The Effect of Increase in Chelate Ring Size beyond Six-membered on the Metal Ion Size Selectivity Patterns of Tetra-aza Macrocycles

Robert D. Hancock* and **M. Patrick Ngwenya**
Department of Chemistry, University of the Witwatersrand, Johannesburg, South Africa

The complex-formation constants and protonation constants of the ligand 1,4,7,10-tetra-aza-cyclopentadecane, which forms three five- and one eight-membered chelate ring, are reported. The protonation constants measured by glass-electrode potentiometry in 0.1 mol dm^{-3} $NaNO_3$ at 25 °C are pK_1 9.83, pK_2 8.95, pK_3 5.40, and pK_4 1.6, while the complex-formation constants, log K_1, were 19.25 (Cu^{2+}), 11.74 (Ni^{2+}), 10.70 (Zn^{2+}), 10.18 (Cd^{2+}), and 9.50 (Pb^{2+}). These constants were compared to those of other tetra-aza macrocycles with three five-membered chelate rings plus a fourth chelate ring which varied regularly from five- to seven-membered, as well as of series of open-chain ligands in whose complexes a single chelate ring varied in size in the same manner. It was concluded that (*a*) the size of the macrocyclic ring plays very little part in determining complex stability, (*b*) the main determining factor in controlling complex stability is the size of the chelate ring formed, (*c*) an increase in chelate ring size from five- to six-membered produces a differentiation in complex stability dependent on the size of the metal ion, such that complexes of larger metal ions are destabilized relative to those of small metal ions, and (*d*) an increase in chelate ring size beyond six-membered produces a fairly uniform decrease in complex stability which does not show any strong dependence on the size of the metal ion.

An important idea[1] in macrocyclic chemistry is that macrocyclic ligands might form complexes of increased stability with metal ions which best match in size a relatively rigid cavity in the centre of the ligand. In recent studies[2,3] of the set of tetra-aza macrocyclic ligands L^1 to L^5 shown in Figure 1 it became clear that the observed stability patterns did not accord with this idea. Indeed, the results obtained were almost exactly opposite to what one might have expected on the basis of the most stable complex being formed where the metal ion fitted best into the macrocycle, lying in the plane of the four nitrogens. The hole sizes shown for L^1 to L^5 are those calculated by molecular mechanics for the metal ion lying in the plane of the nitrogen donors of the ligand.[4,5] It was found[2,3] that the largest metal ions, such as Pb^{2+} or Cd^{2+}, formed their most stable complexes with the ligand L^1, which has the smallest cavity, while the smaller a metal ion became the more strongly was the larger cavity L^3 co-ordinated relative to the other ligands in the set. This result was interpreted in terms of the findings of recently reported molecular mechanics calculations.[6] These calculations showed that the metal ions could escape compression by changing from the *trans*-I conformer (Figure 2) to the *trans*-III or *cis*-V conformers, which do not involve co-ordination of the metal ions lying in the plane of the nitrogen donors. In this out-of-plane mode of co-ordination the macrocycle is highly flexible, and the factors which govern the metal ion selectivity are almost identical to those for open-chain ligands.[2,3] The over-riding factor which controls the metal ion size-based selectivity of saturated ligands at least, both macrocyclic and open chain, is the sizes of the chelate rings formed on complex formation. Thus, if in the complex of an existing ligand, a chelate ring is increased in size from five- to six-members, this will increase the selectivity of the ligand for small relative to large metal ions. For example, on passing from L^1 to L^2 in Figure 1, the stability of the complex of the large metal ion Pb^{2+} decreases by 2.6 log units, whereas that of the small Cu^{2+} rises by 1.1 log units.[3] Exactly the same pattern is seen for pairs of open-chain ligands[7] where one forms a five-membered chelate ring and the other a six-membered ring. Examples of such pairs of ligands are L^8 and L^9, and L^{14} and L^{15} (Figure 1).

