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Chelate ring geometry, and the metal ion selectivity of macrocyclic ligands. Some recent developments

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Chelate ring geometry, and the metal ion selectivity of macrocyclic ligands. Some recent developments

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The idea (Hancock, 1992) that the dominant architectural feature in controlling metal ion selectivity in both open-chain and macrocyclic ligands is the size of the chelate ring is pursued further. It is shown that when more than one or two six-membered chelate rings are present in the complex of a nitrogen donor macrocycle, the steric requirements of the six-membered chelate ring of a M-N bond length of 1.6 Å and N-M-N angle of 109.5° become particularly severe, and can only be met by a small tetrahedral metal ion. Thus, the ligand 16-aneN$_4$ (1,5,9,13-tetraazacyclohexadecane) forms complexes of low stability with all metal ions studied to date, but a conformer of 16-aneN$_4$ is identified by MM calculation which is predicted to form complexes of high stability with very small tetrahedral metal ions. The question of the M-O bond length and O-M-O angles that will produce minimum strain in chelate rings containing neutral oxygen donor is addressed. The observation (Hay, 1993) that the geometry around an ethereal oxygen coordinated to a metal ion approximates to trigonal planar rather than tetrahedral leads to ideal M-O-C angles of about 126°, which leads to minimum strain energy with much longer M-L lengths in chelate rings containing neutral oxygen donors than neutral nitrogen donors. It is suggested that this fact accounts for the general tendency of crown ethers to form their most stable complexes with potassium out of the alkali metal ions, and also accounts for the very small macrocyclic effect observed in complexes of macrocycles containing mixed nitrogen and oxygen donor groups. The preferred geometry of four-membered chelate rings is discussed, and it is shown that higher coordination numbers of metal ions are associated with four membered chelate rings, and that four membered chelate rings may be used to engineer preference for larger metal ions. Very rigid reinforced chelate rings are discussed, and it is shown that open-chain ligands with reinforced bridges between the donor atoms can display all the thermodynamic and kinetic aspects associated with macrocyclic ligands.

INTRODUCTION

The first indication that chelate ring size might be important in metal ion selectivity was obtained from an analysis of the formation constants of tetraaza macrocycles[1]. Since then, this idea has been extended to many ligand types, both macrocyclic and non-macrocyclic[2–7], and has led to a rule of ligand design: "*increase of chelate ring size leads to an increase in selectivity of a ligand for smaller relative to larger metal ions*". An example of the effect of chelate ring size on metal ion selectivity is seen in Figure 1, where the change in stability for complexes of the macrocycle py-12-aneN$_4$ relative to py-14-aneN$_4$ (see Figure 2 for key to ligand abbreviations) is plotted as a function of metal ion radius[8]. This type of correlation is obtained for many ligand pairs where one ligand forms a chelate ring which is six-membered, where in its otherwise identical analogue there is formed a five-membered chelate ring in the same position. Since the effect of chelate ring size on

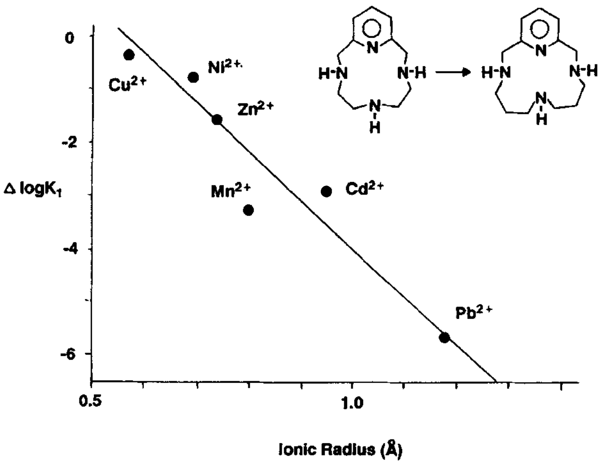

Figure 1 The change in complex stability (ΔlogK) on increase of chelate ring size from five membered in py-12-aneN$_4$ to six membered in py-14-aneN$_4$, as a function of metal ion radius. Formation constants from Costa, J.; Delgado, R. *Inorg. Chem.* **1993**, *32*, 5257. Ionic radii (Å) from reference 8.

