1968 *Inorg. Chem.* **1990**, *29*, 1968-1974

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Ligand Design for Complexation in Aqueous Solution. 2. Chelate Ring Size as a Basis for Control of Size-Based Selectivity for Metal Ions

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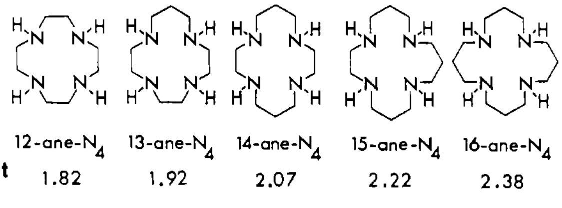
Received August 16, 1989

The role of chelate ring size in complex stability, and selectivity based on metal ion size, is examined. Formation constants of pairs of ligands which differ in that one member of the pair forms a five-membered chelate ring where the other forms a six-membered chelate ring are reported with metal ions ranging in ionic radius from small (e.g. Be(II), Cu(II), Al(III)) to medium sized (e.g. Zn(II), In(III)) and large (e.g. La(III), Pb(II)). Pairs of ligands studied, and whose formation constants are combined with literature values already available, are as follows: 9-aneN_2O (1-oxa-4,7-diazacyclononane) and 10-aneN_2O (1-oxa-4,8-diazacyclodecane); 15-aneN_4O (1-oxa-4,7,10,13-tetraazacyclopentadecane) and 16-aneN_4O (1-oxa-4,7,11,14-tetraazacyclohexadecane); TIRON (4,5-dihydroxy-1,3-benzenedisulfonate) and CTA (chromotropic acid, 4,5-dihydroxynaphthalene-2,7-disulfonate); TM-cyclen (1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclododecane) and TMC (1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane). Except for the pair of rigid small macrocycles 9-aneN_2O and 10-aneN_2O, chelate ring size dominates macrocyclic ring size in controlling metal ion size-based selectivity so that complexes of larger metal ions are destabilized relative to those of smaller metal ions by increase in chelate ring size from five to six membered. For the TIRON/CTA pair of ligands, rigidity introduced into the single chelate ring by aromatic rings gave sharper size selectivity than for pairs of flexible ligands such as oxalate/malonate. With high levels of steric crowding, as in TM-cyclen and TMC, size selectivity was still controlled by chelate ring size. The strain energy (*U*) of five- and six-membered chelate rings of the ethylenediamine (EN) and 1,3-diaminopropane (TN) type was calculated by molecular mechanics (MM) as a function of M-N bond length and N-M-N angle. The MM showed that minimum *U* occurred for the EN chelate ring when the M-N bond length was 2.5 Å and the N-M-N angle was 70°, while for the TN chelate ring *U* was minimum for M-N bond length 1.6 Å and N-M-N angle 109.5°. MM studies on alkali-metal ion complexes with crown ethers with different chelate ring sizes present showed that even with highly ionic M-L bonding the effect of chelate ring size on metal ion selectivity should be present.

Introduction

In this second paper in the series[1] the effect of chelate ring size on metal ion size-based selectivity is examined. It is perhaps surprising that, although the chelate effect[2] has been widely studied, and as far back as 1959 Corey and Bailar[3] carried out simple molecular mechanics (MM) calculations on isolated chelate rings, there has been almost no consideration given to what might be the optimum size of metal ion for coordination in chelate rings of different sizes. Preoccupation with transition-metal ions has meant that chelate rings have been considered in terms of metal ions such as Cu(II), Ni(II), or Co(III), which are all similar in size. Recently,[4] it has been recognized that selectivity patterns of ligands such as tetraazamacrocycles are better interpreted in terms of control of selectivity by the presence of six-membered as against five-membered chelate rings in the resulting complex, rather than by matching of size of metal ion to size of macrocyclic cavity (size-match selectivity). For tetraazamacrocycles macrocyclic ring size is increased along the series 12-aneN_4 through 16-aneN_4 by increasing the chelate ring sizes from five- to six-membered. The best-fit M-N lengths indicated are those calculated from molecular mechanics to be the best M-N bond length for fitting into the cavity of each macrocycle (Chart I). Analysis[5-8] of formation constants of complexes of macrocyclic and nonmacrocyclic ligands has confirmed that chelate ring size is important in controlling metal ion size-based selectivity and usually outweighs macrocyclic ring size in this regard. *One can distinguish between the effects of chelate and macrocyclic ring size.* In nonmacrocyclic ligands an increase of chelate ring size leads to a *decrease* in complex stability with larger metal ions; increase in macrocyclic ring size accompanying an increase in chelate ring size in the series 12-aneN_4 through 16-aneN_4 is expected to *increase* complex stability with large metal ions.

Chart I



Molecular mechanics (MM) calculations[10] show that the small effect of macrocyclic ring size on complex stability arises from flexibility of the large macrocyclic ring.[10] Small macrocyclic rings of the 9-aneX_3 type (X = N, O, S) may be rigid enough[11] to compete with chelate ring size as a factor controlling selectivity. Smaller rings are generally more rigid than larger rings, so that dominance of the chelate ring over the macrocyclic ring in controlling selectivity is due to the smaller size and hence greater rigidity of the chelate ring. Of course, the metal ion does not enter the cavity of these small macrocycles, so that these do not represent examples of size-match selectivity. Rather, the metal ions are responding to the geometrical requirements for coordination out of the plane of the three donor atoms.