A point of interest in metal ion size-based selectivity patterns is how they will be affected by increasing the chelate ring beyond six-membered to seven- or eight-membered. Some information is already available on the stabilities of complexes of ligand L^{12} with a few metal ions,[8] while the ethylenediaminetetra-acetate (edta) analogues with various chelate ring sizes involving the two nitrogen donor atoms, L^{14} to L^{18} in Figure 1, have been extensively studied by Anderegg.[9] We have recently completed[10] a study of the stability of the complexes of ligand L^6 with the metal ions Cu^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}. The interest in this paper is how progressively increasing chelate ring size along the series L^1, L^2, L^6, and L^7 (hereafter referred to as series B) affects the stability with the set of metal ions Cu^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}. This set of metal ions presents a very convenient range of metal-ion sizes from very small (low-spin Ni^{2+}) to very large (Pb^{2+}). It will thus be possible to compare the stability patterns in series B (the macrocycles) with those in series D (open-chain polyamines) and E (the edta series) to see whether once again the stability patterns as the size of the chelate ring is increased to seven- and then eight-membered are the same whether the ligand is macrocyclic or open-chain. We thus report a study of the stability of the complexes formed in aqueous solution by the ligand L^7, whose synthesis has recently been reported,[11] with the metal ions Cu^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}.

Experimental

Materials.—The ligand L^7 was synthesized as described by Sugimoto *et al.*,[11] as the trihydrobromide. The bromide was removed by passing the hydrobromide salt of the ligand down a column containing strong-base resin beads (Amberlite IRA 401, BDH) in the hydroxide form. This yielded a bromide-free stock solution of the ligand which was standardized by acid–base titration. The metal nitrate salts used were prepared from the AR salts and standardized by routine methods.

Potentiometry.—Measurements were made using a G202B glass electrode and a Radiometer PHM 84 pH meter with Ag–$AgNO_3$ reference electrode connected to the titration solution by a salt bridge containing 0.1 mol dm^{-3} $NaNO_3$. The electrode

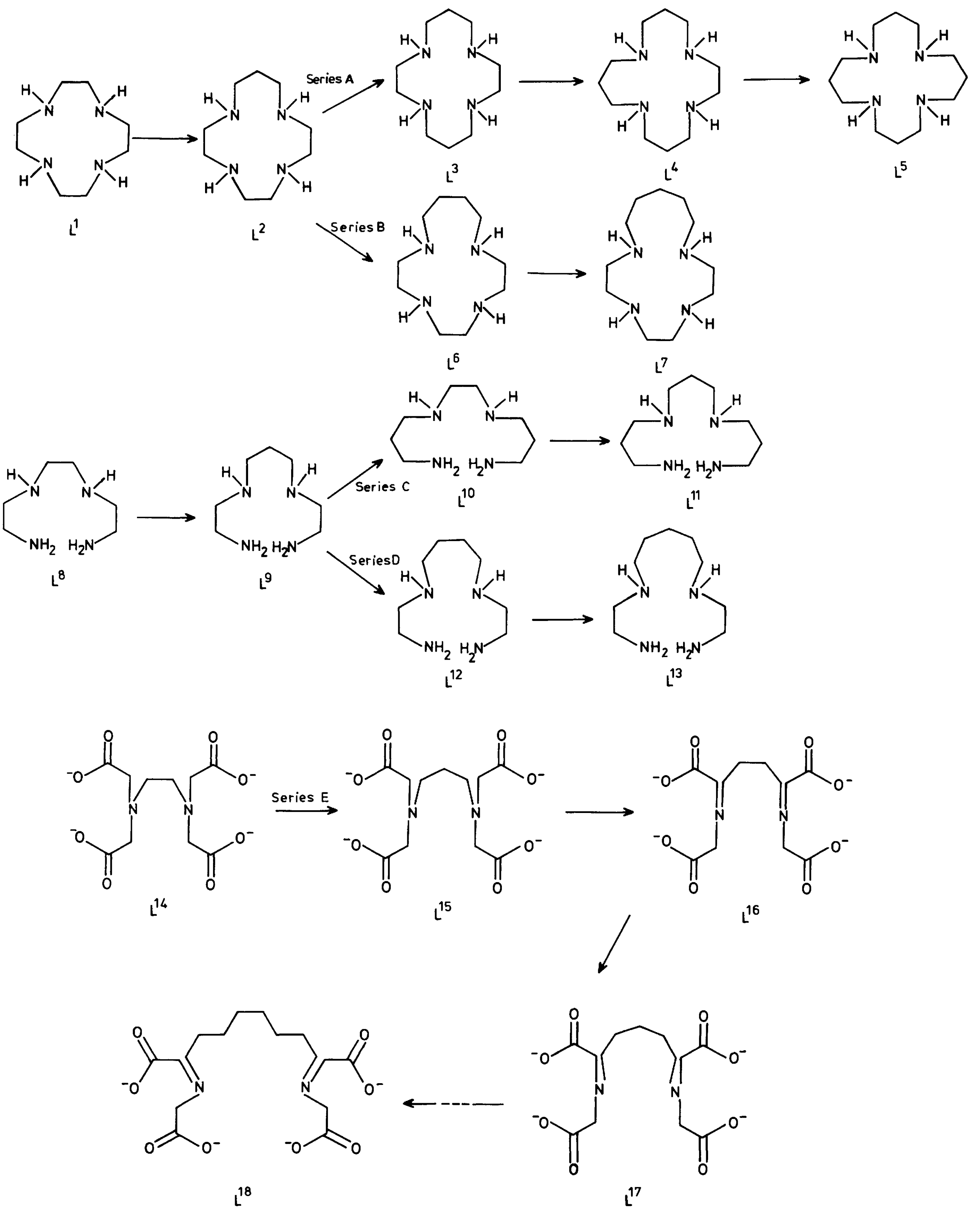
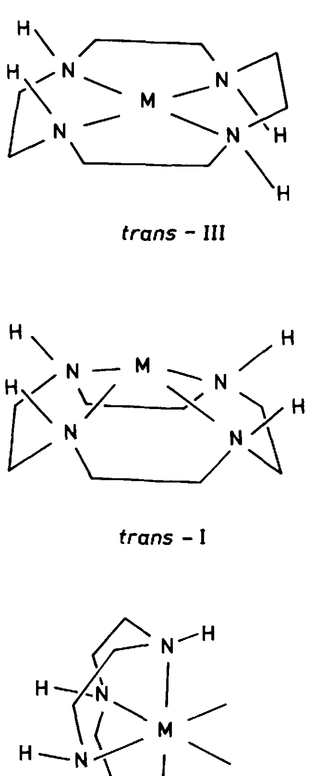


