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Coordination Chemistry Reviews
148 (1996) 315–347

COORDINATION CHEMISTRY REVIEWS

# Macrocyclic ligands with pendent amide and alcoholic oxygen donor groups

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Received 22 February 1995

**Contents**



**Abstract**

Bonding of the neutral oxygen donor to metal ions is discussed in relation to metal ion selectivity. Important factors are (a) inductive effects of alkyl groups attached to the oxygen donor atom, so that donor strength increases $H_2O < ROH < R_2O$, where R is an alkyl group, including ethylene or other alkyl groups forming bridges between donor atoms of multidentate ligands, and (b) size of the chelate ring formed, such that large metal ions achieve minimum strain energy when coordinated as part of five-membered chelate rings, while six-membered chelate rings favor small metal ions. Metal ions coordinate to alcohols or ethers lying in the same plane as the oxygen donor atom, and the two carbon or hydrogen atoms attached to the oxygen donor atom. This is discussed in terms of how the planarity of coordination about the oxygen donor atom alters selectivity patterns relative to neutral nitrogen donor atoms, where the geometry around the nitrogen coordinated to a metal ion is approximately tetrahedral.

Addition of neutral oxygen donors as pendent alcoholic (2-hydroxyethyl and 2-hydroxypropyl) groups, or as amide (acetamide) groups, leads to changes in selectivity

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*SSDI* 0010-8545(95)01190-0

for metal ions that are as expected from arguments in terms of chelate ring size, and the donor strength of the alcoholic or amide oxygen. Thus, ligands based on cyclen (1,4,7,10-tetraazacyclododecane) with alcoholic and amide oxygen donor groups show large shifts in selectivity in favor of large metal ions such as Ca(II), Cd(II), or Pb(II). The potential of such ligands in treating Cd or Pb toxicity is discussed. The effect of addition of C-alkyl groups to the ethylene bridges of oxygen donor ligands is shown to produce shifts in selectivity in favor of small metal ions. This effect is particularly marked in novel ligands that contain cyclohexenyl bridges in place of ethylene bridges between the donor atoms. Such ligands are of potential interest in biomedical applications.

*Keywords:* Metal-ion selectivity; Multidentate ligand; Neutral oxygen donor; Oxygen donor group; Pendant donor ligand

## 1. Introduction

The neutral oxygen donor has become of great interest [1], firstly because it is the donor atom of the most important solvent, water, and secondly because it is a donor atom in the crown ethers [2] and cryptands [3], which have proved so important in the chemistry of the alkali and alkaline-earth metal ions. Macrocyclic chemistry as it pertains to the complexation of metal ions has now entered a mature phase, where the feeling is that the basics of the field are well understood. A point that will be made in this review is that this feeling is probably premature, but the emphasis now is certainly on applications of macrocyclic ligands.

One of the most important areas of macrocyclic chemistry is presently in biomedical applications. Areas that are covered are Gd(III) complexes [4] in magnetic resonance imaging (MRI), and complexes of metal ions such as $^{111}$In and $^{99m}$Tc in radiography [5,6], as well as $^{68}$Ga in positron emission tomography (PET) [7]. Long-neglected metal ions such as Bi(III) are now of medical interest in applications such as the use of the subsalicylate to kill the bacterium *H. pylori*, a cause of gastric and duodenal ulcers [8]. The $^{212}$Bi isotope is of potential interest in cancer therapy [9] when attached via a bifunctional ligand to a monoclonal antibody which is selective for cancerous cells. There are many exciting new developments, such as the development of Mn(II) pentaaza macrocyclic complexes as superoxide dismutase mimics to prevent damage from free radicals in cases of heart attacks, where restoration of circulation to areas starved of oxygen leads to a damaging burst of free-radical formation [10].

There has been a tendency to view the neutral oxygen donor as a weak donor that forms essentially electrostatic bonds, and to believe that there is probably no difference between the bond formed to the solvent water and that formed to the ethereal oxygens of a crown ether, for example. Fig. 1 shows the enthalpies of complex formation in the gas phase of $Li^+$ complexes with a variety of ligands [11,12]. It is evident that in the gas phase the order of complex stability is $H_2O < CH_3OH < (CH_3)_2O$, which is the order of the increasing inductive effect of the methyl groups. A similar inductive effect order of $NH_3 < CH_3NH_2 < (CH_3)_2NH < (CH_3)_3N$ is observed [12] for $Li^+$.

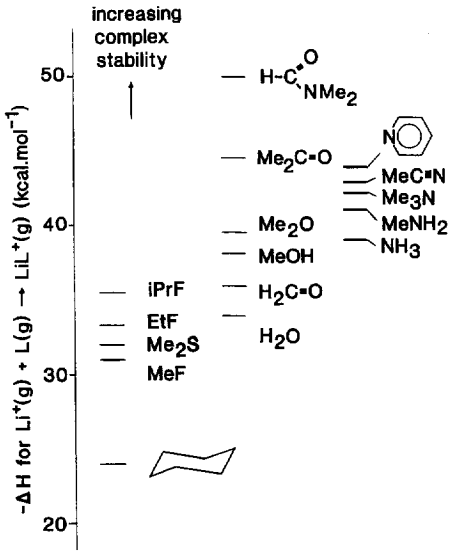



Fig. 1. Enthalpies of complex formation of $Li^+$ complexes in the gas phase. Data from Ref. [12].

One might expect from the inductive-effect order that all metal ions in aqueous solution would form stronger complexes with ethers than water itself, but this is not the case. Examination of the selectivity patterns shows that, in general, what determines the stability of complexes formed by metal ions with ligands containing neutral oxygen donors is metal ion size [13]. One should state at once, however, that this is not the popular *size-match selectivity* idea that is repeated over and over in textbooks, even though there is little evidence to support it. (By "size match selectivity" is meant that the most stable complex will be formed when the match between the size of the cavity in the macrocycle and the radius of the metal ion is closest). The metal ions that complex well with crown ethers such as 18-crown-6 (see Fig. 2 for key to ligand abbreviations) all have an ionic radius ($r^+$) [13] in excess of 1.0 Å. This is the key to understanding the metal-ion selectivity of crown ethers. The only things common to metal ions that complex well with crown ethers are an $r^+$ above 1.0 Å and a cationic charge of two or less. The metal ions that generally complex well with crown ethers are shown in Table 1.

This observation is a natural consequence of the ligand design rule proposed [13] for neutral oxygen donor groups: *the addition of neutral-oxygen-donor-containing groups to a ligand will increase the selectivity of the ligand for large metal ions relative*

Table 1
Octahedral $r^+$ [14] in ångströms in parentheses

| | | | | |
|---|---|---|---|---|
| $Na^+$ (1.00) | $K^+$ (1.38) | $Rb^+$ (1.52) | $Cs^+$ (1.67) | (large alkali metal ions) |
| $Ca^{2+}$ (1.00) | $Sr^{2+}$ (1.18) | $Ba^{2+}$ (1.35) | | (large alkali earth metal ions) |
| $Tl^+$ (1.50) | $Pb^{2+}$ (1.19) | $Ag^+$ (1.15) | $Hg^{2+}$ (1.02) | (large post-transition metal ions) |

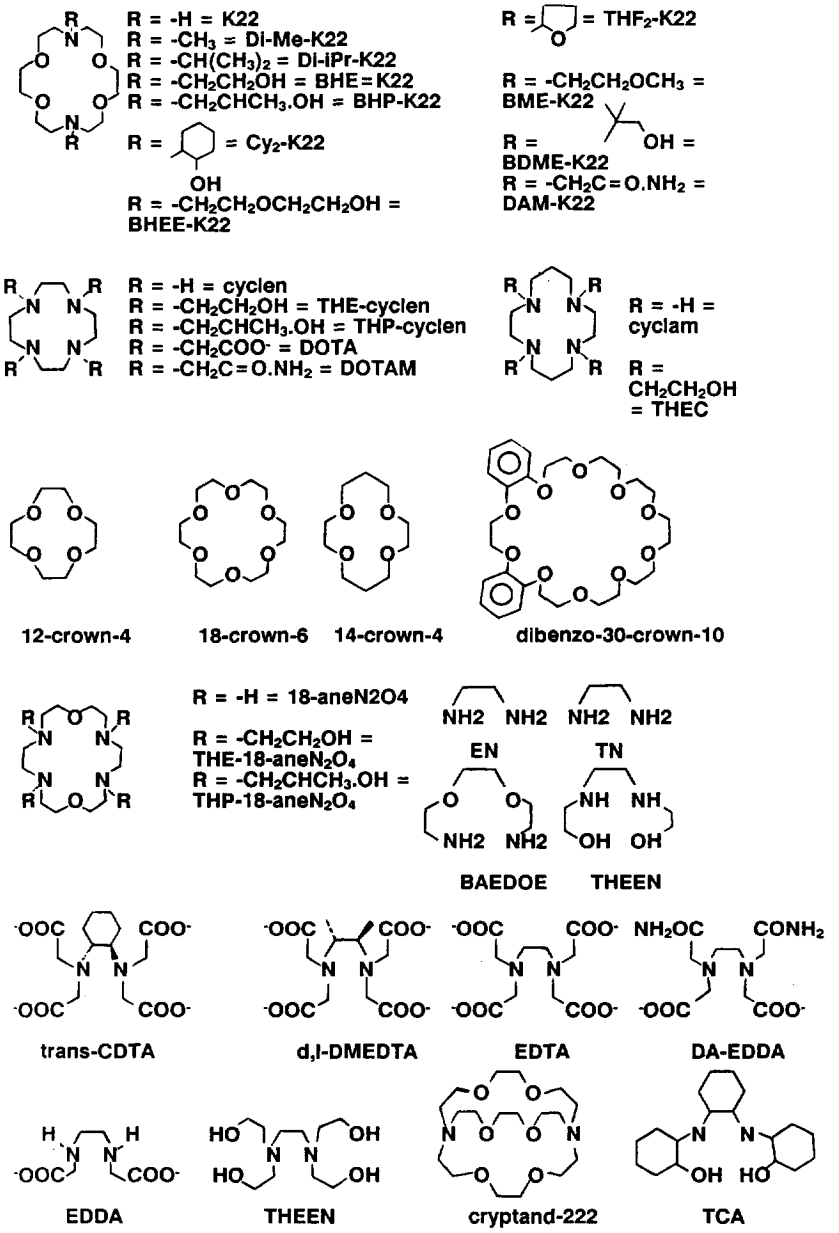



Fig. 2. Ligands discussed in this review.