In this paper the role of chelate ring size in controlling selectivity for metal ions on the basis of their size is examined in greater detail. The role of chelate ring size has been examined[6] only for polydentate ligands with more than one chelate ring. The selectivity effect of chelate ring size may be sharpened by the greater rigidity imposed by more than one connected chelate ring. To examine size selectivity effects of chelate ring size in a ligand consisting of a single chelate ring, formation constants of a selection of metal ions offering a range of metal ion radii[12] were determined with CTA (chromotropic acid, Figure 1). This ligand forms a six-membered chelate ring in contrast to the five-membered ring formed by the similar TIRON (Figure 1) on complex

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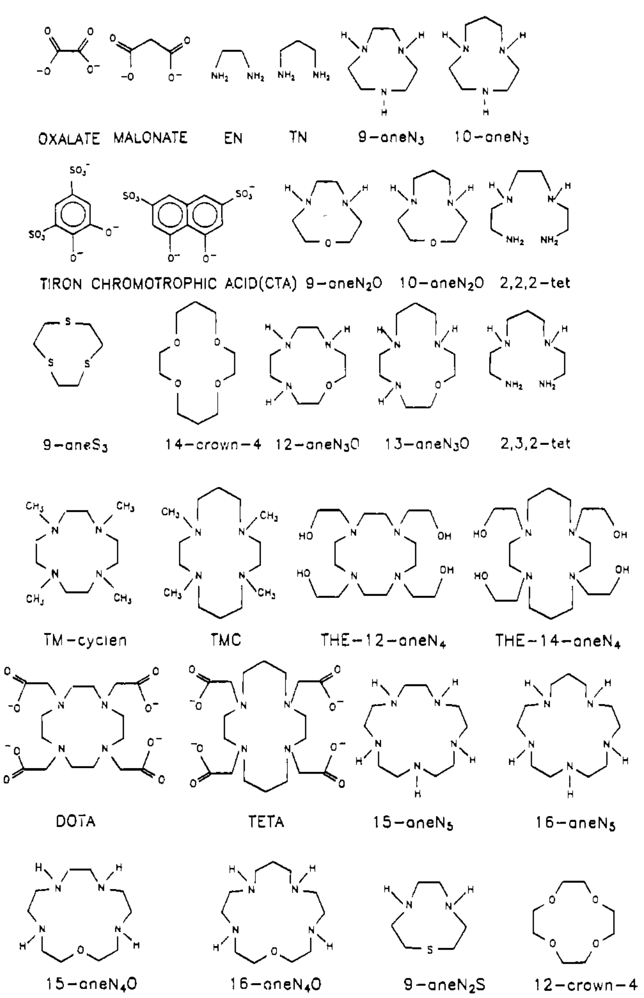

Figure 1. Abbreviations used for ligands discussed in this work.

formation. This type of relationship, where the change in the logarithm of the formation constant, $\Delta \log K$, for a metal ion in passing from a ligand such as TIRON to a ligand such as CTA, is plotted against ionic radius, will be referred to as the relationship for TIRON/CTA. The relationship for TIRON/CTA, and that for oxalate/malonate, which can be drawn from literature values,[9] is used to assess the response of complex stability to metal ion size as the size of the chelate ring is increased from five to six membered. the TIRON and CTA ligands are based on rigid aromatic rings, in contrast to the flexible oxalate and malonate, which should indicate the effect of flexibility of the chelate ring on metal ion size selectivity.

To understand the role of adjacent joined chelate rings in sharpening size selectivity, molecular mechanics (MM) calculations were carried out on five- and six-membered chelate rings in bidentate as well as tetradentate ligand systems where the size of a single chelate ring was altered from five to six membered. Calculations were also carried out on crown ether complexes of the small Li^+, the medium large Na^+, and large K^+ ions by using the electrostatic MM model of M-O bonding of Kollman et al.,[13] in order to assess the role of chelate ring size for highly ionic metal to ligand bonding.

Size-match selectivity appears[11] important in small 9-aneX_3 type (X_3 = N_3, N_2O, N_2S) macrocycles. Therefore, the metal ion size selectivity of macrocycles as a function of macrocycle ring size from small tridentate to large pentadentate or hexadentate nitrogen donor macrocycles is reported. Formation constants[7] are available on ligand pairs such as 9-aneN_3 and 10-aneN_3 (Figure 1) or 15-aneN_5 and 16-aneN_5, in which the second member of the pair has a six-membered chelate ring whereas in the first there is a five-membered ring. However, the level of agreement among reported formation constants for these ligands[9] is poor, which probably relates to the low lability of their complexes. Complexes of mixed-donor macrocycles containing even a single oxygen donor are far more labile[14] than their all-nitrogen donor analogues. A study is reported here of the thermodynamics of complex formation of the Cu(II), Ni(II), Zn(II), Cd(II), and Pb(II) complexes with mixed-donor macrocyclic ligands forming chelate rings of different sizes. Thus, the stability of complexes of 10-aneN_2O, which is compared with the stability[14] of the complexes of 9-aneN_2O, and of the pair of ligands 15-aneN_4O and 16-aneN_4O, is reported. A final point of interest is how complex and bulky the ligand can be with the effect of five- versus six-membered chelate rings still dominant in controlling metal ion size selectivity. Metal ion selectivity patterns of tetraazamacrocycles with *N*-methyl, *N*-acetate, and *N*-(2-hydroxyethyl) substituents are examined. The stability of complexes of Cu(II), Zn(II), Cd(II), and Pb(II) with the *N*-methyl substituted TM-cyclen (Figure 1) is reported, which may be compared with the previously reported[15] values for TMC. The effect of *N*-acetate or *N*-(2-hydroxyethyl) substituents on 12-aneN_4 or 14-aneN_4 complex stability as a function of metal ion size is evaluated with literature[9,15] values of formation constants.

Experimental Section

Materials. Metal ion solutions used in stability constant determinations were prepared from AR nitrate salts and standardized by usual methods. The ligand CTA (Aldrich) was used to make up stock solutions, which were shown by standardization with base to be better than 99% pure.

The ligand 4-oxa-1,7-diazacyclotane (10-aneN_2O) was prepared by modification of the method of Ewin and Hill.[16] In the preliminary steps diethyl ether rather than toluene as solvent gave better results, and triethylamine was used instead of pyridine to take up liberated HCl. It was difficult to remove phenol from the final product after detosylation with phenol. The alternative hydrobromic/glacial acetic acid method of Koyama and Yoshino[17] gave a yield of 64% on the hydrolysis step. Attempts to prepare 15-aneN_4O by the methods of Rasshofer et al.[18] and Atkins et al.[19] were unsuccessful. The method of Ciampolini et al.,[20] involving reaction of bis(2-iodoethyl) ether with the tetratosylate of triethylenetetramine worked well, giving the ligand as a hydrobromide, recrystallized from HBr, in 67% yield. The ligand 16-aneN_4O was synthesized in 59% yield by the method of Ciampolini et al.[20] The ligand TM-cyclen was synthesized from 12-aneN_4, prepared by the method of Richman and Atkins,[19] by methylation according to literature methods.[21]