Figure 1. Ligands discussed in this work. Each series of ligands from series A to series E shows an increase in chelate ring size. Series A and C show a steady change in the number of six-membered relative to five-membered chelate rings, whereas B, D, and E show a steady increase in size of only one chelate ring from five- to eight-membered. Molecular mechanics has been used[4,5] to calculate the M–N bond lengths for metal ions which fit best into series A as 1.82 (L^1), 1.92 (L^2), 2.07 (L^3), 2.22 (L^4), and 2.38 Å (L^5)



trans - III

trans - I

cis - V

Figure 2. Diagrammatic representation of some different conformers of tetra-aza macrocycles. The *trans*-III conformer has the two pairs of adjacent N–H hydrogens on opposite sides of the plane of the macrocyclic ligand. The metal ion is not able to rise out of the plane of the ligand, and therefore this conformer shows sharp metal ion size-based selectivity.[6] However, the metal ions which are too large for the *trans*-III conformer are able to avoid compression[6] by complexing as the *trans*-I conformer, which has all the N–H hydrogens on the same side of the ligand. Here the metal ion is easily co-ordinated out of the plane of the nitrogen donors, and the metal ion size-based selectivity patterns are like those of open-chain ligands.[2,3] The *cis*-V conformer has the pairs of diagonally opposite N–H hydrogens on opposite sides of the ligand. This conformer is important[6] where a too-large metal ion causes folding of the ligand