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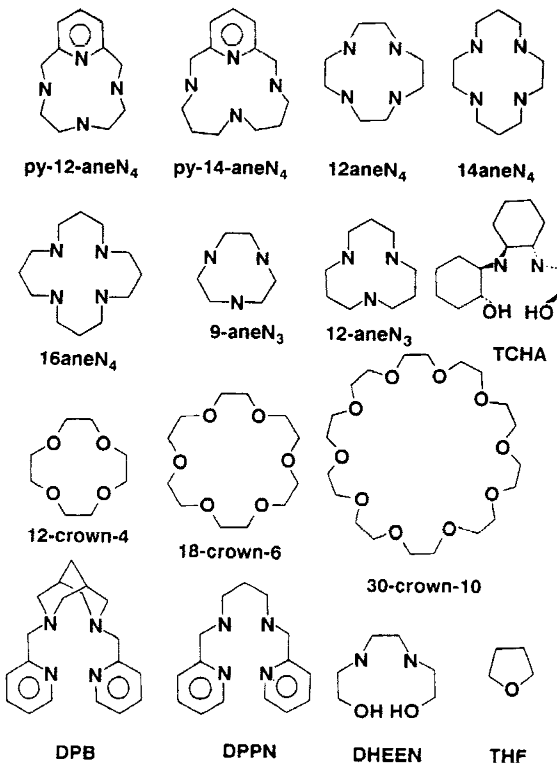


Figure 2 Ligands discussed in this paper.

metal ion selectivity has been discussed in some detail previously[1-7], the general aspects of this idea will not be covered in detail here. Rather, some recent developments will be discussed as they relate to progress in this general area.

A. Low strain energy conformers of 16-aneN$_4$ and 12-aneN$_3$

The first problem to be discussed in relation to the above idea is the fact that the effect of changing a chelate ring from five membered to six membered has an unpredictable effect[3] after one or two chelate rings have been so increased in size. In the series of tetraaza macrocycles 12-aneN$_4$ through 16-aneN$_4$, the progressive increase of size of chelate rings from five membered to six-membered has the expected effect on complex stability[9] (logK$_1$) for a large[8] metal ion such as Pb^{2+} (Table 1). However, for the small Cu^{2+} ion there is an initial rapid rise in logK$_1$ from 12-aneN$_4$ to 14-aneN$_4$, (Table 1), followed by a rapid drop in logK$_1$ from 14-aneN$_4$ to 16-aneN$_4$. In Figure 3 is shown the best fit size and geometry of metal ions for coordinating with representative chelate rings of size five and six, obtained[10] by Molecular Mechanics (MM) calculation for chelate rings of ethylenediamine (EN) and 1,3-propanediamine (TN). What is seen is that, in addition to the requirements of M-N bond length, there are N-M-N bond angle requirements that must be met for coordinating to these rings. What has become apparent is that the bond angle requirements for the six-membered ring become particularly severe when more than one or two six-membered chelate rings are present. This is illustrated by MM calculations[11] using the program SYBYL[12] on macrocycles such as 9-aneN$_3$ compared to 12-aneN$_3$, and the set of macrocycles 12-aneN$_4$, 14-aneN$_4$, and 16-aneN$_4$.

In their classic paper on hole sizes in tetraaza macrocycles, Busch and coworkers[13] studied only conformers of the macrocycles consistent with square planar coordination. Under these constraints, Busch *et al.*[13] calculated by MM the best fit M-N lengths seen in Table 1. These calculations show a steadily increasing best-fit M-N length with increasing macrocyclic ring size. We have considered whether coordination geometries other than square planar might not reveal other conformers of 16-aneN$_4$ which are of low strain energy, and should lead to complexes of high stability, unlike the situation of the square planar Cu(II) complex of 16-aneN$_4$ in Table 1. We discovered by MM calculation the conformer of 16-aneN$_4$ complex shown in Fig. 4. It consists of four chair-form chelate rings centered on a small tetrahedral metal ion of M-N bond length 1.81 Å. Only small tetrahedral metal ions such as Be(II), or B(III) would be small enough to comply with the size and geometry requirements of 16-aneN$_4$. Figure 4 shows the minimum strain energy conformers of 12-aneN$_4$ (++++ conformer), 14-aneN$_4$ (++-- conformer with square planar metal ion) and 16-aneN$_4$ (+-+- conformer with tetrahedral metal ion). No structure of a small tetrahedral metal ion with 16-aneN$_4$ is known, but it is predicted that such a complex will have the conformer seen in Figure 4. What is apparent here is that the low stability of complexes with 16-aneN$_4$ with all metal ions studied to date arises because they are too large, and the wrong geometry for coordinating to 16-aneN$_4$.