*to small metal ions.* Crown ethers are merely the ultimate expression of the above rule, in that they are ligands that have no donor atoms other than neutral oxygen donors, and so complex well only with very large metal ions.

The rule regarding neutral oxygen donors and metal-ion-size-based selectivity holds [13] with considerable accuracy. Thus, in Fig. 3 are shown plots of change in complex stability ($\Delta$ log $K$) as a function of metal ion radius [14] on addition of neutral oxygen donor groups to a variety of ligands. Thus, four 2-hydroxyethyl groups are added to EN to give THEEN, two acetamide groups are added to EDDA to give DA-EDDA, and a bridge containing two oxygen donors is added to DHEEN to give the macrocycle K-22. Fig. 3 shows that the response in terms of change in thermodynamic complex stability in relation to metal ion radius is similar for all three types of change. This is true whether the added neutral oxygen donors are alcoholic, amide, or ethereal oxygens, and whether the resulting ligand is a macrocycle or an open-chain ligand. As we shall demonstrate in this review, the results shown in Fig. 3 lead to a powerful ligand design tool, which is far more useful than the size match selectivity idea as a guide to successful ligand design.

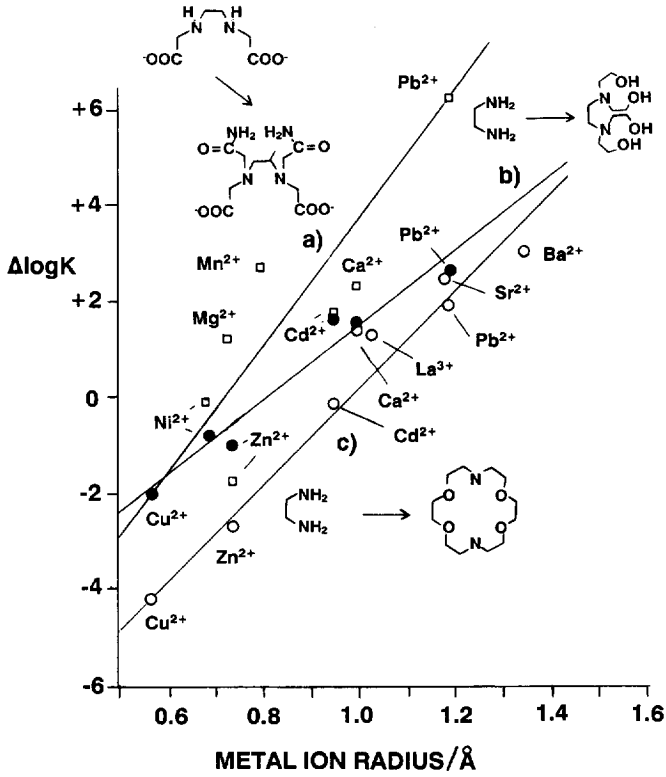



Fig. 3. Effect of addition of donor groups containing neutral oxygen on metal-ion selectivity. For each correlation, the change in complex stability, $\Delta$ log $K$, on adding groups containing neutral oxygen donors to a ligand, is plotted as a function of metal ion radius. In group (a), two acetamide groups are added to EDDA to give DA-EDDA; in group (b), four hydroxyethyl groups are added to EN to give THEEN; in group (c), bridges containing ethereal oxygens are added to EN to give K-22. (Formation constants from Ref. [33], and ionic radii ($r^+$) from Ref. [14].)

## 2. The origin of the preference of neutral oxygen donors for large metal ions

The preference of neutral oxygen donors for coordination with larger metal ions has been a puzzling phenomenon. It was suggested [1] that it arose from the fact that nearly all crown ethers and cryptands form exclusively five-membered chelate rings on complex formation. This is important in relation to a further rule of ligand design [13] which states: *increase of chelate ring size from five-membered to six-membered will favor ligand selectivity for small over large metal ions.* Thus, the presence of five-membered chelate rings will promote selectivity for large metal ions. The rule regarding size of chelate ring and metal-ion-size-based selectivity is derived [15–18] from purely geometric arguments. Molecular mechanics (MM) calculations [17–18] show that minimum steric strain will result for the five-membered chelate ring of EN when the metal ion is large with M–N bond lengths of 2.5 Å and N–M–N angles of 69°. Similarly, minimum steric strain will result for six-membered chelate rings of TN when the metal ion is small with M–N lengths of 1.6 Å, and N–M–N angles close to 109.5°. This is shown in Fig. 4.

If one assumes that the geometric arguments for complexes with neutral oxygen donor atoms in the place of saturated nitrogen donors will be similar, then one can account for the preference of crown ethers with their five-membered chelate rings in terms of the chelate ring size arguments. In agreement with this argument, it is found [19] that only crown ethers incorporating six-membered chelate rings show selec-

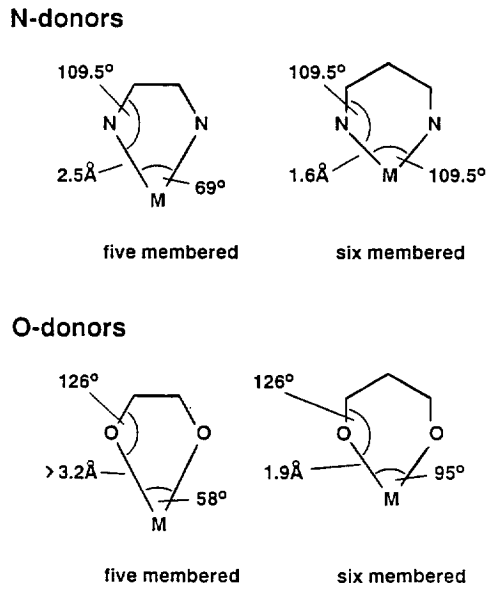
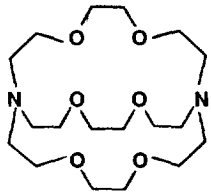
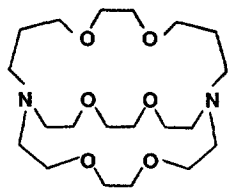



Fig. 4. M–L bond lengths and L–M–L bond angles that give chelate rings of minimum strain energy for chelating ligands with saturated nitrogen and saturated oxygen donors. It should be noted that other geometries will be observed for metal ions of other sizes, but these will produce higher steric strain. Redrawn from Ref. [17] and unpublished work of the present authors.

tivity for the small $Li^+$ ion over the other larger alkali metal ions. One can read in textbook after textbook, such as Refs. [20,21], that the small 12-crown-4 complexes the small $Li^+$ ion better than the large $K^+$ ion, which in turn fits better into the large cavity of 18-crown-6. *This is not true.* 12-Crown-4 complexes $K^+$ better than $Li^+$ in all solvents [22]. Thus, in methanol [22], log $K_1$ for $Li^+$ with 12-crown-4 is equal to or less than zero; for $K^+$ log $K_1$ with 12-crown-4 in methanol it is 1.72. In fact, except in the most weakly coordinating solvents, $Li^+$ does not appear [22] to complex significantly with any crown ethers whatsoever, except those such as 14-crown-4 which form six-membered chelate rings.

An interesting example of the effect of chelate ring size on complex stability has been reported [23] for the cryptand A below, which resembles cryptand-222, but which forms two six-membered chelate rings on complex formation. In contrast to what one might have intuitively expected from hole-size arguments, there is a dramatic drop in log $K_1$ for the complexes of the large metal ion which were studied with cryptand A, and the drop in log $K_1$ is larger for the larger metal ions. This result is exactly what one would have expected from the rule [16] concerning chelate ring size and metal-ion-size-based selectivity.





| Metal ion | Radius[a] (Å) | Cryptand-222 log $K_1$ | Cryptand A log $K_1$[b] |
|---|---|---|---|
| $Na^+$ | 1.00 | 4.11 | 1.3 |
| $K^+$ | 1.38 | 5.58 | 1.2 |
| $Ca^{2+}$ | 1.00 | 4.57 | 1.7 |
| $Ba^{2+}$ | 1.35 | 9.7 | 4.4 |

[a] From Ref. [14]. [b] From Refs. [22,23], in methanol at 25 °C.

In spite of the popularity of the size match selectivity idea, one would do better at predicting the affinity of crown ethers for the different alkali metal ions by stating that crown ethers tend to prefer potassium. Thus, the small 12-crown-4, the medium size 18-crown-6, and the very large dibenzo-30-crown-10 all form [22] their most stable complexes with $K^+$ of the alkali metal ions. This would make perfect sense [1] in terms of chelate ring size arguments if it was postulated that what really controlled selectivity in complexes of crown ethers was chelate ring size, and $K^+$ has K–O bond lengths of just the right size to fit with least steric strain into the five-membered chelate rings formed by all these crown ethers. A problem with this proposal is that the calculations [15–18] on the nitrogen donor ligands EN and

TN suggest that a metal ion with M–N length of 2.5 Å would fit best into the five-membered chelate ring formed by EN. Thus, if the geometric aspects of coordination to neutral oxygen donors and neutral nitrogen donors are similar, one might expect metal ions of about the same size, i.e. with M–O bond lengths close to 2.5 Å, to complex best with neutral oxygen donors. The M–N bond length is usually some 1.43 Å longer than the $r^+$ of the metal ion [24], which would mean that a metal ion of $r^+$ about $2.5-1.43=1.07$ Å should form the most stable complexes with five-membered chelate rings, which is smaller than the $r^+$ of $K^+$ at 1.38 Å.