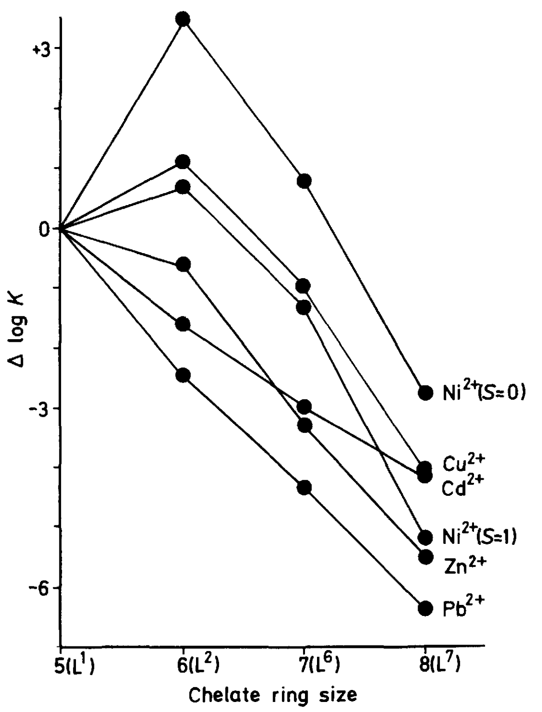


Figure 3. Variation of log *K* with chelate ring size for the series of tetra-aza macrocycles B in Figure 1; Δ log *K* is the change in complex stability relative to the stability with L^1 for each metal ion shown as the chelate ring size is increased. Formation-constant data from refs. 2, 3, 10, and 15; see also footnotes *i* and *j* in the Table. The ionic radii of the metal ions shown are (R. D. Shannon, *Acta Crystallogr., Sect. A*, 1976, **32**, 751): 0.49, Ni^{2+} ($S = 0$); 0.57, Cu^{2+}; 0.69, Ni^{2+} ($S = 1$); 0.74, Zn^{2+}; 0.95, Cd^{2+}; and 1.19 Å, Pb^{2+}. All the radii are for six-co-ordination, except for low-spin Ni^{2+} ($S = 0$), and Cu^{2+}, which are for the square-planar forms

system was calibrated for each titration by titrating an acid solution with base, both in 0.1 mol dm^{-3} $NaNO_3$, in the range pH 2—11, and fitting the Nernst equation to the potentials recorded for each addition of base. For each metal ion with L^7, three titrations were carried out at different metal to ligand ratios. The glass-electrode potentiometry thus yielded protonation constants for L^7, plus formation constants, log K_1, for Pb^{2+}, Cd^{2+}, Zn^{2+}, and Cu^{2+} in 0.1 mol dm^{-3} $NaNO_3$. Equilibration of L^7 with these metal ions during the potentiometric titrations was reasonably rapid, but with Ni^{2+} the equilibration times were in the range hours to days, which indicated that electronic spectroscopic techniques would be more suitable for Ni^{2+}. Reduction of the potentiometric data to yield formation constants was carried out using the program MINIQUAD,[12] and these results are given in the Table.

Spectroscopy.—The study of the formation constant of L^7 with Ni^{2+} was carried out as described previously.[2] A dozen solutions containing 0.1 mol dm^{-3} $NaNO_3$ plus 1.75×10^{-3} mol dm^{-3} Ni^{2+} and 3.84×10^{-3} mol dm^{-3} L^7 were prepared. Differing amounts of HNO_3 were present in each solution so as to give a range of pH from 2 to 5, in which the electronic spectra indicated that the extent of complex formation of Ni^{2+} with L^7 ranged from 0 to 100%. The pH value of each solution was recorded on the apparatus described above. The value of log *K* for Ni^{2+} with L^7 in each solution was thus calculated from the extent of complex formation indicated by the electronic spectra, plus the free-ligand concentration calculated from the mass-balance equation involving the protonated forms of L^7 plus its complex with Ni^{2+}. The highly consistent value of log K_1 for Ni^{2+} with L^7 calculated for each solution suggested that only the simple metal–ligand complex of 1:1 stoicheiometry was of any importance in these solutions. That the latter complex is the dominant species is supported by the fact that the very intense band associated with the low-spin form of the complex forms isosbestic points with the spectrum of free Ni^{2+}. It must be mentioned that equilibration of the solutions was fairly rapid for a complex of Ni^{2+}, appearing to take a few hours, but the solutions were kept in a constant-temperature bath for a week at 25 °C before the spectra were recorded. The u.v.–visible spectra of the solutions were recorded on a Cary 2300 spectrophotometer.

