-crown-6 ', an oxygen-substituted analogue, which seizes only ' hard ', non-polarizable cations: *e.g.* log $K_{ML} = 2.03$ ($K^+$), $<0.5$ ($Ca^{2+}$), or 2.72 ($Sr^{2+}$) in aqueous solutions.[9] Like the cyclic polyethers,[9] enthalpy-controlled complexation is demonstrated by the thermodynamic parameters with $Ca^{2+}$. Special about the 18-azacrown-6 is the fact that it favours the dipositive $Ca^{2+}$ over the unipositive $K^+$ ion. Presumably the chelation involves partial σ bonding, rather than mere electrostatic interactions as so interpreted for 18-crown-6.[9] Interestingly, $Na^+$ and $Mg^{2+}$ show little interaction with $L^1$; *i.e.* no pH depression was seen during the titrations. The well theorized cation selectivity of 18-crown-6, $Ca^{2+} > Mg^{2+}$ and $K^+ > Na^+$, based on the cation size *vs.* cavity size correlation[9] may also be prevalent in the present 18-azacrown-6.

The greater complexing ability of $L^1$ relative to that of quinquedentate $L^3$ with $Co^{2+}$ (ref. 10) and $Ni^{2+}$ (ref. 11) suggests the presence of six co-ordinating bonds in the $L^1$ complexes. The restriction of the $L^1$ macrocyclic structure would tend to favour six-co-ordination around the $d^7$ and $d^8$ metal ions in an octahedral mode. Very slow and difficult oxygenation of the $Co^{2+}$–$L^1$ complex (which shows a very weak visible absorption at *ca.* 480 nm, indicative of a high-spin octahedral complex) may well be accounted for by the difficulty of dissociating an axial amine to leave a vacant site for attack of $O_2$. This is in contrast to the ready oxygenation of $[Co(NH_3)_6]^{2+}$ to yield $[(H_3N)_5Co(O_2)Co(NH_3)_5]^{4+}$,[12] or of the cobalt(II) macrocyclic penta-amine 1,4,7,10,13-penta-azacyclohexadecane complex to yield LCo-$O_2$-CoL.[10] The visible spectrum of the $Ni^{2+}$–$L^1$ complex displaying three absorption peaks at 360, 530, and 840 nm is indicative of high-spin octahedral geometry.[13]

For the chelation to $Cu^{2+}$, we could resolve the buffer titration curve at $2.8 < a < 3.7$ in terms of $[M(HL)]^{3+}$ and $[M(H_2L)]^{4+}$ formation. Strong Cu–N planar co-ordination would permit the double protonation to $[ML]^{2+}$. The magnitude of $K_{ML}$ is presumed to be exceedingly large, which may be the reason for failure to determine $K_{ML}$ potentiometrically. In a previous determination of similarly very large $K_{ML}$ values for macrocyclic polyamines ($N_3$ to $N_5$), we have successfully employed polarographic techniques.[14] Irreversible polarographic reduction waves of a solution of $Cu^{2+}$–$L^1$ prevented this approach.

The macrocyclic hexa-amine co-ordination (with respect to the macrocyclic penta-amine, see ref. 1 for detailed equilibrium parameters) is not particularly stable for complexes with $d^{10}$ cations for enthalpic ($Zn^{2+}$) or for entropic reasons ($Cd^{2+}$, $Pb^{2+}$, and $Hg^{2+}$). The cyclization effect on the magnitude of $K_{ML}$ (' macrocyclic effect ') [15] for hexa-amine appears less remarkable than with penta-amines (though the reference data are limited), probably due to the increase in flexibility of the larger macrocycle.

We are currently exploring the potential of the dual properties of polyamines and polyethers which the macrocyclic hexa-amine specifically possesses.

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REFERENCES

[1] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1978, **1081** and refs. therein.

[2] J. E. Richman and T. J. Atkins, *J. Amer. Chem. Soc.*, 1974, **96**, 2268.

[3] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1980, 327.

[4] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1976, 2335.

[5] ' Stability Constants of Metal Ions,' eds. L. G. Sillén and A. E. Martell, *Special Publ.*, The Chemical Society, London, 1964, no. 17.

[6] M. Kodama and E. Kimura, *J.C.S. Dalton*, 1979, 325.

[7] I. M. Kolthoff, *Analyt. Chem.*, 1979, **51**, No. 5, 1R.

[8] N. S. Poonia and A. V. Bajaj, *Chem. Rev.*, 1979, **79**, 389.

[9] R. M. Izatt, R. E. Terry, B. L. Haymore, L. D. Hansen, N. K. Dalley, A. G. Avondet, and J. J. Christensen, *J. Amer. Chem. Soc.*, 1976, **98**, 7620; J. D. Lamb, R. M. Izatt, J. J. Christensen, and D. J. Eatough, ' Co-ordination Chemistry of Macrocyclic Compounds,' ed. G. A. Melson, Plenum Press, New York, 1979, p. 145.

[10] M. Kodama and E. Kimura, *Inorg. Chem.*, 1980, **19**, 1871.

[11] M. Kodama and E. Kimura, unpublished work.

[12] A. Werner and A. Myellius, *Z. anorg. Chem.*, 1898, **16**, 245.

[13] F. A. Cotton and G. Wilkinson, ' Advanced Inorganic Chemistry,' 3rd edn., Interscience, New York, 1972, p. 893.

[14] See, for example, M. Kodama and E. Kimura, *J.C.S. Dalton*, 1978, 104.

[15] D. K. Cabbiness and D. W. Margerum, *J. Amer. Chem. Soc.*, 1969, **91**, 6540; 1970, **92**, 2152.