Molecular Mechanics Calculations. These were carried out as described previously,[10] with the energy of a single chelate ring containing either ethylenediamine (EN) or 1,3-diaminopropane (TN) calculated as a function of ideal (strain-free) M-N bond length and N-M-N bond angle in the range of M-N bond lengths from 1.5 to 2.8 Å and N-M-N angles from 60 to 120°. Force constants involving the metal atom in the chelate ring were kept constant at those for high-spin nickel(II), as was done previously.[10] The potential energy as a function of M-N lengths and N-M-N angles for five- and six-membered chelate rings are seen in Figures 5 and 6. Calculations on the Li^+, Na^+, and K^+ complexes of 12-crown-4 and 14-crown-4 were also carried out with the force field described by Kollman et al.[13] with a locally modified version of MOLBLD originally due to Boyd.[22] As a test of reliability of the procedure, the program reproduced satisfactorily the energies of the 18-crown-6 complexes of Na^+, K^+, Rb^+, and Cs^+ reported by Kollman et al.[13]

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Table I. Formation Constants and Protonation Constants for Ligands Studied in This Paper, with Literature Values for Comparison[a]

	ligand						
	9-aneN_2O[b]	10-aneN_2O[c]	15-ane$_4O$[c]	16-aneN_4O[c]	TM-cyclen	TMC	CTA
pK_1[d]	9.60	9.56 (2)	9.56 (2)	9.75 (3)	11.07 (2)	9.34	
pK_2[d]	5.34	8.53 (2)	8.75 (2)	8.61 (3)	8.95 (2)	8.99	
pK_3[d]			5.31 (2)	5.89 (3)			
pK_4[d]				3.17 (3)			
log K_1(Cu(II))[e]	10.86	8.55	20.07	22.18	18.37	18.3	13.45 (2)
log K_2(Cu(II))[e]	8.68	6.41					10.26 (3)
log K_1(Ni(II))	8.49	5.28	13.33	13.15		8.4	9.55 (3)
log K_1(Zn(II))	6.36	4.94	13.11	11.72	14.04	10.4	10.03 (3)
log K_1(Cd(II))	4.48	4.06	13.41	13.44	13.06 (2)	9.0	8.90 (4)
log K_1(Pb(II))	5.17	*f*	12.28	10.07	13.91 (2)		11.17 (3)
log K_1(Be(II))							16.3
log K_1(La(III))							9.82 (5)
log K_1(In(III))							16.04 (5)
log K_1(Al(III))							17.18 (2)
log K_2(Al(III))							12.92 (3)
log K_1(Fe(III))							20.6 (3)
log K_2(Fe(III))							12.90 (5)

[a] Constants reported in this work are in 0.1 M $NaNO_3$ at 25 °C. For key to ligand abbreviations, see Figure 1. [b] Reference 14. [c] This work; 0.1 M $NaNO_3$ at 25 °C. [d] These constants refer to the protonation equilibria of the ligands, L, as follows: pK_1, $LH^+ = L + H^+$; pK_2, $LH_2^{2+} = LH^+ + H^+$; pK_3, $LH_3^{3+} = LH_2^{2+} + H^+$; pK_4, $LH_4^{4+} = LH_3^{3+} + H^+$. [e] The formation constants correspond to the equilibria of the metal ions M and the ligands L as follows: log K_1, M + L = ML; log K_2, ML + L = ML_2. [f] Metal ion hydrolyzed before complex formation occurs.

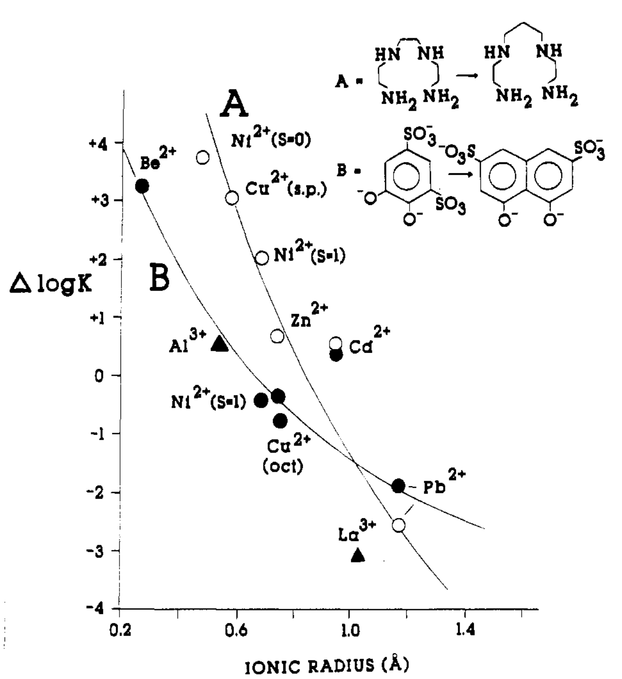

Figure 2. Relationship between the change in formation constant, Δ log *K*, on increase in size of a chelate ring from five membered to six membered, and the ionic radii[12] of the metal ions for (A) the pair of ligands 2,2,2-tet and 2,3,2-tet (○) compared with (B) the pair of ligands TIRON and CTA (●). Data are from ref 9 and this work (CTA). Triangles indicate trivalent metal ions.

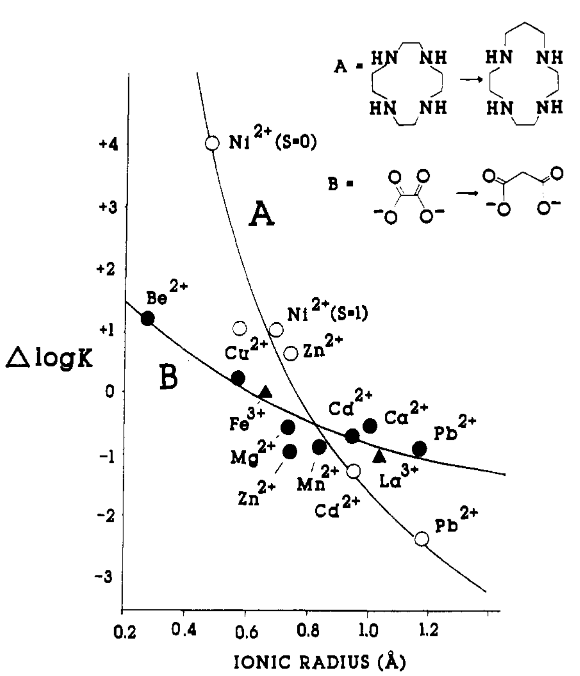

Figure 3. Relationship between the change in formation constant, Δ log *K*, on increase in size of a chelate ring from five membered to six membered, and the ionic radii[12] of the metal ions for (A) the pair of ligands 12-aneN_4 and 13-aneN_4 (○) compared with (B) the pair of ligands oxalate and malonate (●). Data are from ref 9. Triangles indicate trivalent metal ions.