Table 1 Formation constants of tetraza macrocyclic ligands with a small, intermediate, and large metal ion to show the relation between metal ion size and macrocyclic ring size[a]

ionic radius of metal ion (Å)[b]		*12-aneN$_4$*	*13-aneN$_4$*	*14-aneN$_4$*	*15-aneN$_4$*	*16-aneN$_4$*
best-fit M-N length (Å)[13]:		1.82	1.92	2.07	2.22	2.38
logK$_1$ Cu(II):	0.57	23.3	24.4	27.2	24.4	21.6
logK$_1$ Zn(II):	0.74	16.1	15.6	15.5	15.0	13.1
logK$_1$ Pb(II):	1.18	15.9	13.5	10.8	10.5	9.3

[a]Best fit lengths from reference 13, logK$_1$ values from reference 9. [b]Ionic radii from reference 8.

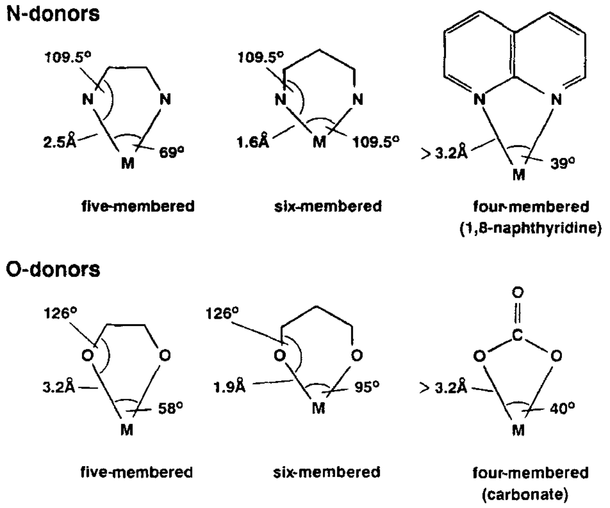


Figure 3 Metal ion M-L lengths and L-M-L angles that produce minimum strain energy for coordination in chelate rings of different sizes. a) the five membered chelate ring of ethylenediamine b) the six membered chelate ring of 1,3-diaminopropane c) the five membered ring of ethylene glycol and d) the six membered chelate ring of 1,3-dihydroxypropane. Also shown is the four membered chelate ring of e) carbonate compared with f) the five membered chelate ring of oxalate. The minimum strain energy geometries from reference 10, or calculated using SYBYL[12].

The best-fit size and geometry of metal ion for coordinating in 9-aneN$_3$, as determined by MM calculation, is seen in Figure 5. This is the R,R,R conformer of 9-aneN$_3$, which is the only type observed[14] in crystal structures of 9-aneN$_3$ complexes. For 12-aneN$_3$, the conformer observed[15] (Fig. 5) with Zn(II) is the *ch,ch,bt* (*ch* = chair, *bt* = boat) conformer. The Zn ions in these complexes have regular tetrahedral coordination geometry, with a bromide[15a] or hydroxide[15b] ion occupying the fourth coordination site. Molecular mechanics calculations[11] show that for a tetrahedral metal ion, the most stable conformer of 12-aneN$_3$ complex, the *ch,ch,ch* (---) conformer, is of lowest energy at short M-N lengths, of less than about 2.1 Å. (The --- indicates that the N-H hydrogens are on the opposite side of the plane of the three nitrogen donor atoms to the metal ion.) Above this