The key to this problem has come from the work [25] of Hay and co-workers, who have shown that the geometry of coordination of metal ions to neutral oxygen donors is very different from the geometry of coordination to neutral nitrogen donors. In the crystal structures of complexes of crown ethers, such as the $K^+$ complex of 18-crown-6 [26], the oxygen donor lies well out of the plane described by the potassium ion, and the two methylene carbons attached to the oxygen donor atom. This gives the impression that the oxygen is using only one of its two lone pairs to coordinate to the potassium, making the geometry of the coordinated ether oxygen similar to that of a coordinated secondary nitrogen, with the non-coordinated lone pair on the oxygen donor situated analogously to the hydrogen on the nitrogen donor. However, Hay and co-workers have shown [25] that, for unidentate ethers with no steric constraints on how they might coordinate to the metal, the oxygen donor lies in the plane of the metal ion and the two carbons attached to the oxygen donor. This means that, for example, strain-free M–O–C angles are close to 126°, rather than the approximately 109.5° found for the M–N–C angle. The coordination of THF to $Li^+$ is shown in Fig. 5. The minimum strain geometry for coordination of neutral oxygens to metal ions is thus rather different from the geometry of coordination of neutral nitrogens to metal ions. If the strain-free M–O–C angle is taken to be 126°, then the minimum strain geometry for coordination of metal ions as part of chelate rings which have neutral oxygen donors is as seen in Fig. 4. The minimum strain for coordination of metal ions with neutral oxygen donors as part of five-membered chelate rings is thus (Fig. 4) very long, and in effect requires an infinitely

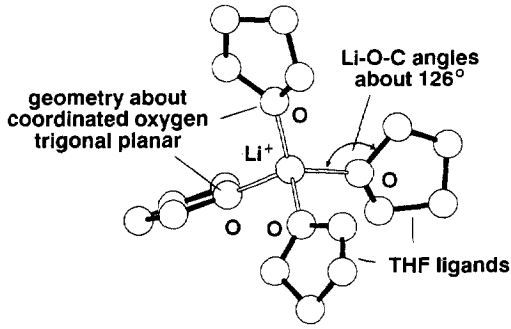
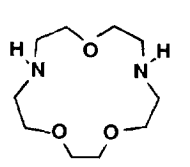



Fig. 5. Structure of the complex of $Li^+$ with tetrahydrofuran (THF), showing the planar coordination geometry around the oxygen donors of THF. Redrawn with coordinates available in Ref. [68].

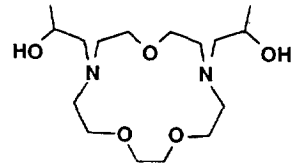
large metal ion to achieve minimum steric strain. We have simply indicated the best-fit M–O length as greater than 3.2 Å, the latter being approximately the longest observed M–O bond lengths.

This general observation accounts for the rule that neutral oxygen donors promote selectivity for large metal ions, but it is clearly too long to account for the fact that a metal ion the size of $K^+$ complexes best with crown ethers. The K–O bonds tend to be about 2.9 Å, which is rather shorter even than the value of 3.2 Å typical for Cs–O bonds. What has been suggested [25] is that there is a balance between M–O bond-strength effects, and strain effects deriving from coordination with crown ethers. The M–O bond strength for alkali metal ions will decrease $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$, while the strain arising from coordinating with the crown ethers will decrease $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$, and the balance between these two factors will mean that $K^+$ will tend to form the most stable complexes.

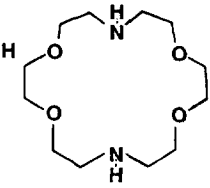
The consequences of the rule regarding neutral oxygen donors and metal-ion-size-based selectivity can be [27] most interesting. Thus one deduces that, if two metal ions are the same size, then the stabilization produced by adding neutral oxygen donors to any ligand must always be the same for both metal ions. The ions Sr(II) and Pb(II) have almost identical radii [14] at 1.18 and 1.19 Å respectively, so one expects similar structural changes involving neutral oxygen donors to have the same effect on complex stability. Conversely, if the structural changes are all made to the same starting ligand, then there should be a constant difference in log $K_1$ between the two metal ions. All of the ligands shown below have two saturated nitrogen donors, but otherwise differ considerably in number of oxygen donors and structural



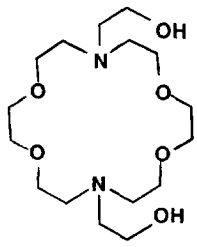
Pb/Sr selectivity = 4.1



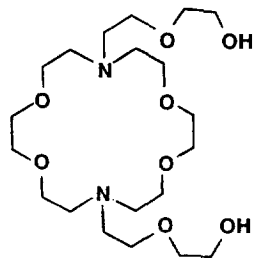
Pb/Sr selectivity = 4.8



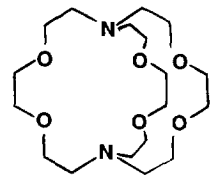
Pb/Sr selectivity = 4.2



Pb/Sr selectivity = 4.5



Pb/Sr selectivity = 3.9



Pb/Sr selectivity = 4.0

features. It is seen that there is [27] an approximately constant difference in log $K_1$ between the Pb(II) and Sr(II) complexes of 4.2 log units.

## 3. Neutral alcoholic and ethereal oxygen donors

The first example of a macrocyclic ligand with pendent donor groups containing neutral oxygen donors was BHE-K22, reported by Kulstad and Malmsten [28], and also by Gandour et al. [29]. Our interest in this area originated with the synthesis of the ligand THEC by reaction of cyclam with ethylene oxide [30]. An immediate attraction of this area was the ease of synthesis of these ligands. For example, THEC was obtained in 100% yield simply by stirring a cooled solution of cyclam and ethylene oxide in ethanol overnight, which gave the ligand as colorless cubic crystals. The reason for this excellent crystallinity (most polyamines with 2-hydroxyethyl groups are viscous oils) has since become apparent from the internal hydrogen-bonding observed [31] in the structure of THEC (Fig. 6). Hay and co-workers [32] reported the synthesis of THEC at very much the same time as ourselves. What was immediately of interest in the THEC complexes was the very large change in complex stability produced by the presence of the *N*-hydroxyethyl groups, compared to the parent amine cyclam, as shown in Table 2.

The log $K_1$ values for cyclam and THEC show the tendency of *N*-hydroxyethyl groups to depress the complex stability of small metal ions (Cu(II), Ni(II)) very much more than large metal ions (Cd(II), Pb(II)). The fact that Pb(II) shows a somewhat larger depression in log $K_1$ on passing from cyclam to THEC probably

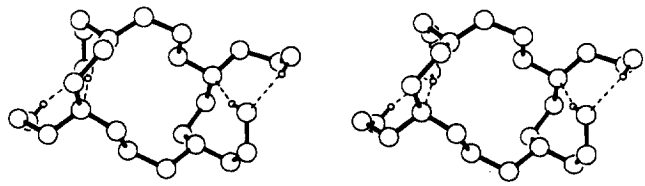


Fig. 6. Stereoview of the free ligand THEC, showing the internal hydrogen bonding (– – –) structure that promotes crystallinity. Redrawn using coordinates in Ref. [31].

Table 2
log $K_1$ values from Refs. [30,33,34]. Ionic radii ($r^+$) from Ref. [14]

| | Metal ion | | | | |
|---|---|---|---|---|---|
| | $Cu^{II}$ | $Ni^{II}$ | $Zn^{II}$ | $Cd^{II}$ | $Pb^{II}$ |
| $r^+$ (Å) | 0.57 | 0.69 | 0.74 | 0.95 | 1.19 |
| log $K_1$ cyclam | 27.2 | 20.1 | 15.5 | 11.2 | 10.8 |
| log $K_1$ THEC | 15.7 | 7.3 | 6.4 | 9.4 | 6.3 |
| Change in log $K_1$ | −11.5 | −12.8 | −9.1 | −1.8 | −4.5 |

relates to the presence [35] of a stereochemically active lone pair on Pb(II) in its cyclam complex, which considerably decreases the $r^+$ of Pb(II).

The tendency of hydroxyethyl groups to depress log $K_1$ values of small metal ions more than those of large metal ions was not noticed in the work on THEC [30], largely because the log $K_1$ values were not available for all of the cyclam complexes. The effect of 2-hydroxyethyl groups on complex stability was first noticed to be related to metal ion size in a paper [36] on BHP-K22. Subsequently, it was observed [13] that the relationship between $\Delta$ log $K$ when groups bearing neutral oxygen donors were added to ligands, and the ionic radii of the metal ions, was sufficiently exact that good linear correlations of $\Delta$ log $K$ vs. $r^+$ could be obtained. A correlation of $\Delta$ log $K$ vs. $r^+$ for the pairs of ligands K-22 and cryptand-222, and of 18-ane$N_4O_2$ and THE-18-ane$N_4O_2$, is seen in Fig. 7. It is of interest to note that even the cryptand selectivity appears to follow the rule of metal-ion-size-based selectivity when neutral oxygen donors are added.