Formation Constant Determination. These were carried out as described previously[23] at 25 °C in 0.1 M $NaNO_3$, using glass electrode potentiometry. Formation constants were calculated from potentiometric data with the program MINIQUAD.[24] Formation constant studies were straightforward, except that solutions of the ligand CTA tended to discolor on standing, so that these were prepared fresh and standardized on a daily basis, and protonation constant determinations were repeated as a check on purity after each day's work to ensure that no significant decomposition had occurred. The mono complex of Fe(III) and CTA was undecomposed at pH 2, so that glass electrode potentiometry could not be used to determine log K_1 for this system. Instead, electronic spectra of 10^{-3} M solutions of Fe^{3+} and 10^{-2} M CTA in 0.1 M $NaNO_3$ were recorded in the pH range 1–2, and log K_1 was calculated from the variation in intensity of the band at 460 nm as a function of pH. In spite of the high value of log K_1 determined for Fe(III) with CTA, log K_2 for this system was low, and precipitation of ferric hydroxide prevented determination of log K_3. The rate of equilibration of ligand with metal ion for complexes of TM-cyclen was too slow for study by conventional glass electrode potentiometry, so that an "out-of-cell" technique[25] was used in which sealed flasks with solutions of the ligand plus metal ion were allowed to equilibrate at different acid concentrations before pH values were recorded. Protonation constants and formation constants for ligands studied in this work are in Table I, along with literature[9] values of constants for ligands required for purposes of comparison.

Results and Discussion

Formation constants determined in this study, together with literature values required for discussion, are seen in Table I.

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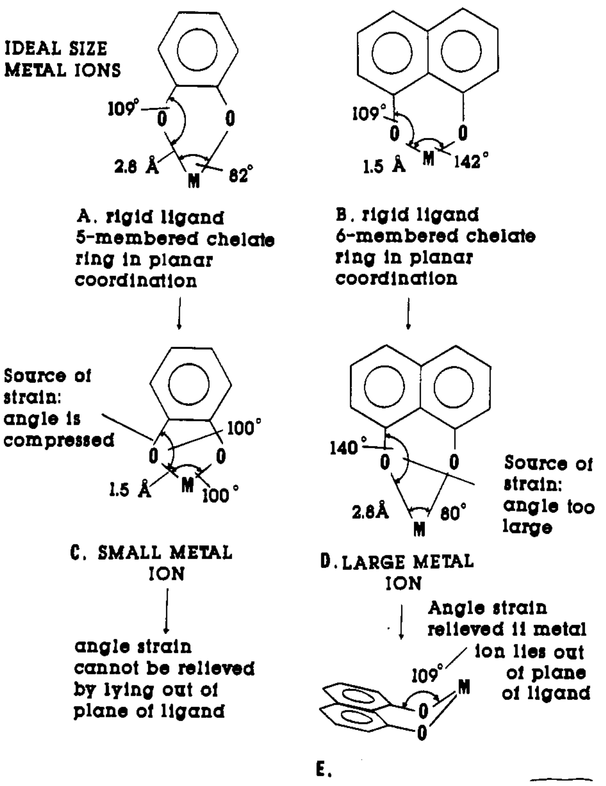

Figure 4. Diagrammatic representation of rigid five-membered and six-membered chelate rings involving aromatic rings fused into the chelate ring, showing steric aspects of coordination to metal ions of different sizes. Large metal ions coordinate with minimum strain to the five-membered chelate ring (A), and small metal ions do so with the six-membered chelate ring (B). The origin of steric strain lies in C–O–M angle deformation, being compressed at (C) with a small metal ion in a five-membered chelate ring and opened up at (D) with a large metal ion in a six-membered chelate ring. The metal ion is able to reduce the C–O–M angle by lying out of the plane of the chelate ring, which helps the large metal ion in the six-membered ring at (D), where the C–O–M angle is too large, as seen at (E), but does not help the small metal ion at (C) because the C–O–M angle is already too small.

Several issues arise from this work:

(1) Bidentate Ligands of Chelate Ring Size Five and Six [TIRON and Chromotropic Acid (CTA)]. In Figure 2 the change in the logarithm of the formation constant, Δ log *K*, accompanying change in chelate ring size from five in TIRON complexes to six in CTA complexes, is plotted as a function of metal ionic radius.[12] In Figure 3 is seen a similar relationship for oxalate/malonate. Included in Figure 2 is the relationship for 2,2,2-tet/2,3,2-tet, which has a slope typical of changes in ring size from five to six in polyamines, and in Figure 3 is included the slope for 12-aneN_4/13-aneN_4, also giving a typical slope as a reference for the oxalate/malonate relationship. The response of the oxalate/malonate relationship to metal ion radius is much weaker than typically found for polydentate ligands such as 12-aneN_4/13-aneN_4. However, the response of the TIRON/CTA relationship in Figure 2 does not seem markedly weaker than that of the reference pair of ligands 2,2,2-tet/2,3,2-tet. It seems probable that the shallow slope of the oxalate/malonate relationship relates to flexibility of the oxalate and malonate ligands, which may allow the metal ion to achieve close to ideal O–M–O and M–O–C angles without large increases in the strain energy of the ligand. It appears in Figure 2 that the selectivity of six-membered chelate rings against large metal ions such as Pb(II) is somewhat weakened for CTA as compared with the 2,2,2-tet/2,3,2-tet relationship, in that the slope for TIRON/CTA relationship becomes less steep at large metal ion radius. This might be explicable in terms of the metal ion not coordinating coplanar with the CTA ligand, as shown in Figure 4, which would allow too-large metal ions to coordinate with less strain in the rigid six-membered chelate ring.