Results and Discussion

The protonation constants for ligand L^7, together with the complex formation constants with Cu^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}, are given in the Table. Also shown are the

Table. Protonation constants and formation constants with a variety of metal ions for the series of tetra-aza macrocycles having three five-membered chelate rings in their complexes, plus a fourth ring which varies progressively from five- to eight-membered; at 25 °C and 0.1 mol dm^{-3} $NaNO_3$ unless indicated otherwise

	Ligand[a]			
	L^1	L^2	L^6	L^7
Protonation constants[b]				
pK_1	10.97[c]	11.02[d]	10.92[e]	9.83 ± 0.02[f]
pK_2	9.87[c]	9.96[d]	9.40[e]	8.95 ± 0.02[f]
pK_3		1.96[d]	4.62[e]	5.40 ± 0.02[f]
pK_4				1.6 ± 0.1[f]
Formation constants ($\log K_1$)[g]				
Cu^{2+}	23.29[h]	24.36[h]	22.36[i]	19.25 ± 0.05[f]
Ni^{2+}	16.4[d]	17.98[d]	15.47[e]	11.74 ± 0.05[f]
Zn^{2+}	16.2[j]	15.6[j]	12.90[e]	10.70 ± 0.03[f]
Cd^{2+}	14,3[j]	12.71[d]	11.30[e]	10.18 ± 0.03[f]
Pb^{2+}	15.9[j]	13.48[d]	11.59[e]	9.50 ± 0.03[f]

[a] For ligands see Figure 1. [b] The protonation constants refer to the following equilibria: pK_1, $L + H^+ \rightleftharpoons HL^+$; pK_2, $HL^+ + H^+ \rightleftharpoons H_2L^{2+}$; pK_3, $H_2L^{2+} + H^+ \rightleftharpoons H_3L^{3+}$; pK_4, $H_3L^{3+} + H^+ \rightleftharpoons H_4L^{4+}$. [c] $I = 0.5$ mol dm^{-3}, from ref. 12. [d] From refs. 2 and 3. [e] From ref. 10. [f] This work. The constants were determined at 25 °C in 0.1 mol dm^{-3} $NaNO_3$. The uncertainties indicated are three times those calculated by the program MINIQUAD (A. Sabatini, A. Vacca, and P. Gans, *Talanta*, 1974, **21**, 53), which was used for calculating the formation constants from the potentiometric data. [g] The formation constant refers to the equilibrium $M^{2+} + L \rightleftharpoons ML^{2+}$. [h] From ref. 3, at $I = 0.5$ mol dm^{-3}. [i] M. Micheloni, P. Paoletti, A. Poggi, and L. Fabbrizzi, *J. Chem. Soc., Dalton Trans.*, 1982, 61; $I = 0.5$ mol dm^{-3}. [j] M. Kodama and E. Kimura, *J. Chem. Soc., Dalton Trans.*, 1977, 2269; $I = 0.2$ mol dm^{-3}.

corresponding constants for L^1, L^2, and L^6. It is seen that, for all the metal ions studied here, there is after L^2 a steady decrease in complex stability to L^6, and thence a further decrease to L^7. This can be best appreciated by presenting the results graphically, as shown in Figure 3. Here the change in complex stability for each metal ion, Δ log *K*, is calculated relative to the complex with L^1, where all the chelate rings in the complex are five-membered. One thus sees that there is a spread in the response of the metal ions to the change of one of the five-membered chelate rings in L^1 to a six-membered ring in L^2 such that small metal ions such as Cu^{2+} show a strong increase in complex stability, whereas large metal ions such as Pb^{2+} show a strong decrease in complex stability. However, with a further increase in the size of the chelate ring to seven-membered in L^6 there appears to be little further differentiation amongst the metal ions on the basis of their size. Instead, there appears to be a uniform drop in complex stability for all the metal ions in passing from L^2 to L^6 and thence to L^7. The only metal ion which appears to be somewhat out of step with this behaviour is Cd^{2+}, where the drop in complex stability appears to be less steep with increasing chelate ring size than is found for the other metal ions in the set. Without supporting evidence to back up such an idea, one should perhaps not speculate too much on the origin of the different behaviour of Cd^{2+} in Figure 3. However, it does seem possible that the increase in chelate ring size from five-membered in L^1 to eight-membered in L^7 does allow the Cd^{2+} ion to adopt more easily a tetrahedral structure as the size of the chelate ring increases.