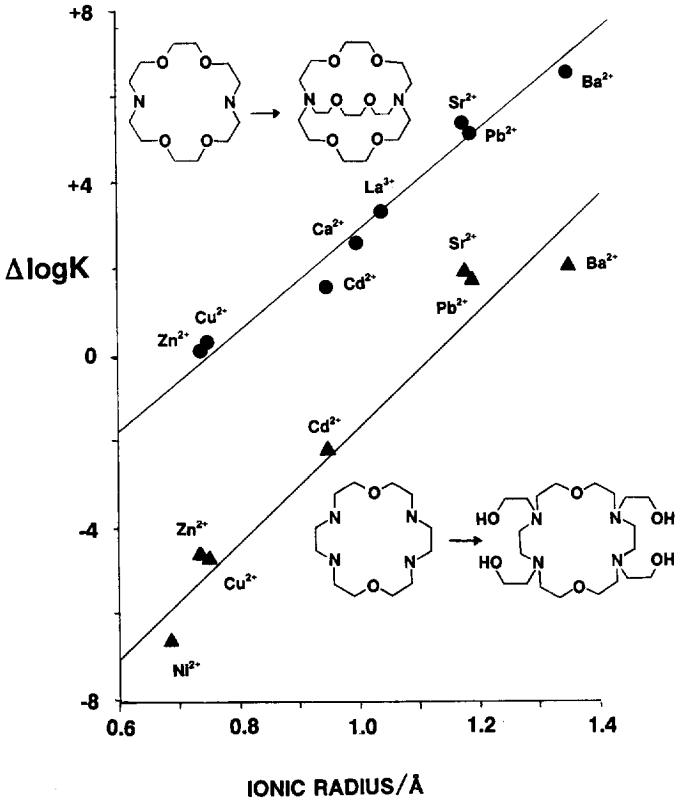
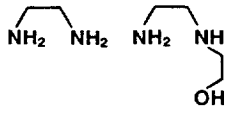



Fig. 7. Change in complex stability, $\Delta$ log $K$, that occurs on adding neutral oxygen donors to ligands, as a function of metal ion size. The upper curve (● points) shows the change that occurs on passing from K-22 to cryptand-222; the lower curve (▲ points) shows the change from 18-ane$N_4O_2$ to THE-18-ane$N_4O_2$. Formation constants from Refs. [27,33].

From the discussion so far, it now appears that two factors probably act to control the fact that neutral oxygen donors increase the selectivity of ligands for larger relative to smaller metal ions. It was originally suggested [36] that the selectivity for larger metal ions was due to the ability of larger metal ions to tolerate the steric crowding produced by addition of neutral oxygen donors. In addition, the ligands produced by addition of neutral oxygen donors might as a result have denticities that exceed the coordination numbers of the metal ions. These factors must in some cases play a part, but the fact that the selectivity for large metal ions is produced [37] even when a single hydroxyethyl group is added to EN to give HEEN shows that steric crowding and exceeding of the coordination number of a metal ion cannot be the only contributing factor.

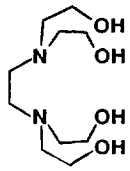
Ligand:



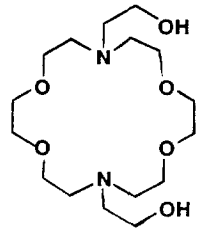

EN




HEEN




THEEN

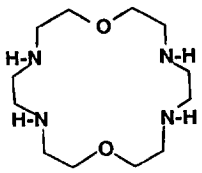



BHE-K22

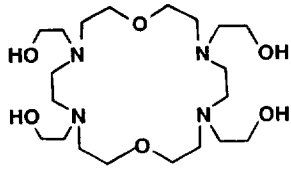
| | EN | HEEN | THEEN | BHE-K22 |
|---|---|---|---|---|
| log $K_1$ Cu(II) (radius 0.57 Å) | 10.5 | 10.1 | 8.5 | 6.6 |
| log $K_1$ Pb(II) (radius 1.19 Å) | 5.0 | 5.6 | 7.6 | 9.2 |

The sequence clearly shows the response of a small metal ion (Cu(II)) and a large metal ion (Pb(II)) to the addition of more and more neutral oxygen donor groups. In passing from EN to HEEN, the denticity of the ligand increases from only two to three, and clearly here the effect on metal ion selectivity which favors the larger metal ion must be due to chelate ring size effects. At the other end of the sequence, the ligand BHE-K22 is octadentate, and the decrease in stability of the Cu(II) complex must have a large contribution from simple steric crowding and the inability of the Cu(II) to achieve a coordination number of eight.

The design approach in engineering selectivity using neutral oxygen donors is simply to add neutral oxygen donors until the required selectivity is achieved. Of course, selectivity is not the only thermodyanamic criterion that the ligand must satisfy, and attention must also be paid to the absolute stability of the complexes formed, since very high selectivity without sufficient complex stability will not be adequate. One thus sees that the selectivity of 18-ane$N_4O_2$ for the large Pb(II) and Cd(II) ions over the small Zn(II) ion is not adequate for use in treating lead and cadmium poisoning [27]. Addition of four 2-hydroxyethyl groups to 18-ane$N_4O_2$ to give BHE-18-ane$N_4O_2$ now raises the Pb/Zn and Cd/Zn selectivity to adequate levels [27].




18-aneN$_4$O$_2$

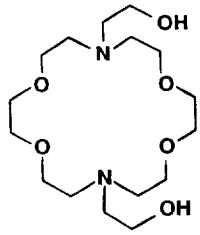



BHE-18-aneN$_4$O$_2$

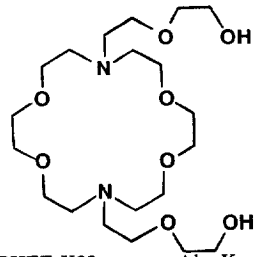
| | | |
|---|---|---|
| log $K_1$ Zn(II) | 10.51 | 5.90 |
| log $K_1$ Cd(II) | 10.90 | 8.84 |
| log $K_1$ Pb(II) | 9.01 | 10.72 |
| Pb/Zn selectivity[a] | −1.50 | +4.82 |

[a] Pb/Zn selectivity is simply log $K_1$ for the Pb(II) complex minus log $K_1$ for the Zn(II) complex. The log $K_1$ values are from Ref. [27].

Addition of sufficient neutral oxygen donors can be used to suppress the stability of all but the very largest metal ions. Thus, BHE-K22 is octadentate, but still complexes [27] quite strongly with metal ions such as Ca(II) which are fairly large ($r^+ = 1.00$ Å [14]). Using the design principle developed so far, to limit complex stability to the largest metal ions such as Ba(II), Sr(II) or Pb(II), an extra neutral oxygen donor is added to each pendent donor group to give BHEE-K22.




BHE-K22




BHEE-K22 ΔlogK

| Metal ion | Ionic radius[a] Å | log $K_1$ | log $K_1$ | Δlog $K_1$ |
|---|---|---|---|---|
| Cu(II) | 0.57 | 6.6 | NEC[b] | >5 |
| Cd(II) | 0.95 | 8.0 | 3.3 | 4.7 |
| Ca(II) | 1.00 | 4.1 | NEC[b] | >3 |
| Sr(II) | 1.18 | 4.7 | 3.3 | 1.6 |
| Pb(II) | 1.19 | 9.2 | 7.2 | 2.0 |
| Ba(II) | 1.25 | 5.3 | 4.9 | 0.4 |

[a] Formation constants from Ref. [27]. Ionic radii ($r^+$) from Ref. [14]. [b] NEC means no evidence of complex formation.

The very large Ba(II) ion suffers only a slight drop in log $K_1$ in passing from BHE-K22 to BHEE-K22, which shows its ability to accommodate ligands of high denticity. The crystal structure of $[Ba(BHEE\text{-}K22)H_2O]^{2+}$ in Fig. 8 shows [37] that the Ba(II) not only accommodates all of the donor atoms of BHEE-K22 with ease, but even coordinates a water molecule to achieve a coordination number of eleven.

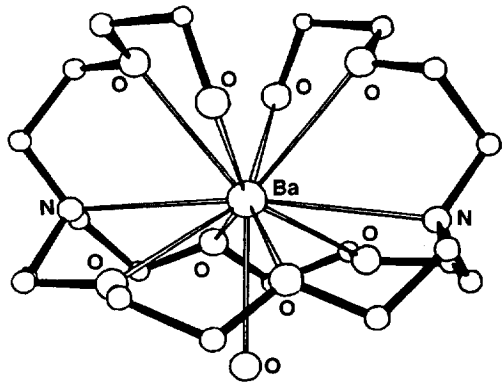
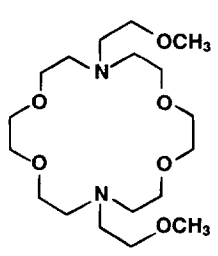


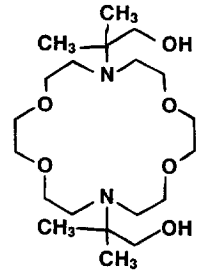

Fig. 8. Drawing of the $[Ba(BHEE\text{-}K22)H_2O]^{2+}$ cation, showing how the large Ba(II) ion can accommodate all of the donor atoms of the decadentate BHEE-K22 ligand, and still be able to coordinate a water molecule to achieve a coordination number of eleven. Redrawn from Ref. [37].

## 4. Structurally more complex pendent donor groups with neutral oxygen donors

So far the discussion has focused on ligands where the pendent donor groups containing neutral oxygens have simple ethylene bridges connecting the donor atoms together. In nature, antibiotics such as monensin have ethereal oxygen donors as part of THF groups, so that it is of interest to evaluate other types of pendent donor group that contain neutral oxygen donors [38]. It was found that the tetrahydrofurfuryl pendent groups of $THF_2$-K22 had similar effects on complex stability to those of 2-hydroxyethyl groups, but that the methoxyethyl groups of BME-K22 and the 1,1-dimethyl-2-hydroxyethyl groups of BDME-K22 had interesting and important effects on selectivity. For both BME-K22 and BDME-K22 the simple 2-hydroxyethyl group is being altered by the addition of methyl groups, but in the case of BME-K22 the methyl group is added to the neutral oxygen donor of the pendent donor group, while for BDME-K22 the two methyl groups are added as C-methyl groups.




BME-K22




BDME-K22

The effects on complex stability of the two ways of adding methyl groups to a ligand are quite opposite with respect to metal ion size. As a general rule, one finds [11]

that addition of methyl groups to the donor atoms (oxygen or nitrogen) of the ligand leads to a drop in complex stability which is more marked for small than for large metal ions. This is seen in Fig. 9, where Δ log $K$ for passing from BHE-K22 to K22 is plotted as a function of metal-ion radius. As is typically the case, the small metal ions show the largest decrease in log $K_1$ when alkyl groups are added to donor atoms. In contrast, the plot of Δ log $K$ vs. $r^+$ for passing from K22 to BDME-K22 shows exactly the opposite effect. The addition of C-methyl groups leads to a greater decrease in complex stability for larger metal ions. The extent to which this type of relationship is quantitative is seen in Fig. 10, where Δ log $K$ for passing from EDTA to DMEDTA is plotted as a function of metal-ion radius. One may postulate here two further ligand design rules: (1) addition of C-alkyl groups to ligands tends to increase the selectivity of the ligand for small relative to large metal ions, and (2) addition of alkyl groups to the donor atoms of ligands tends to increase the selectivity of the ligands for large relative to small metal ions.