One should point out at this stage that all the ionic radii[12] used in Figures 2 and 3, and also Figures 7–9 discussed below, are for octahedral coordination, except for Cu(II) (square planar) and Be(II) (tetrahedral). One might try to assess the actual coordination numbers of the metal ions, but this complicating feature would add little, since in general the tendency to achieve higher coordination number and ionic radius is related to larger octahedral radius. The Cu(II) ion fits on correlations of the type seen in Figures 2,3, and 7–9, only if its square-planar radius is used. An exception occurs where the ligands must enforce facial coordination, as in the case of 9-aneN_2O seen in Figure 7, where the octahedral radius becomes appropriate. Tetrahedral coordination geometry is so dominant for Be(II) that it would hardly seem realistic to use its octahedral radius, although this would not materially alter the correlations found. The Cd(II) ion also occasionally behaves in such correlations as though the tetrahedral radius were more appropriate, as discussed further below.

Figures 2 and 3 indicate that chelate ring rigidity may promote size selectivity. This has implications for ligand design, since rigid six-membered chelate rings may act to promote selectivity for small metal ions of toxicological interest[26] such as Al^{3+} (ionic radius[12] 0.54 Å) relative to Fe^{3+} (ionic radius 0.65 Å). It should be noted that selectivity of Al^{3+} relative to Fe^{3+} (selectivity = log K_1(Al(III)) − log K_1(Fe(III)) is improved by 5 log units in passing from EDTA (chelate ring size five) to TMDTA (chelate ring size six). These considerations are also important in designing siderophores,[27,28] since the Fe^{3+} ion is fairly small compared to other ions of biological interest such as Zn(II). On the other hand, metal ions such as In(III) or Gd(III), used as imaging agents,[29] are large, and six-membered rings should be avoided to maximize selectivity for them. Figures 2 and 3 suggest that fusion of rigid aromatic rings into the macrocyclic ring should enhance metal ion size selectivity. This should also be important for macrocycles containing fused aromatic rings, such as the ligands investigated by Lindoy et al.[30]

Of interest for the CTA complexes is a comparison of the stability of the bis complexes of Al(III) and Fe(III) (where values with asterisks were estimated by assuming that log K_2 − log K_3 equals log K_1 − log K_2):

	log K_1	log K_2	log K_3	log β_3
Al(III)	17.2	12.9	(8.6)*	(39)
Fe(III)	19.2	12.9	(6.6)*	(39)

Stability constants of complexes of metal ions with negatively charged oxygen donor ligands are usually[31] directly related to the acidity[9] of the metal ion (log $K_1(OH^-)$), so that for Al(III) (log $K_1(OH^-)$ = 9.1) stability of complexes with siderophores that have negatively charged oxygen donors will be considerably lower than for those of Fe(III) (log $K_1(OH^-)$ = 11.8). What is interesting about the CTA constants with Al(III) relative to Fe(III) is the much more rapid rate of fall off of log K_n with increasing *n* for Fe(III) than for Al(III). This may mean that the proposed bending of the metal ion out of the plane of the chelate ring as the metal ion becomes too large, as indicated in Figure 4, has more severe steric consequences for larger metal ions. Possibly coordination of Al(III) in the plane of the CTA ligand leads to less steric crowding than for Fe(III), where the chelate ring may be

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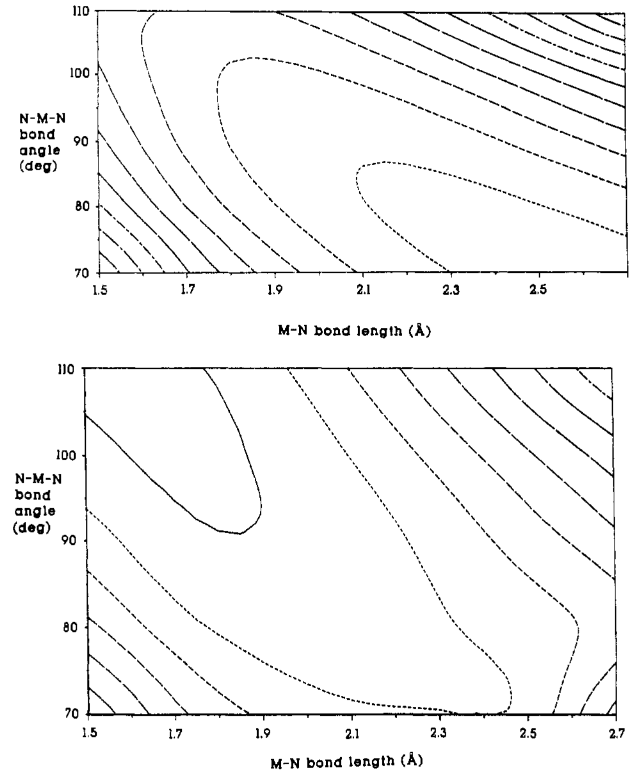


Figure 5. Strain energy surfaces for (A, top) the five-membered EN chelate ring and (B, bottom) the six-membered TN chelate ring, as a function of initial strain-free M–N bond length and N–M–N angle, calculated as described in the text. The contour lines indicate energies increasing in steps of 1 kcal·mol^{-1} from the lowest energy point at 0.5 (—), 1.5 (---), 2.5 (—) kcal·mol^{-1}, and so on.

buckled. This implies that enhanced selectivity for Al(III) over Fe(III) might be achieved with 1,8-dihydroxynaphthalene groups in place of catecholates in an enterobactin analogue of the type studied by Raymond et al.[27]