The question raised by Figure 3 is the origin of the variation in complex stability seen as the chelate and macrocyclic ring size are simultaneously varied. In Figure 4 is shown the change in complex stability relative to L^8 as the chelate ring size is varied along series D in Figure 1. Unfortunately, no stability constants have been reported for the complexes of L^{13}, but the somewhat incomplete series comprising L^8, L^9, and L^{12} shows behaviour very similar to that seen in Figure 3. Thus, an increase in chelate ring size from five- to six-membered yields the same spread in complex stabilities according to metal-ion size as seen in Figure 3. Figure 4 then shows a fairly uniform decrease in stability with increasing chelate ring size to seven-membered. Thus, a comparison of the complex stabilities as the chelate ring size is increased in the macrocycles in Figure 3 shows that very similar behaviour is found with the open-chain analogues. It would thus seem that the stabilities of the complexes of the tetra-aza macrocycles should not be interpreted in terms of macrocyclic ring size, but rather in terms of chelate ring size, and that the same factors control metal-ion selectivity in both the macrocycles and their non-cyclic analogues.

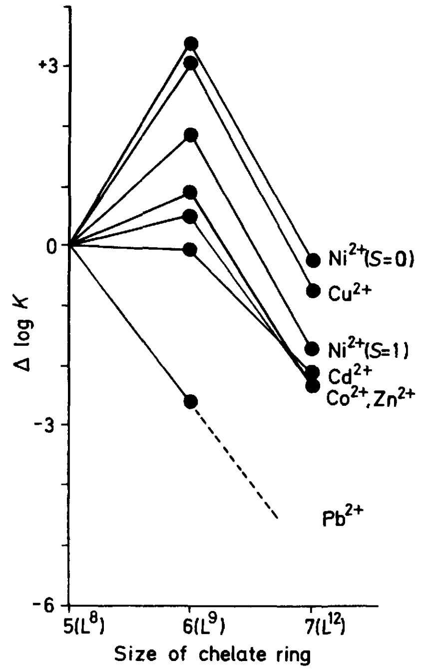


Figure 4. Variation of log *K* with chelate ring size for the series of open-chain tetra-aza polyamines D in Figure 1. The value of Δ log *K* is the change in complex stability relative to the complex with L^8 for each metal ion shown as the size of the central chelate ring is varied from five- to seven-membered. Formation-constant data from refs. 8 and 15

In Figure 5 is plotted the change in complex stability relative to L^{14} as the chelate ring size is increased progressively in the series of edta analogues represented by L^{14} to L^{17} in Figure 1. Although the behaviour is not as regular as seen in Figures 3 and 4, essentially the same features emerge. In other words, an increase in chelate ring size from five- to six-membered produces a spread in complex stability according to the size of the metal ion, with greater destabilization being found for the complexes of larger metal ions. Thereafter, there is a drop in complex stability which appears to be somewhat erratic, but largely independent of the size of the metal ion. What is important in Figure 5 is the wide range of metal-ion types, which suggests that the dominant factor in the response of the metal ion to change in chelate ring size is indeed the size of the metal ion. Thus, the small metal ion Mg^{2+} which has[13] very ionic metal to ligand bonding behaves similarly to the small Cu^{2+} which has much more covalent M–L bonding, while the