Again, these two rules provide a means for controlling selectivity for metal ions on the basis of size. Addition of alkyl groups to ligands can increase the stability of the complexes as well, provided that the overall increase in steric crowding does not

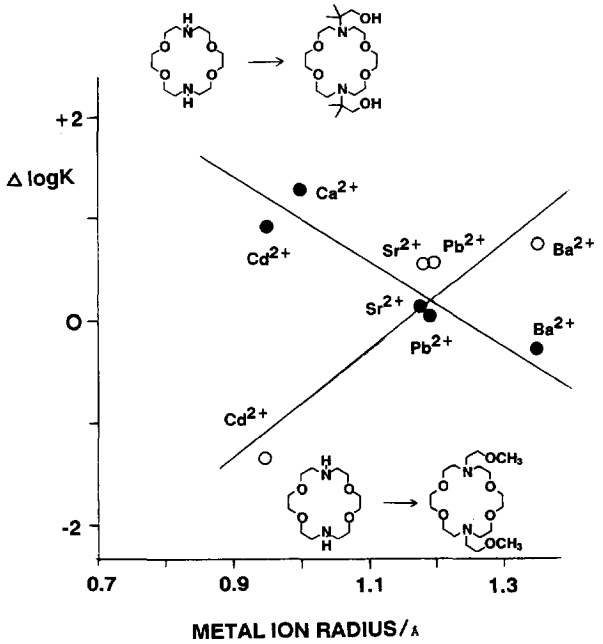



Fig. 9. Effect of methyls (a, ● points) attached to the oxygen donors and (b, ○ points) attached as C-methyl groups, to the ligand BHE-K22, on metal-ion selectivity. The value of Δ log $K$ is log $K_1$ for each complex of BME-K22 minus log $K_1$ for the corresponding K22 complex, or log $K_1$ for the BDME-K22 complex minus log $K_1$ for the K22 complex. The Δ log $K$ values are plotted against ionic radius ($r^+$) [14] of the metal ions to show that addition of alkyl groups as O-methyl groups (a) increases selectivity for large metal ions, while addition as C-methyl groups (b) increases selectivity for small metal ions. Stability constant data from Ref. [39].

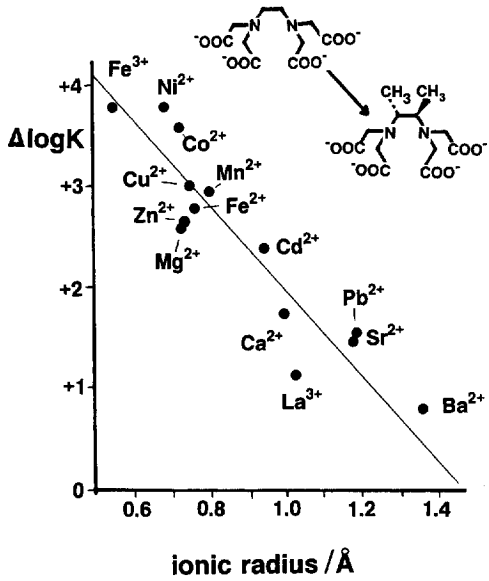
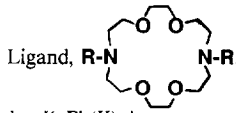


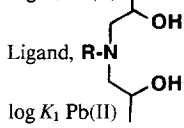

Fig. 10. Effect of the C-methyl groups of DMEDTA on complex stability, as illustrated by the relationship between Δ log $K$ for passing from DMEDTA to EDTA as a function of radius [14] of the metal ion. Stability constant data from Ref. [33]. The relationship shows that C-methyl groups tend to increase the selectivity of ligands for small metal ions relative to large metal ions.

overcome the effects that tend to increase complex stability. The latter effects appear [11] to be (a) inductive effects of the added alkyl groups, which increase donor atom basicity, and (b) *preorganization* of the free ligand. By "preorganization" is meant that the free ligand is constrained to be more nearly in the conformation required for complexing the metal ion. Thus, the two C-methyl groups on the ethylene bridge of DMEDTA lower the energy barrier between the anti conformation which is preferred by the free ligand, and the syn conformation which is required to complex the metal ion. This is shown in Fig. 11 for the pair of ligands EN and DMEEN, as a simple model for EDTA and DMEDTA. The syn conformation of EN is destabilized by increased electrostatic repulsion between the lone pairs on the nitrogen donor atoms. However, the anti conformation of DMEEN is destabilized by steric repulsion between the C-methyl groups, making adoption of the syn conformer easier.

The $N$-alkyl groups have favorable effects on complex stability only in the most sterically favorable situations. Thus, with the very large Pb(II) ion, on addition of C-alkyl groups to K-22 to give DiMe-K22 [39], there is a modest increase in log $K_1$ when a methyl group is added, but, for the larger isopropyl group, there is a drop in complex stability in the complexes of Di-$^i$Pr-K22. However, for the small R-N($CH_2CHCH_3OH)_2$ ligands, there is a steady increase [39] in log $K_1$ as R is increased in size along the series $CH_3-<(CH_3)_2CH-<(CH_3)_3C-$.



| Ligand, R-N N-R, | R = H | R= $CH_3$ | R = $CH(CH_3)_2$ | R = $C(CH_3)_3$ |
|---|---|---|---|---|
| log $K_1$ Pb(II) | 6.8 | 7.79 | 6.19 | |

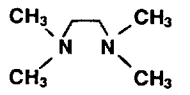


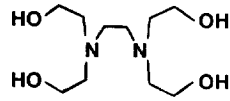
| Ligand, R-N | | | | |
|---|---|---|---|---|
| log $K_1$ Pb(II) | 3.4 | 3.70 | 4.14 | 4.33 |

One sees that in the sterically favorable situation of the small R-N($CH_2CHCH_3OH$)$_2$ ligands, there is a steady increase in log $K_1$ right up to the case where R is the bulky *tert*-butyl group. However, for the larger ligands based on K-22, even the large Pb(II) ion shows a drop in complex stability as R becomes more bulky than a methyl group. It should be noted, however, that Pb(II) is the only metal ion of a wide range of metal ions studied [39] for which a complex with Di-$^i$Pr-K22 could be detected, so that even here bulky alkyl groups may be a viable strategy for depressing the complex stability of metal ions other than the large Pb(II). What one is seeing with these ligands, where R is varied in size and inductive strength at the same time along the series methyl < ethyl < iso-propyl < *tert*-butyl [40,41], is that there is a delicate balance between the steric destabilization of the complex and the stabilization due to inductive effects.

One should point out here that the addition of 2-hydroxyalkyl groups and of alkyl groups to donor atoms of ligands have similar effects on selectivity, in that both tend to promote selectivity for large relative to small metal ions. However, the absolute effect on complex stability is very different. Thus, if we take a series of complexes of the small Ni(II) ion and the large Cd(II) ion, it is seen that addition of four *N*-methyl groups to EN to give TMEEN has a very different effect on complex stability compared to the addition of four 2-hydroxyethyl groups to give THEEN.

**Ligand:**





| | EN | TMEEN | THEEN |
|---|---|---|---|
| log $K_1$ [Ni(II)] ($r^+$ = 0.69 Å) | 7.34 | 3.57 | 6.5 |
| log $K_1$ [Cd(II)] ($r^+$ = 0.95 Å) | 5.45 | 3.87 | 7.04 |
| Selectivity Cd(II)/Zn(II) | −1.89 | +0.30 | +0.54 |

(Ionic radii ($r^+$) from Ref. [14], log $K_1$ values from Ref. [33], selectivity = log $K_1$[Cd(II)] − log $K_1$[Zn(II)]).

Thus, although the effect on Cd(II)/Zn(II) selectivity is similar, the addition of *N*-methyl groups to EN togive TMEEN causes an absolute decrease in log $K_1$ that is far larger than the decrease caused by addition of 2-hydroxyethyl groups to EN to give THEEN. One suggests that the effect of addition of *N*-methyl groups and *N*-2-hydroxyalkyl groups on metal-ion-size-based selectivity is similar because both effects cause steric problems that are worse for smaller metal ions. However, these