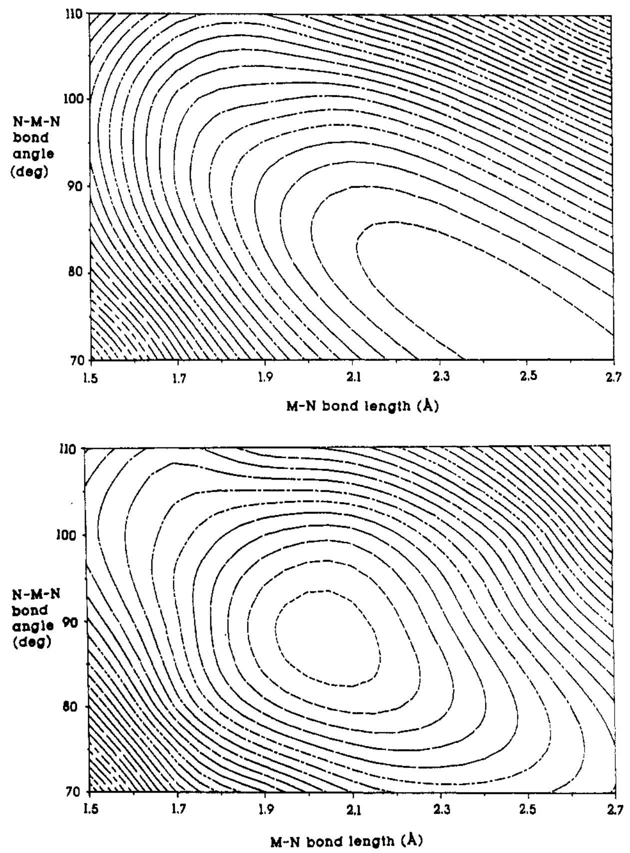


Figure 6. Strain energy surfaces for (A, top) $[M(2,2,2\text{-tet})]^{n+}$ and (B, bottom) $[M(2,3,2\text{-tet})]^{n+}$ complexes, as a function of initial strain-free M–N bond length and N–M–N angle, calculated as described in the text. The energies of the contour lines are as for Figure 5.

Table II. Energies Calculated by Molecular Mechanics for Alkali Metal Ion Complexes of 12-Crown-4 and 14-Crown-4[a]

	energy of complex[b]		
	12-crown-4[c]	14-crown-4[c]	ΔH(solv)[d]
Li$^+$	+41.7	-62.2	-133.5
Na$^+$	+61.4	-36.1	-106.1
K$^+$	+78.5	-13.6	-86.1
Li$^+$ - K$^+$	-36.8	-48.6	-47.4

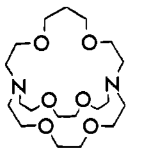
[a] Carried out with the force field of Kollman et al.[13] [b] Energies are kcal·mol^{-1}. [c] For identities of ligands, see Figure 1. [d] Heats of hydration of the alkali-metal ions.[32]

(2) MM Calculations on the Relationship of Metal Ion Size and Geometry, and Chelate Ring Size, to Complex Stability. In Figure 5 are seen the strain energy surfaces as a function of M–N bond length and N–M–N angle for chelate rings containing EN (five-membered) and TN (six-membered) chelate rings. As required by previous qualitative discussion,[4-8] the minimum in strain energy occurs for the five-membered chelate ring at a M–N length of 2.5 Å and N–M–N angle of 70°. For the six-membered chelate ring the minimum appears to be in the vicinity of a M–N length of 1.6 Å and a N–M–N angle of 100°. The strain energy surfaces in Figure 5 show that chelate ring size preference is a function of metal ion size. That the six-membered ring is the more stable in organic chemistry is a function of the fact that a "chelate ring" with a sp^3-hybridized carbon atom in place of a metal atom, as in cyclohexane, has a "metal atom" that is small in size. The minima in Figure 5A,B are fairly shallow, whereas the minima in the analogous potential energy surfaces calculated for 2,2,2-tet and 2,3,2-tet in Figure 6A,B are much steeper. This supports the idea that in multidentate ligands the extra chelate rings limit the ability of the metal ion to tilt out of the plane and so overcome steric problems associated with too-large metal ions coordinating to a six-membered chelate ring, for example. The strain energy surface for 2,3,2-tet shows a minimum at an M–N length of 2.03 Å and N–M–N angle of 88°; the minimum has not moved all the way to M–N = 1.6 Å and N–M–N = 109.5°, since the 2,3,2-tet ligand has still two five-membered chelate rings in its complexes, in addition to the central six-membered chelate ring. The strain energy minimum moves to an M–N distance of about 1.8 Å and an N–M–N angle of about 100° in the strain energy surface for 3,2,3-tet. The different positioning of such minima for different ligands may account for the differing extents of curvature of the relationships in diagrams such as Figures 2, 3, and 7–9. Different points on the strain energy surfaces in Figure 5 and 6 may be related directly to different metal ions, and one may read off the differences in strain energy at that point and compare them with the differences in free energies of complex formation:

	metal ion				
	Be(II)	Ni(II) (S = 0)	Ni(II) (S = 1)	Cd(II)	Pb(II)
M–N, Å	1.6	1.9	2.1	2.3	2.6
N–M–N, deg	109.5	90	90	90	70
$U_{2,3,2} - U_{2,2,2}$, kcal·mol^{-1}	-7	-3	-2	-0.5	+5
$\Delta G_{2,3,2} - \Delta G_{2,2,2}$, kcal·mol^{-1}		-5.2	-2.2	-0.8	+3.5

The MM calculations account well for the effect on complex stability of change of chelate ring size from five membered in 2,2,2-tet to six membered in 2,3,2-tet.