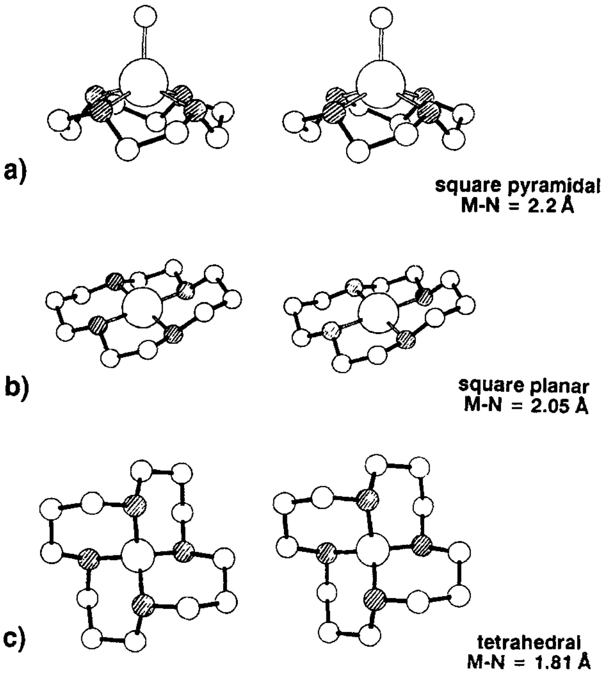


Figure 4 Minimum strain energy conformers as indicated by molecular mechanics calculation[10], a) the ++++ conformer of [M(12-aneN$_4$)]$^{n+}$ b) the ++-- conformer of [M(14-aneN$_4$)]$^{n+}$ c) the +-+- conformer of [M(16-aneN$_4$)]$^{n+}$.

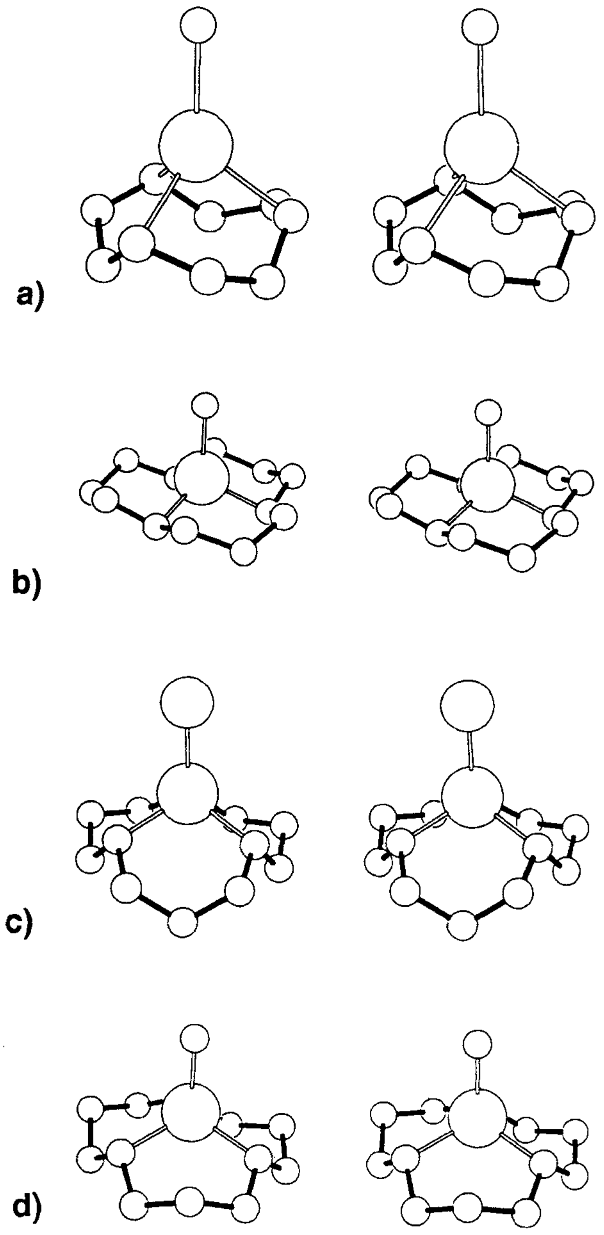


Figure 5 Minimum strain energy conformers as indicated by molecular mechanics calculation[10], a) [M(9-aneN$_3$)]$^{n+}$ and b) the --- (*ch,ch,ch*) conformer of [M(12-aneN$_3$)]$^{n+}$. Also shown is c) the +++(*ch,ch,bt*) conformer of [M(12-aneN$_3$)]$^{n+}$ observed for a Zn(II) complex, and d) the higher energy +++(*ch,ch,ch*) conformer of [M(12-aneN$_3$)]$^{n+}$.