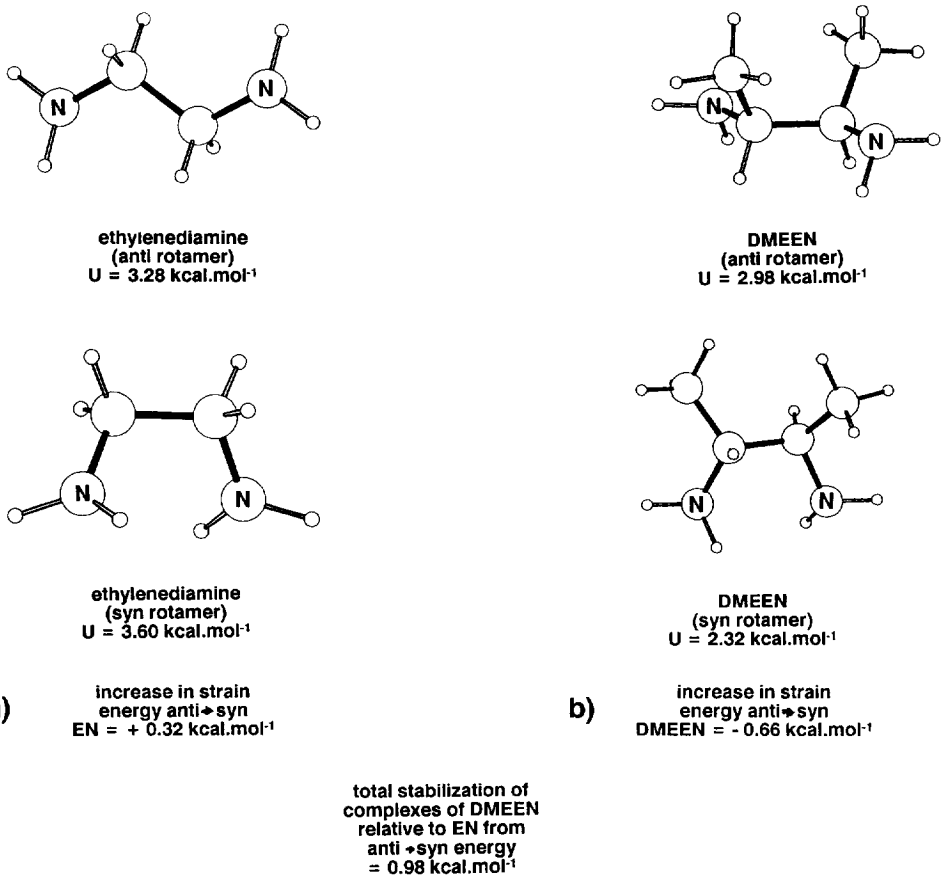



Fig. 11. Change in strain energy on passing from anti to syn forms of the ligands (a) EN and (b) DMEEN (D,L-2,4-diaminobutane). The syn form is that required for complex formation, so energy has to be expended in turning the anti form of EN into the syn form. For DMEEN the syn form is more stable, which means that the complexes of DMEEN are stabilized by the difference in the energies (0.98 kcal $mol^{-1}$) for the anti-to-syn conversion. The free energy of formation of the Cu(II) complex of DMEEN is [33] 0.93 kcal $mol^{-1}$ higher than that of the EN complex. The same type of effect would stabilize the complexes of DMEDTA relative to those of EDTA. Unpublished work of the present authors, calculated using SYBYL, with the TAFF force field [44], and charges calculated by the Marsili–Gasteiger method [45].

effects are different in origin, representing simple steric crowding in the case of *N*-alkyl groups, but metal-ion size preferences of chelate rings for addition of 2-hydroxyalkyl groups. The severe effects on log $K_1$ values caused by addition of simple *N*-alkyl groups means that this approach is unlikely to be useful in ligand design, whereas 2-hydroxyalkyl groups are likely to be very useful.

The use of cyclohexene oxide in synthesis, as seen in Fig. 12, produces [42,43] pendent donor groups that are highly preorganized, with excellent diastereomeric

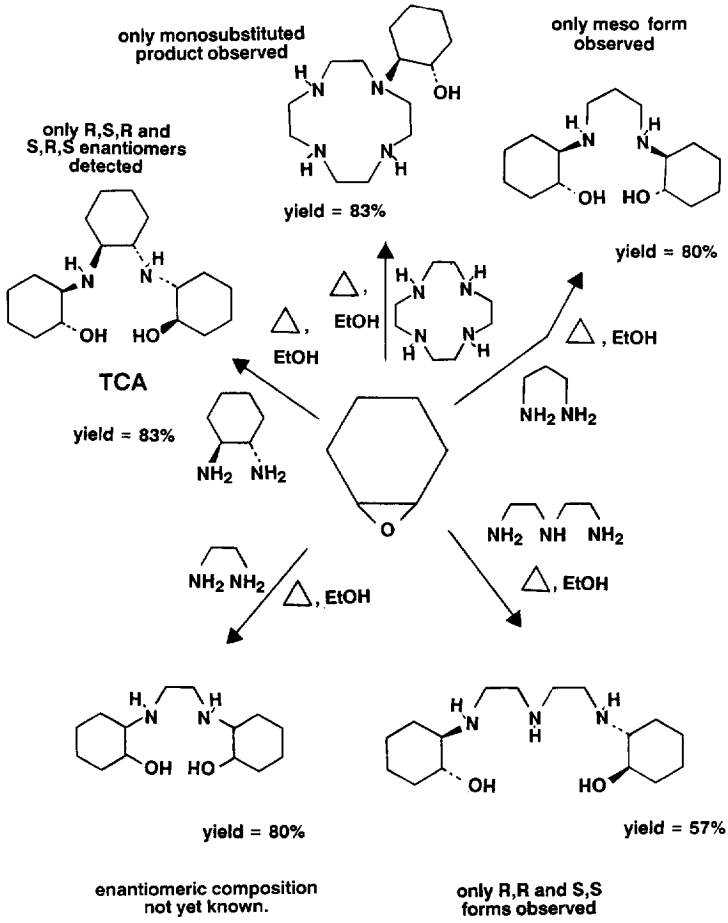



Fig. 12. Use of cyclohexene oxide in the synthesis of highly preorganized ligands from polyamines and nitrogen-donor macrocycles. The reported yields are unoptimized and are of crystalline material [42,43].

selectivity. Thus, when cyclohexene oxide is reacted with ethylenediamine, only the *N,N'*-disubstituted product is obtained, which is revealed by X-ray analysis of the crystals to be the meso form. The presence of a cyclohexenyl bridge in *trans*-CDTA was shown by Schwartzenbach et al. [46] to give rise to increases in log $K_1$ of up to five log units. Thus, the incorporation of cyclohexenyl bridges into the pendent donor groups by facile synthesis using cyclohexene oxide is most attractive. The effect on complex stability of the presence of the cyclohexylene bridges in $Cy_2$-K22 compared to the simple BHE-K22 is shown in Fig. 13, where $\Delta$ log $K$ as a function of $r^+$ is shown for these ligands. Also shown in Fig. 13 is the relationship of $\Delta$ log $K$ for the pair of ligands DHEEN and TCA to $r^+$, where again it is seen that the presence of cyclohexenyl groups alters selectivity in favor of smaller metal ions. It

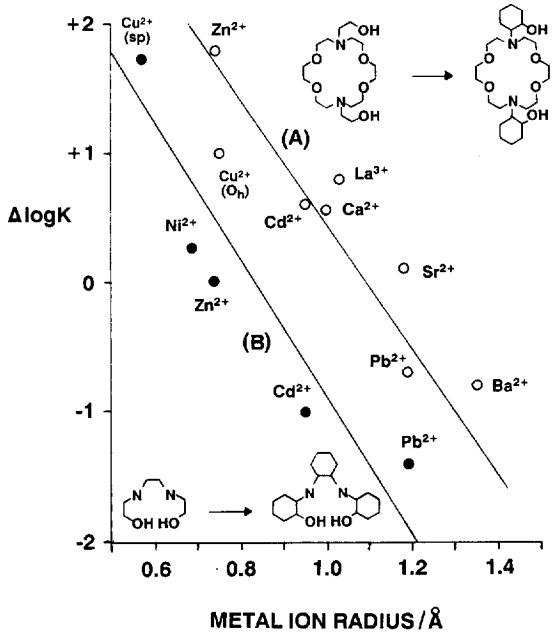
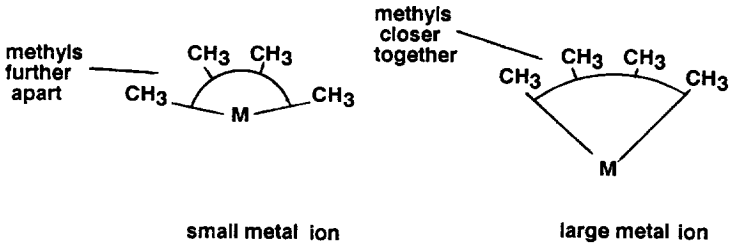



Fig. 13. Effect of cyclohexenyl bridges on complex stability [42,43], illustrated by a plot of Δ log $K$ vs. metal ionic radius ($r^+$) [14] in passing (A) from the BHE-K22 ligand to $Cy_2$-K22, and (B) from DHEEN to CTA. The diagram shows that replacement of ethylene bridges with cyclohexenyl bridges leads to an increase in selectivity for small metal ions [42,43]. For $Cu^{2+}$ the square planar radius is used for the tetradentate TCA, and octahedral radius for octadentate $Cy_2$-K22. Formation constant data from Refs. [42,43].

seems surprising at first [42] that the presence of cyclohexenyl groups would alter selectivity in favor of smaller metal ions. The chelate ring formed by the cyclohexenyl bridge and its trans donor atoms is a five-membered ring, and five-membered rings should favor larger metal ions [16]. The extra rigidity imparted to the chelate ring by the cyclohexenyl bridge might even be expected [42] to enhance the preference for larger metal ions by inhibiting the distortions of the chelate ring that are necessary to allow for complexation of smaller metal ions.

However, it now seems [43] that the effect of cyclohexenyl groups on selectivity for metal ions on the basis of their size derives from the same factors as do the selectivity patterns produced by any C-alkyl groups, such as the C-methyl groups on BME-K22 in Fig. 9, or DMEDTA in Fig. 10. The presence of C-alkyl groups on a ligand leads to steric crowding on the outer surface of the complex, which is relieved when the ligand coordinates to a small metal ion. Coordination to a smaller metal ion increases the curvature of the ligand, which moves the C-alkyl groups further apart. Although the present authors are now engaged in demonstrating this effect by MM calculation, it is easily visualized by a diagrammatic representation of this idea.