Calculations on the Li$^+$, Na$^+$, and K$^+$ complexes of 12-crown-4 and 14-crown-4 yield the energies shown in Table II. The energies of the 12-crown-4 and 14-crown-4 complexes in Table II show that the small Li$^+$ ion coordinates, relative to the large K$^+$ ion, much more strongly with 14-crown-4 than with 12-crown-4, in accordance with observation.[33] The MM calculations indicated that for all the alkali-metal ions the trans-I, or ++++,[10] conformer of the complexes with 12-crown-4 and 14-crown-4 was lowest in energy, except for the Li^+ complex with 14-crown-4, where the trans-III, or ++—, conformer was lowest. [The conformers of these crown ethers are the same as for the corresponding tetraazamacrocycles,[10] except that the lone pairs on the oxygens occupy the positions of the N–H hydrogens. The convention used in describing[10] these conformers indicates whether the hydrogens on the nitrogen donors of the complex lie above or below the plane of the macrocyclic ligand, indicated by a + or – respectively, in the ++++ or ++— conformers.] It must be emphasized that the hole size increases from 12-crown-4 to 14-crown-4 and that the observed fact[33] that ligands based on 14-crown-4 show stronger selectivity for the small Li^+ over the large K^+ than ligands based on 12-crown-4 is in accord with control of selectivity by chelate ring size rather than macrocyclic ring size. These calculations show that, even with a totally electrostatic representation of the M–O bond, the selectivity effects of the chelate ring are maintained through distortion of the ligand produced in the process of the metal ion drawing the oxygen donor atoms to the equilibrium M–O distance. One anticipates that the effect of five- and six-membered chelate rings on complex stability would hold generally for purely electrostatic bonding, although more weakly because of a lack of directionality in the M–O bonds. Ligands such as I are much weaker ligands for alkali-metal ions than is the normal cryptand-2,2,2 (II).[34] this leads to a rather different interpretation of the fact that crown ethers coordinate well only with large metal ions such as alkali-metal ions, Ca(II), Sr(II), Ba(II), Pb(II), and Hg(II). The neutral oxygen donor of crown ethers is unusual in that it is not a much better donor than water with which it competes in the process of complex formation. Crown ethers are thus more sensitive to steric effects on complex formation than are other more conventional ligands such as amines. Amines have in the neutral nitrogen donor, with many metal ions, a much stronger donor than water, so that steric effects are a relatively smaller contribution to the overall free energy of complex formation in these cases. *Crown ethers, even those with small cavities such as 12-crown-4, complex well only with large metal ions because the crown ethers form five-membered chelate rings on complex formation.* Where six-membered chelate rings are introduced, the affinity improves for small metal ions, in spite of the increase in macrocyclic ring size. It might be possible to design ligands containing neutral oxygen donors only that coordinate well to small metal ions by forming six-membered chelate rings, although extrapolation from formation constants[14] of all-nitrogen donor macrocycles such as 13-aneN_4 through 13-aneN_2O_2 suggests that stability of the Cu(II) complex of 13-crown-4 would be very low. Presumably the increase in steric strain[8] that occurs on complex formation (ΔU) would be large enough that even a complex such as $[Cu(13\text{-crown-}4)]^{2+}$ would be unstable in water. The value of ΔU for the formation of $[Cu(13\text{-ane}N_4)]^{2+}$ would be equally large, but the presence of Cu–N bonds leads to much greater complex stability in aqueous solution than the presence of Cu–O bonds to neutral oxygen, which outweighs and masks this unfavorable contribution (ΔU) to complex formation.



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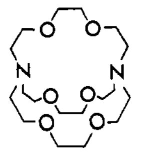

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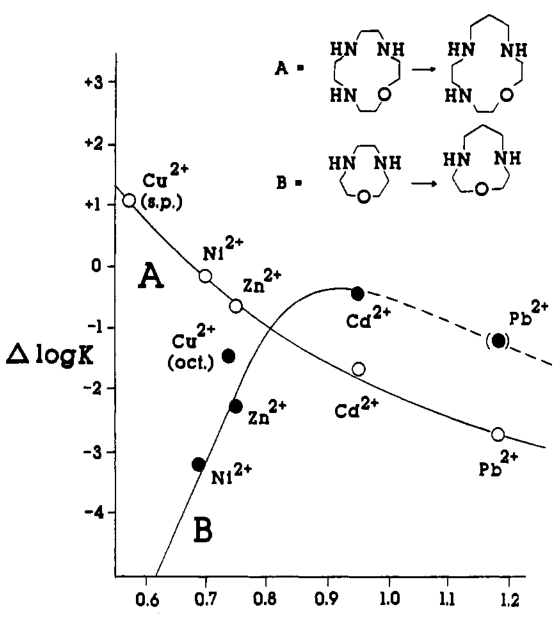

Figure 7. Relationship between the change in formation constant, $\Delta \log K$, which occurs on increase of chelate ring size from five membered to six membered, and the ionic radii[12] of the metal ions for (A) the pair of ligands 12-aneN_3O and 13-aneN_3O (○) and (B) for the pair of ligands 9-aneN_2O and 10-aneN_2O (●). The point for Pb(II) in (B) refers to 9-aneN_3 and 10-aneN_3 and so is shown in parentheses. Data are from ref 9 and this work.

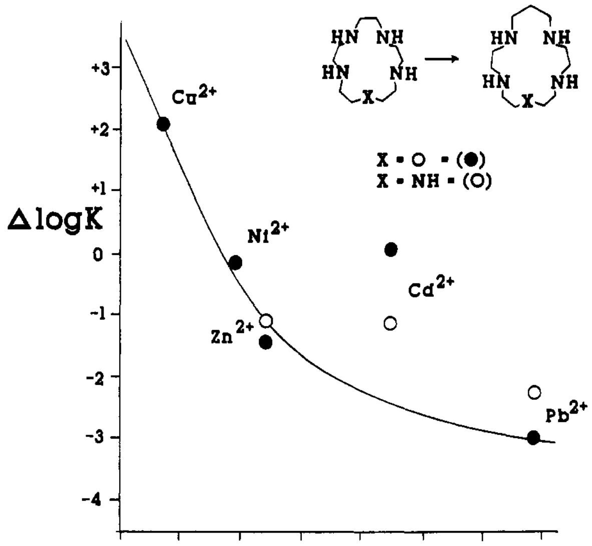

Figure 8. Relationship between the change in formation constant, $\Delta \log K$, which occurs on increase of chelate ring size from five membered to six membered, and the ionic radii[12] of the metal ions for the pairs of ligands 15-aneN_4O and 16-aneN_4O (●) and 15-aneN_5 and 16-aneN_5 (○). Data are from ref 9 and this work.