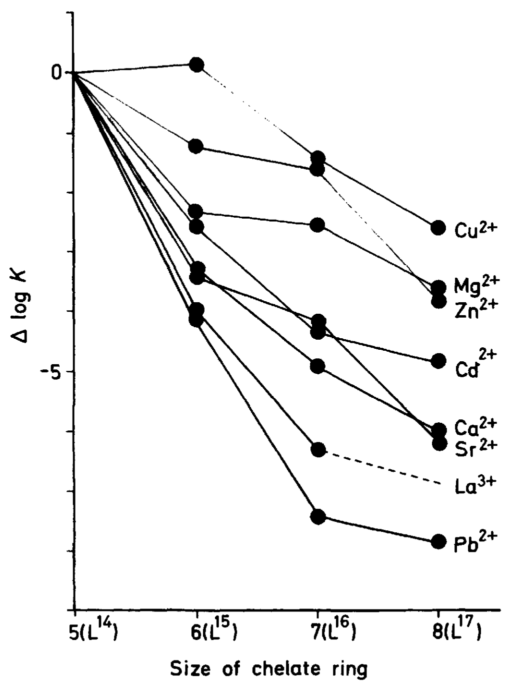


Figure 5. Variation of log K with chelate ring size in the series of edta analogues E in Figure 1. The value of Δ log K is the change in complex stability relative to the complex with L^{14} (edta) for each metal ion shown, as the size of the chelate ring is increased from five- to eight-membered. Formation-constant data from ref 5. Ionic radii for metal ions, which are not given in Figure 3 are: 0.72, Mg^{2+}; 1.00, Ca^{2+}; 1.18, Sr^{2+}; and 1.03 Å, La^{3+}.

large Cd^{2+} with its covalent M–L bonds[13] behaves like the similarly sized but more ionically bound Ca^{2+}. One should note, however, that there is[10] a strong contribution from the oxidation state of the metal ion, in that increasing oxidation state leads to a greater sensitivity to increase in chelate ring size. Thus, metal ions of higher oxidation state will show a greater decrease in complex stability on increasing the chelate ring size than will metal ions of the same size but lower oxidation state. A major difference between Figures 3 and 4 on the one hand, and Figure 5 on the other, is the fact that in the former an increase in chelate ring size from five- to six-membered is accompanied for the smaller metal ions by a strong increase in complex stability, whereas for the edta analogues in Figure 5 even the smallest metal ion, Cu^{2+}, shows only a slight increase in complex stability, while for fairly small metal ions such as Zn^{2+} which show increases in complex stability in Figures 3 and 4 there is an immediate drop in complex stability in Figure 5. A possible explanation here is that the more crowded co-ordination sphere of the six-co-ordinate edta analogues leads to a more unfavourable response to the six-membered chelate ring than for the quadridentate tetra-aza macrocycles and their open-chain analogues. Molecular mechanics calculations have already demonstrated that the complex destabilization which is found as five-membered rings are increased in size to give six-membered chelate rings is due to steric crowding.[14]

A point of interest in the Table is the set of protonation constants for L^7. It is seen that these are more like the protonation constants found for open-chain ligands. For example, the values for the open-chain trien (3,6-diazaoctane-1,8-diamine) are[15] pK_1 9.74, pK_2 9.08, pK_3 6.56, and pK_4 3.25. One observes that with the larger cavity in L^7 the nitrogens no longer appear to be favourably situated for multiple hydrogen bonding to the proton, which possibly accounts for the typically high first protonation constants of tetra-aza macrocycles.[16] Thereafter the precipitate drop in protonation constant from pK_2 to pK_3, almost always found for tetra-aza macrocycles, is not found for L^7. The large drop in protonation constant between pK_2 and pK_3 found for tetra-aza macrocycles has been attributed[16] to the difficulty of fitting three protons into the cavity of these ligands, so that the ligand is forced to assume an *exo* conformation, where the protons on the nitrogens are not directed into the cavity of the ligand but rather out into the solvent. Presumably L^7 has a large enough cavity that this is not necessary, so that the decrease between pK_2 and pK_3 is not unusually large.

One concludes from this study that, for both the tetra-aza macrocycles and their open-chain analogues, the dominant factor in the response in terms of complex stability is the size of the chelate ring, such that larger chelate rings will lead to greater complex destabilization for larger metal ions. For the macrocycles there appears to be very little contribution from the size of the macrocyclic ring as distinct from the size of the chelate ring, in determining complex stability. Considering the results obtained for the series A and B in Figure 1, as compared with series C and D, we conclude that hole-size arguments do not pertain to the stabilities of the complexes of these tetra-aza macrocycles as a function of metal-ion size.

Acknowledgements

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