length the *ch,ch,bt* conformer is of lower strain energy, with a tetrahedral metal ion. The *ch,ch,ch* (+++) conformer is of higher energy than the *ch,ch,bt* conformer at all M-N lengths, and so will probably not be observed. These observations are summarized for tetrahedral metal ions in Figure 6, where the strain energy, ΣU, for each conformer is plotted as a function of M-N bond length. This type of calculation has been described in detail elsewhere[10]. What Fig. 6 shows is that the *ch,ch,ch* (---) conformer is of low energy only for very small tetrahedral metal ions. This low energy conformer cannot form the basis of effective ligands with pendent donor groups on the nitrogens, since the donor groups would be on the opposite side of the ligand to the metal ion. Rather, the higher energy *ch,ch,ch* (+++) or *ch,ch,bt* conformer would be present in pendent donor ligands based on 12-aneN_3, and it is seen in Figure 6 that these conformers are of high strain energy at all M-N lengths. An important aspect of 12-aneN_3 and 16-aneN_4 chemistry is that complexes of very low strain energy can only be formed with very small tetrahedral metal ions.

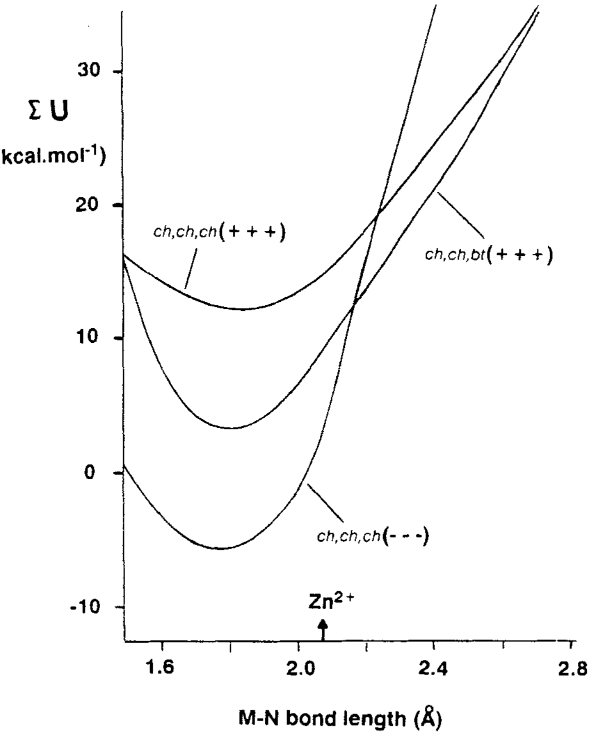


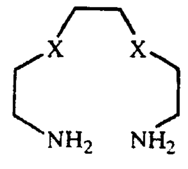
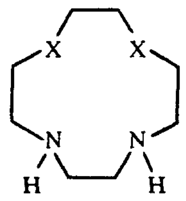
Figure 6 Strain energy of 12-aneN_3 complexes as a function of strain-free M-N length, calculated as described previously[10]. The metal ions have tetrahedral coordination geometry for all of the calculations. The calculations show that the --- (*ch,ch,ch*) conformer is most stable only for very small tetrahedral metal ions, whereas the +++(*ch,ch,bt*) conformer is more stable at M-N lengths above 2.1 Å. The +++(*ch,ch,ch*) conformer appears to be at higher energy than the +++(*ch,ch,bt*) at all M-N lengths, and is thus unlikely to be observed. The +++(*ch,ch,bt*) conformer is that found in the crystal structure[18] of tetrahedrally coordinated [Zn(12-aneN_3)Br]$^+$.