(3) Relative Importance of Chelate and Macrocyclic Ring Size in Controlling Metal Ion Size Selectivity as the Size of the Macrocyclic Ring Decreases. In Figure 7 $\Delta \log K$ for 9-aneN_2O/10-aneN_2O is plotted against ionic radius.[12] Also plotted in Figure 7 as having a typical slope for increase of ring size is the relationship for 12-aneN_3O/13-aneN_3O. The relationship for 9-aneN_3/10-aneN_3, although not shown, is very similar to that for 9-aneN_2O/10-aneN_2O, with a downturn in $\Delta \log K$ at small metal ion radii. The 9-aneN_2O/10-aneN_2O relationship is consistent with control of size-based selectivity for metal ions by the size of the macrocyclic ring rather than the chelate ring. Thus, the increase in chelate ring size from five (9-aneN_2O) to six (10-aneN_2O) would be expected to result in a steady increase in $\Delta \log K$ as ionic radius decreases, whereas a downturn occurs, consistent with the idea that the macrocyclic ring of 10-aneN_2O

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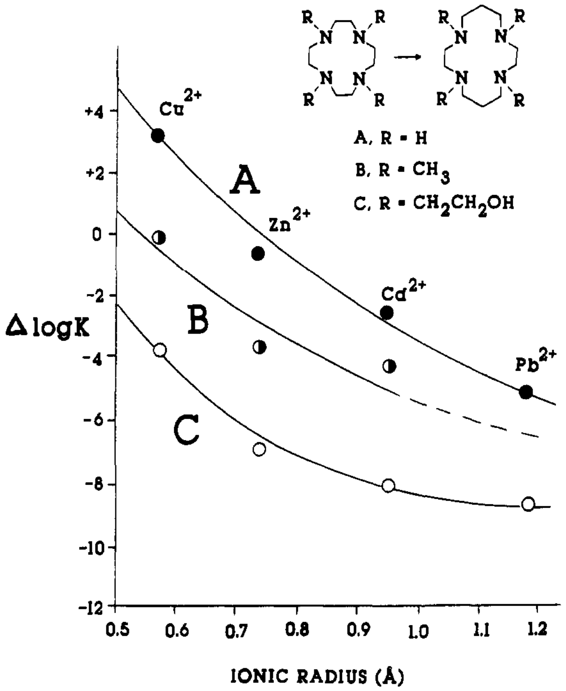

Figure 9. Relationship between the change in formation constant, Δ log *K*, which occurs on increase of chelate ring size from five membered to six membered, and the ionic radii[12] of the metal ions for (A) 12-aneN_4 and 14-ane_4 (R = H), (B) TM-cyclen and TMC (R = CH$_3$), and (C) THE-12-aneN$_4$ and THE-14-aneN$_4$ (R = $-$CH$_2$CH$_2$OH). Data are from ref 9 and this work.

has become too large for these small metal ions.

In Figure 8 is shown Δ log *K* for 16-aneN$_4$O/15-aneN$_4$O as a function of ionic radius. Also shown as open circles are some points for 16-aneN$_5$/15-aneN$_5$. The relationship shows the usual decrease in Δ log *K* as ionic radius increases, in accord with the idea that large metal ions form less stable complexes when six-membered chelate rings are formed. The only unusual feature on the diagram is the high Δ log *K* value for Cd(II) with 16-aneN$_4$O/15-aneN$_4$O. This effect is much less marked for 16-aneN$_5$/15-aneN$_5$. The Cd(II) ion occasionally shows[7] such aberrant behavior, which may relate to the presence of lower than six-coordination, with accompanying decrease in ionic radius. Such behavior for the Cd(II) ion is apparent for TIRON/CTA in Figure 2. One might also expect changes in coordination number to occur for other metal ions. This is found for Cu(II) in particular, which is usually taken to be square-planar, but its behavior is occasionally consistent with octahedral coordination where the ligands enforce higher coordination numbers. A good example of this is seen in Figure 7, where 9-aneN$_2$O is likely to enforce octahedral coordination to Cu(II).

(4) Effect of High Denticity and High Levels of Steric Crowding on the Size Selectivity Effects of Chelate Rings as a Function of Metal Ion Size. In Figure 9 is shown the plot of Δ log *K* versus ionic radius for 12-aneN$_4$/14-aneN$_4$, TM-cyclen/TMC, and THE-12-aneN$_4$/THE-14-aneN$_4$. Even with the high levels of steric crowding caused[35] by *N*-methyl groups, the dependence of metal ion selectivity on chelate ring size is strong, as is also the case with *N*-(2-hydroxyethyl) groups present. Although not shown in Figure 9, the DOTA/TETA relationship[6] is almost superimposable on that for TM-cyclen/TMC. Figure 9 shows that the control of metal ion size-based selectivity by chelate ring size extends even to fairly complex ligands, such as tetraazamacrocycles with *N*-methyl or *N*-(2-hydroxyethyl) substituents.

Conclusions

(1) The chelate ring is an important factor in controlling metal ion size-based selectivity of ligands, such that the selectivity of the ligand for larger over smaller metal ions is decreased by an increase in size of the chelate ring from five membered to six membered.

(2) In line with conclusion 1, molecular mechanics calculations indicate that the five-membered chelate ring of the ethylenediamine type has minimum strain energy when incorporating a metal ion with M–N bond length of 2.50 Å and N–M–N angle of 70°, i.e. a large metal ion of high coordination number. The six-membered chelate ring of the 1,3-diaminopropane type is at a minimum strain energy with a metal ion of M–N bond length of 1.6 Å and N–M–N angle of 109.5°, i.e. a small tetrahedral metal ion.

(3) The selectivity of ligands for metal ions based on their sizes appears to be weak for flexible bidentate ligands forming a single chelate ring, such as oxalate and malonate. This selectivity is sharpened by making the chelate ring rigid, as when a benzo group is fused to the chelate ring or the ability of the metal ion to rotate out of the plane of the chelate ring is reduced by incorporating the chelate ring into a polydentate ligand.

(4) The macrocyclic ring is more flexible than the chelate ring, so that the effects of chelate ring size on metal ion size-based selectivity usually dominate those of macrocyclic ring size, in line with conclusion 1 above. However, with sufficiently small macrocyclic rings, such as tridentate 9-aneN$_3$ type macrocycles, the macrocyclic ring is rigid enough to compete with the chelate ring, and selectivity may then be controlled by macrocyclic ring size. Larger macrocyclic rings may be made more rigid by structural reinforcement,[35] which may lead to size selectivity controlled by the macrocyclic rather than the chelate ring.

(5) The effect of chelate ring size in controlling metal ion size-based selectivity persists even in complex and bulky ligands such as tetraazamacrocycles with N-substituents such as *N*-methyl, *N*-(2-hydroxyethyl), and *N*-acetate.

Acknowledgment. We thank the University of the Witwatersrand and the Foundation for Research Development for generous support for this work.

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