The fact that the methyl groups are forced closer together on the outside of the complex of the larger metal ion by the smaller curvature of the ligand leads to greater Van der Waals repulsion between these methyl groups, and hence greater steric destabilization for the complex of the larger metal ion. As an indication that the alcoholic oxygens of the pendent donor groups of $Cy_2$-K22 are indeed coordinated to the metal ion, the structure [47] of $[Sr(Cy_2\text{-}K22)(H_2O)](NO_3)_2$ is shown in Fig. 14. It is interesting to note that, in line with the strong stereoselectivity found [43] for syntheses involving cyclohexene oxide, the ligand $Cy_2$-K22 appears to form

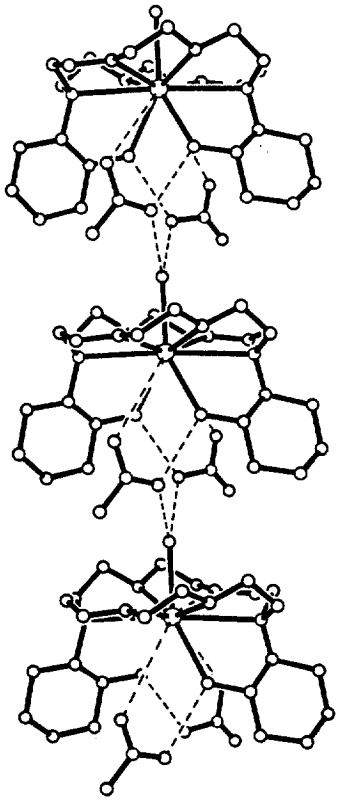


Fig. 14. Structure [47] of *R,R*-$[Sr(Cy_2\text{-}K22)(H_2O)](NO_3)_2$. Unpublished work of the present authors.

with high diastereoselectivity as the enantiomeric *R,R* and *S,S* pairs, without any indication of the *meso*-R,S form, and $[Sr(Cy_2\text{-}K22)(H_2O)](NO_3)_2$ crystallizes in the optically active space group *Cc* with individual crystals containing only the *R,R* or the *S,S* forms of the complex.

The fact that very large metal ions are better able to tolerate placement of alkyl groups directly on the donor atoms rather than on the carbon backbone relates to the fact that the donor atoms are further apart on these large metal ions. Large metal ions appear able to tolerate alkyl groups only on small ligands, where the issue of curvature of the ligand is less important, and the important factor is probably to get the *N*-alkyl or *O*-alkyl groups further away from coordinated solvent molecules. With constant coordination geometry, as the metal ion gets larger, so the donor atoms should get further apart. With unidentate ligands, where the steric interaction is with coordinated solvent molecules, the only factor is how far apart the donor atoms are, and very large metal ions such as Ag(I) or Pb(II) are unique in showing tolerance [40,41,48] even for such sterically crowded ligands as *tert*-butylamine or triethylamine, which form no complexes at all with smaller metal ions.

## 5. Ligands with pendent oxygen donors derived from amide groups

Fig. 1 shows that amide oxygens are stronger donors in the gas phase than alcoholic or ethereal oxygen donors, and so we might logically expect that analogs of the ligands described to this point, which have amide donors in place of the alcoholic or ethereal oxygen, would be superior ligands. The literature [22,33] contains little data on formation constants of ligands containing amide donor groups that might allow us to evaluate the effect that amide donors have on complex stability. Thus, a derivative of K22 with two acetamide pendent donors, DAM-K22, has been reported [49], as well as a derivative of cyclen with four *N,N*-dimethylacetamide donor groups [50]. In addition, single amide groups have been added to cyclen, with subsequent addition of three acetate groups [51], which renders the complexes of these ligands with $Gd^{3+}$ neutral overall, which is desirable from the point of view that neutral complexes when used in MRI will lessen osmotic shock as compared to complexes with charges. Morrow et al. have reported [52] ligands based on cyclen which have four propionamide donor groups. These ligands are not well suited to the complexation of large metal ions such as lanthanides because the coordinated propionamide groups form six-membered chelate rings in complexes with metal ions.

Our interest in metal ion complexation has for some time centered [53] on the removal of the large toxic metal ions Pb(II) and Cd(II) in cases of intoxication, which is discussed in more detail below. In order to maximize selectivity for these metal ions, the ligand THP-cyclen was synthesized, and found to be thermodynamically adequate for complexation of Cd(II) but not for Pb(II). The ligand DOTAM was synthesized for the complexation of Pb(II) and Cd(II), and, as described below, the thermodynamic selectivity for Cd(II) and Pb(II), and the stability of the complexes formed by these ions with DOTAM are remarkable. What is discussed in this

section is the structural features of the complexes of DOTAM. The ligand DOTA [54] has been the prototype of all the ligands based on cyclen, which have pendent donor groups. It has shown remarkable ability to complex large metal ions, and the design of a variety of ligands for biomedical applications has stemmed from DOTA. A disappointing aspect of DOTA chemistry has been the paucity of structural information available on complexes of DOTA, which is limited to a complex with Eu(III) [55]. This appears to relate to the difficulty of obtaining crystals of DOTA complexes. In contrast, the complexes of the rather similar DOTAM crystallize with ease, and to date crystals of the Zn(II), Cd(II), Hg(II), Ca(II), Ba(II) and Pb(II) complexes have been obtained [56].

The series of metal ions studied crystallographically as their DOTAM complexes presents a range in size [14] from the small Zn(II) ion ($r^+ = 0.74$ Å) to the very large Ba(II) ($r^+ = 1.35$ Å). How metal ions adapt that are too small or too large for optimal coordination with a ligand is of interest [11]. In Fig. 15 are shown the structures of the Zn(II) and Ca(II) complexes of DOTAM [56]. The Zn(II) appears to be too small to coordinate in an octadentate fashion to the DOTAM, and it has an irregular six-coordinate structure where two of the amide groups are not coordinated to the Zn(II). In contrast, the larger Ca(II) ion ($r^+ = 1.00$ Å) has a regular structure where the Ca(II) is eight-coordinate, with an approximately square antiprismatic coordination geometry. What is rather surprising is the structure of the DOTAM complex of Cd(II), which is only slightly smaller [14] ($r^+ = 0.95$ Å) than Ca(II). Here the Cd(II) might be described as octadentate, but there are two distinct pairs of Cd–O bond lengths [56]. One pair of oxygen atoms situated trans to each other has a mean length of 2.65 Å, while the other trans pair has shorter Cd–O lengths of 2.45 Å. Both of these pairs of amide oxygens are close enough to the Cd to be considered bonded to it, so the problem is: why the differing Cd–O bond lengths?

Exactly the same type of distortion is found for the Hg(II) structure [56]. Fig. 16

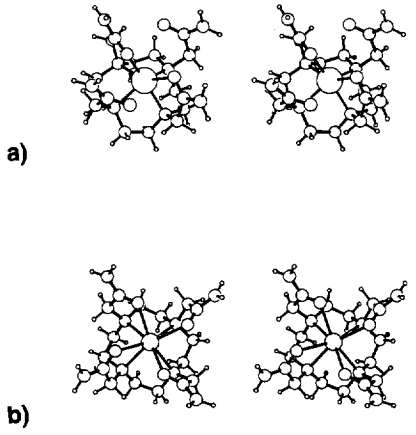



Fig. 15. Structures [56] of the DOTAM complexes of (a) Zn(II) and (b) Ca(II).

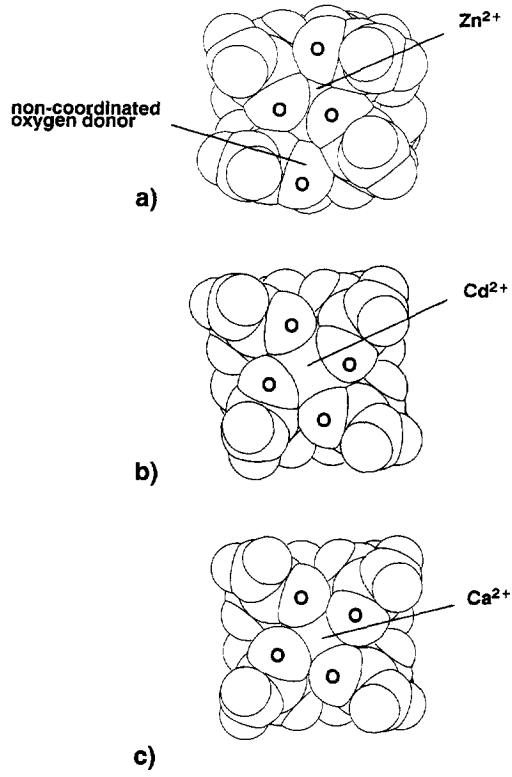



Fig. 16. Space-filling CPK drawings of the DOTAM complexes of (a) Zn(II), (b) Cd(II) and (c) Ca(II), viewed from above the plane of the oxygen donors. Redrawn from Ref. [56].

shows the space-filling CPK drawings of the Zn(II), Cd(II), and Ca(II) DOTAM structures viewed from above the plane of the oxygen donors. Fig. 16 shows that the coordination geometry of the DOTAM complexes is controlled by how well the oxygen donor atoms can pack around the metal ion at bonding distances. The Cd(II) ion is just too small to accommodate the four oxygen atoms at optimal bonding distances, and so a geometry is adopted where two oxygen atoms are held at longer distances by Van der Waals repulsion from the other two oxygens, which are coordinated at shorter distances. The idea that these structures are controlled by Van der Waals contacts can be examined [56] by MM calculation. One can construct [56] a simple MM model in which two oxygen donors and the four nitrogen donors of the DOTAM complex are held to the metal ion by the usual M–L force constants, with ideal M–O and M–L bond lengths. The position of the second pair of oxygen atoms is determined only by Van der Waals contacts with the rest of the complex.

As has been done for many systems, the effect of metal-ion size on the energy and structure of the complex may be investigated [17] by varying the ideal M–N and M–O bond lengths in a systematic manner. In this case it was found that keeping

the M–N bond lengths at a constant 0.1 Å longer than the M–O bond lengths reproduced quite well the observed structures of the DOTAM complexes of Zn(II), Cd(II) and Ca(II). Fig. 17 shows the variation in M–O bond lengths as a function of the M–N bond length, predicted by MM calculation for DOTAM complexes. The calculation shows that at an M–N length of 2.64 Å the M–O bond lengths will become equivalent in length. The experimental M–O bond lengths for DOTAM complexes are shown on Fig. 17, and it is seen that the MM calculation predicts quite well how the M–O bond lengths vary as a function of metal ion size.