B. The macrocyclic effect in complexes of macrocycles with nitrogen and oxygen donors, and mixed nitrogen and oxygen donors

A puzzling feature of the chemistry of macrocycles with mixed oxygen and nitrogen donors[16] is that the macrocyclic effect is much smaller for the mixed donor macrocycles, as seen in Table 2, than for all nitrogen or all oxygen donor analogues. This is difficult to understand, as in the example given, the ethylene bridge added to both open-chain ligands to produce the macrocycle is being added across two nitrogen donors. How could the oxygen donors, which are remote from the site of addition, act to reduce the size of the macrocyclic effect? An answer to this puzzle comes from the important observation by Hay *et al.*[17] that the geometry around the ethereal oxygen donor when coordinated to a large metal ion is trigonal planar rather than tetrahedral, as might be expected from a VSEPR (valence shell electron pair repulsion) type of analysis. This observation is largely supported by some 700 structures of THF complexes of metal ions found in the Cambridge Crystallographic Data Base. The structure of a Li$^+$ complex of THF[18] is shown in Fig 7. In general, the M-O-C angle in THF complexes is about 126°, as compared with the approximately 109.5° for the M-N-C angle in complexes with amines. This means that the steric situation involved in coordinating an ethereal oxygen to a metal ion in a trigonal planar fashion is very different from that in coordinating a saturated nitrogen to a metal ion in a tetrahedral fashion. It seems very likely, and this is currently the subject of a MM investigation, that these differences in preferred geometry of coordination to the metal ion, account for the much smaller size of the macrocyclic effect in complexes with mixed nitrogen and oxygen donors, compared to macrocycles with nitrogen donors only, seen in Table 2.

A further important point is the metal ion selectivities of crown ethers. It has already been pointed out[19] that the

Table 2 The macrocyclic effect in complexes of all-nitrogen donor, and mixed nitrogen-oxygen donor analogues[a]

			Δlog K (macrocyclic effect)
$\log K_1$ Cu(II),			
X = NH	20.1	23.3	3.1
X = O	7.9	8.7	0.8
$\log K_1$ Cd(II),			
X = NH	10.6	14.3	3.7
X = O	5.7	6.6[b]	0.9

[a] From references 9 and 16. [b] Actually for the 1,7 rather than the 1,4 dioxo macrocycle, but this should have only a small effect on $\log K_1$.

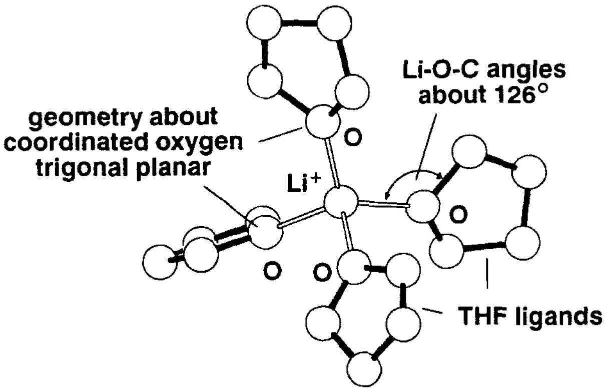


Figure 7 The THF complex of Li^+, redrawn using coordinates in reference 18. Hydrogens have been omitted for clarity. The structure shows the trigonal planar geometry of the coordinated ether oxygen of THF.

best-fit hole-size model for crown ethers does not account for patterns of selectivity found for crown ethers with, for example, alkali metal ions. One might in fact summarize the selectivity patterns of crown ethers with alkali metal ions by saying that crown ethers prefer potassium. Thus, the best-fit model for alkali metal ion selectivity suggests that smaller cavity macrocycles such as 12-crown-4 should complex better with the small Li^+ ion, while very large metal ions such as Cs^+ should complex better with the very large cavity 30-crown-10. In fact, the potassium ion tends to complex better than other alkali metal ions with crown ethers of all ring sizes[20,21]. This could be rationalized[7] in terms of the idea that the chelate rings of virtually all crown ethers are five membered, and the potassium ion is the best fit size for complexing with these chelate rings. However, if the geometry of the five membered chelate ring containing neutral oxygen donors are essentially identical to that containing the saturated nitrogen donor, then the best-fit M-O length for coordinating as part of a typical chelate ring in a crown ether (Figure 3) should be 2.5 Å. This is considerably shorter than typical K-O bond lengths of about 2.9 Å found[22] in the 18-crown-6 complex of K^+. However, if the M-O-C angle is typically about 126°, then the metal ion size requirements of the five-membered chelate ring are going to be rather different from the metal ion size requirements of the five-membered chelate ring containing saturated nitrogen donors. The M-O lengths and O-M-O angles that lead to minimum strain energy in chelate rings containing neutral oxygen donors, obtained by MM calculation, are shown in Figure 3. It is seen that the five membered chelate ring containing neutral oxygen donors is of lowest strain energy with metal ions of M-O length about 3.2 Å. This is somewhat longer than the typical K-O bond length of 2.9 Å. Why complex stability of crown ether complexes is usually at a maximum at K^+ probably derives[23] generally from a balance between steric and M-O bond strength effects. Thus, M-O bond strengths in the gas phase will decrease $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$, and in the absence of steric effects this would be the order of decreasing complex stability. The steric strain that arises from a mismatch in M-O bond length and the requirements of the five-membered chelate ring containing neutral oxygen donors falls off rapidly as the M-O length approaches the required length of 3.2 Å. It seems likely that the peak in complex stability at K^+ with most crown ethers reflects a balance between M-O bond strength and steric strain, such that the order of bond strength $K^+ > Rb^+ > Cs^+$ is not offset by the steric strain arising from the fact that Cs^+ represents a somewhat better fit in the five-membered chelate ring than does K^+.

C. Four membered Chelate Rings

The metal ion size and geometry requirements for coordination as part of four membered chelate rings have not been considered until recently[23(b)]. As seen in Figure 3, the four-membered chelate rings of carbonate and 1,8-naphthyridine require[23(b)] extremely large metal ions. The best-fit M-L lengths shown are merely the longest recognised M-L bonds known, of about 3.2 Å, since, in fact, the M-N bonds of naphthyridine should be parallel, so that only an infinitely large metal ion could coordinate in a totally strain-free fashion with this ligand. The trend outlined above, that six-membered rings require very small tetrahedral metal ions for strain-free coordination, and five membered chelate rings require much larger metal ions of high coordination number to give the smaller L-M-L angles required, is continued for four-membered chelate rings. Four-membered chelate rings will require even larger metal ions of higher coordination number. It is thus no accident that all examples of twelve coordination, such as $[Ce(NO_3)_6]^{2-}$ and $[Pr(1,8\text{-naphthyridine})_6]^{3+}$ involve[24] ligands that form four-membered chelate rings. This is in line with the suggestion[19] that chelate ring size is a major factor in controlling coordination numbers in metal ions with variable coordination numbers. Thus, six-membered chelate rings will cause metal ions to adopt the lower of their accessible coordination numbers, while five, and even more so four-membered chelate rings, will cause the metal ion to adopt the higher of its accessible coordination numbers.

The tendency of four-membered chelate rings to favor coordination with larger metal ions appears to be of importance in biology in producing selectivity for the large Ca^{2+} ion (ionic radius 1.0 Å) over the small Mg^{2+} ion (ionic radius 0.72 Å). Thus, calcium-selective proteins such as parvalbumin coordinate[25] (Figure 8) to the Ca^{2+} through several carbonyl oxygens from peptide linkages, and two carboxylate groups oriented so as to

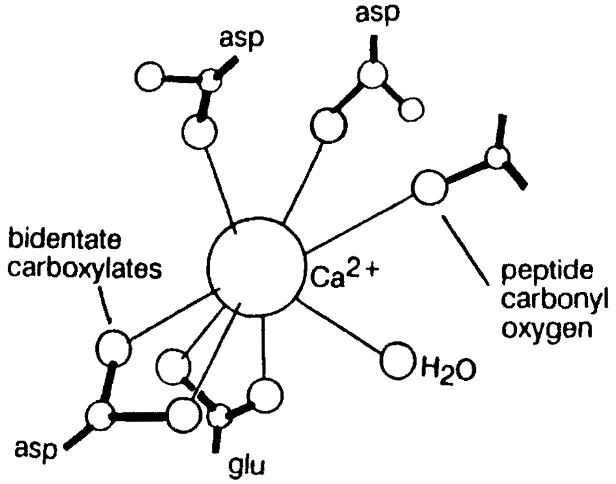
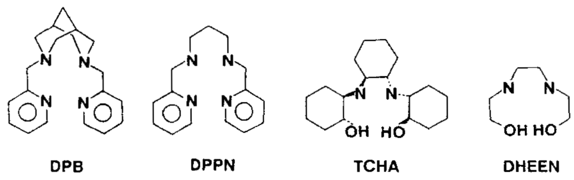


Figure 8 Drawing of the coordination geometry around the Ca^{2+} ion in parvalbumin[25], showing the coordination of amide oxygens, and bidentate carboxylates to form symmetrical four membered chelate rings. (By symmetrical here is meant that the Ca-O distances to the two oxygens of the carboxylate are the same). Both neutral oxygen donors and four membered chelate rings promote selectivity for a large metal ion such as Ca^{2+} over a small metal ion such as Mg^{2+}. asp = aspartate, glu = glutamate.



	DPB	DPPN	TCHA	DHEEN
pK$_1$:	13.1	8.3	11.1	9.2
logK$_1$ Cu(II):	23.0	18.4	12.0	9.7

Figure 9 The structurally reinforced ligands DPB and TCHA, with their non reinforced analogues DPPN and DHEEN. Also shown are the first protonation constants for the ligands, and their logK$_1$ values with Cu(II), showing how reinforcement leads to complexes of considerably greater stability.

favor formation of four-membered chelate rings. Both factors used in parvalbumin to produce selectivity for Ca^{2+} over Mg^{2+}, namely use of neutral oxygen donors, and four-membered chelate rings, are factors identified here and elsewhere[1,19] as being those which will favor complexation of large metal ions over small.

D. Very Rigid Chelate Rings

The flexibility of chelate rings involving saturated nitrogen or oxygen donors means that the size selectivity is not as sharp as might be expected from the geometric requirements of these chelate rings, since metal ions of the 'incorrect' size and coordination geometry are partially accommodated by the ability of the ligand to distort its torsion angles without too great a steric penalty. Thus, the five-membered chelate rings of EN with small metal ions have N-C-C-N torsion angles flattened[26] below the minimum strain value of 60°, to, for example, 54° in $[Co(EN)_3]^{3+}$. Such flexibility can be limited by making bridges between donor atoms much more rigid[27,28], by *reinforcement* of the bridge. Examples of reinforced ligands are seen in Figure 9. The ligands DPB and TCHA both show all of the effects on thermodynamics and kinetics of metallation associated with the *macrocyclic effect*[29], namely slow rates of metallation and demetallation, and much higher complex stability than found for the non-reinforced analogues DPPN and DHEEN shown in Figure 9. In addition, as would be expected from the greater rigidity, the selectivity based on metal ion size is much sharper than found for the non-reinforced analogues. Thus, DPB has effectively two six-membered chelate rings sharing common nitrogen donro atoms, and associated with this it is found that it forms no complex with the very large Pb^{2+} ion up to the point of precipitation of the hydroxide. The structure[30] of the Cu^{2+} complex of TCHA is shown in Figure 10. A requirement of ligands for use as imaging agents in biomedical applications[31] is that rates of demetallation and loss of the generally toxic metal ions in the body should be slow, and in this regard reinforced ligands, particularly reinforced macrocycles where rates of demetallation are many orders of magnitude slower than unreinforced analogues, may have a future role to play.

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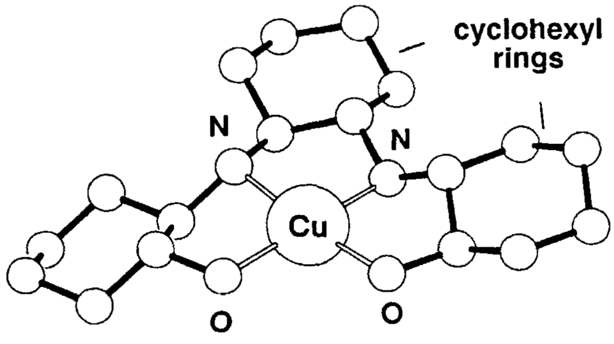

Figure 10 Crystal structure[29] of the complex of Cu(II) with the structurally reinforced ligand DHCA.

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