The large Pb(II) and Bi(III) ions have a lone pair of electrons, and in accord with

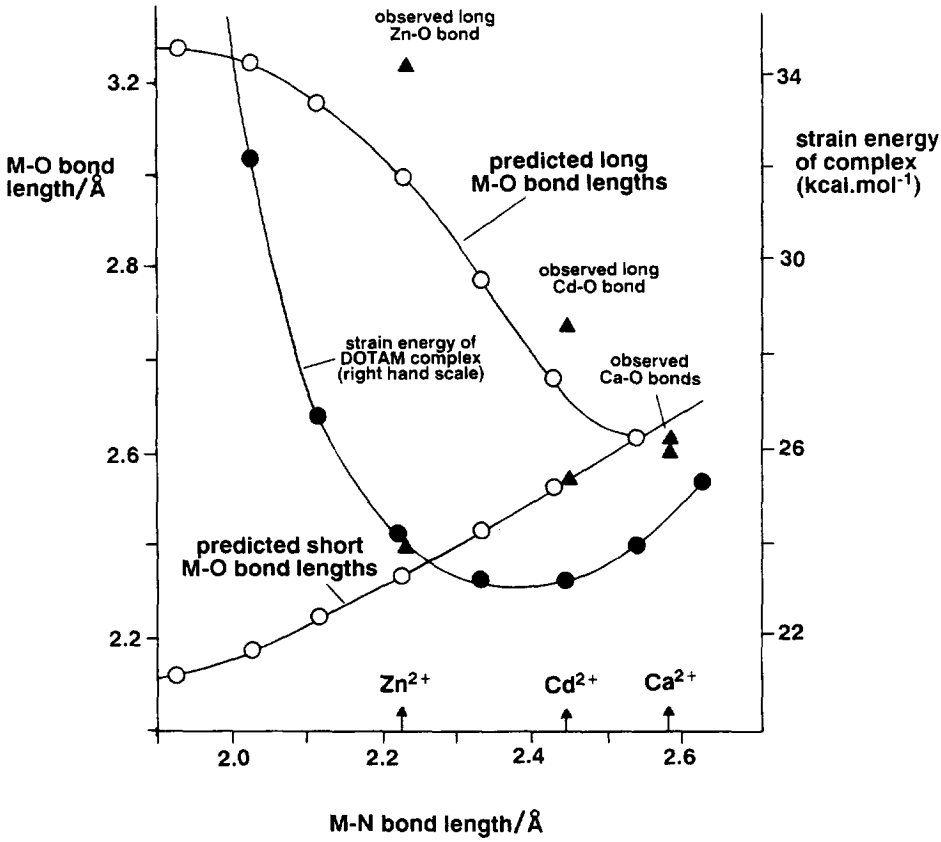



Fig. 17. Distortion of the coordination geometry of DOTAM complexes as a function of metal-ion size, modelled by MM calculation [56]. The model has one pair of amide oxygens coordinated to the metal ion with ideal M–O lengths 0.1 shorter than the ideal M–N bond length, and a M–O force constant of 200 kcal $mol^{-1}$ Å. The position of the second pair of amide oxygens is controlled only by Van der Waals contacts with the rest of the complex. As has been done for many complexes [17], the effect of metal-ion size on structure (M–O length, ○) and energy (●) of the complex is evaluated by calculation of structure and energy of different conformers as a function of, in this case, M–N length. The crystallographic values of the longer and shorter pairs of oxygen donors is indicated (▲) for each metal ion as a function of the crystallographically determined M–N length. Redrawn from Ref. [56].

the valence-shell electron-pair repulsion (VSEPR) theory [57,58] this lone pair may be stereochemically active and occupy a coordination site on the Pb(II) or Bi(III), leading to apparent gaps in the coordination geometry. Unlike the lighter elements, where lone pairs always appear to be stereochemically active, heavy ions such as Pb(II) and Bi(III) may adopt a geometry where the lone pair is in a spherically symmetrical 6s orbital, with the lone pair being stereochemically inactive. Conversely, the lone pair on Pb(II) or Bi(III) may be in a $sp^n$ or $sp^nd^m$ orbital, when it is stereochemically active. When the lone pair is stereochemically active, characteristic features appear [59,60] in the complex, such as shortening of the Pb–L or Bi–L bonds on the side of the complex away from the putative stereochemically active lone pair. Fig. 18 shows the structure [61] of the Bi(III) complex with THP-cyclen. There is a gap in the coordination geometry between the four oxygen donors which appears to be due to a stereochemically active lone pair.

This is the first example of a structure of a complex of Bi(III) with an azamacrocycle. It resembles closely the structure of the Pb(II) complex [35], except that the Bi–N bonds (2.53 Å) and Bi–O bonds (2.58 Å) are shorter than the corresponding Pb–N (2.64 Å) and Pb–O bonds (2.75 Å), which corresponds with the larger ionic radius [14] of Pb(II) (1.19 Å) than Bi(III) (1.03 Å). Fig. 18 shows one of the oxygen atoms from one of three perchlorates in the structure in a position 3.34 Å above the proposed position of the lone pair. This type of very long interaction reinforces the idea of a lone pair of electrons in this position, and is frequently observed in structures of Pb(II) complexes, above the proposed position of the lone pair.

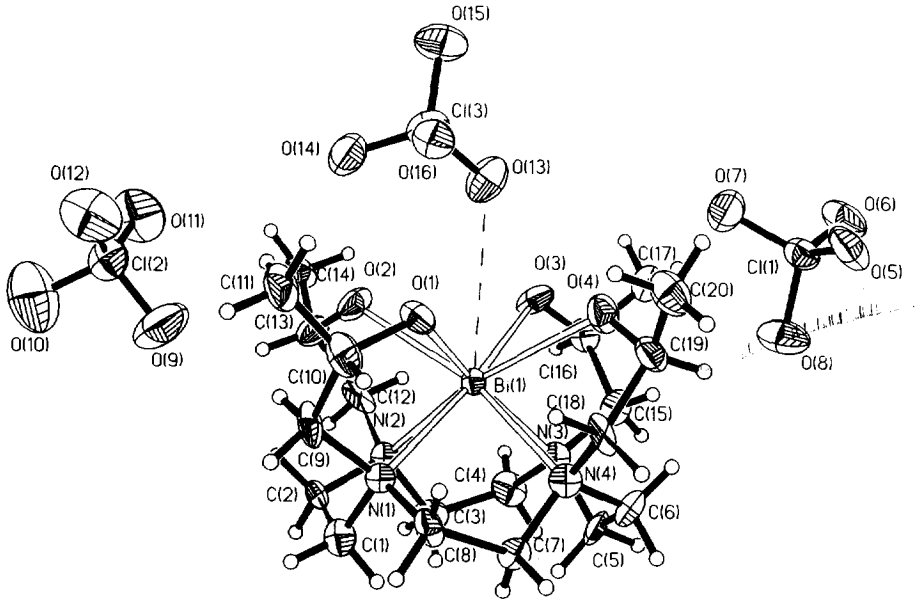



Fig. 18. Structure [61] of the Bi(III) complex of THP-cyclen, showing the suggested position of the stereochemically active lone pair, and its long bond to the perchlorate oxygen placed directly above the gap in the coordination geometry that corresponds to the position of the lone pair.

The odd distorted structures found for the DOTAM complexes of metal ions with an $r^+$ below 1.00 Å are somewhat at odds with results from $^{13}C$ NMR studies of these complexes in aqueous solution [56,62]. The $^{13}C$ NMR (Fig. 19) of the Zn(II) complex in aqueous solution suggests that, on the NMR timescale, all of the acetamide pendent groups are equivalent, not of unequal lengths as seen in the X-ray structure. As the temperature of an aqueous solution of these complexes is varied, the single NMR peaks due to the methylene carbons of the ethylene bridges become resolved into separate peaks owing to the differing environment of the methylene carbons, shown in Fig. 19. This process for each complex corresponds to a rapid reversal of helicity of the complex from clockwise to anticlockwise and back, as shown in Fig. 19. In Table 3 are shown the activation energies for helicity reversal for the DOTAM complexes of a selection of metal ions, arranged in order of decreasing difference in length between the trans pairs of acetamide oxygen donors in the complex. The results suggest that, the greater the difference in length between the two pairs of M–O bonds, the faster the rate of helicity reversal. One imagines a mechanism of helicity reversal where reversal for one pair of acetamide groups is greatly facilitated when they are at the longer M–O distance, and so not sterically encumbered by the rest of the complex. Rapid interchange of M–O distances would then allow the second pair of acetamide groups to undergo helicity reversal.

The coupling between the $^{111/113}Cd$ nuclei and the $^{13}C$ nuclei of the carbonyl groups of DOTAM which is observed [62] suggests that the Cd–O bonds at least are not broken during the process of helicity reversal. What then of the inequality of the Cd–O bonds suggested by the crystal structures of the DOTAM complex? The NMR results suggest that the unequal pairs of Cd–O bonds are exchanging on a timescale faster than the NMR experiment.

What one has to bear in mind is that a crystal structure represents only a single possible conformation for that particular molecule. The energy difference between the irregular structure of $[Cd(DOTAM)]^{2+}$ and a regular structure with equidistant Cd–O lengths may be quite small, and, in solution, populations with varying degrees of distortion of the coordination sphere may be in rapid equilibrium. A similar effect has been found [63] for the THE-cyclen complex of $Na^+$, where the crystal structure reveals the $Na^+$ to be only seven-coordinate, with one 2-hydroxyethyl group not coordinated. In spite of this, $^{13}C$ NMR indicates that on the NMR timescale all of the 2-hydroxyethyl groups in the $Na^+$ complex of THE-cyclen are equivalent [63]. Results such as this, and for the DOTAM complexes, may lead us to revise our ideas of static and fixed coordination numbers and geometries for complexes of metal ions in aqueous solution.

## 6. Pendent donor ligands with tridentate and pentadentate macrocycles

The discussion so far has focused on pendent donor ligands based on the tetradentate cyclen or hexadentate K22 type of macrocycle. Ligands with neutral oxygen donors as pendent donor groups based on tridentate and pentadentate macrocycles have also been widely investigated [22]. We will focus here only on those derived

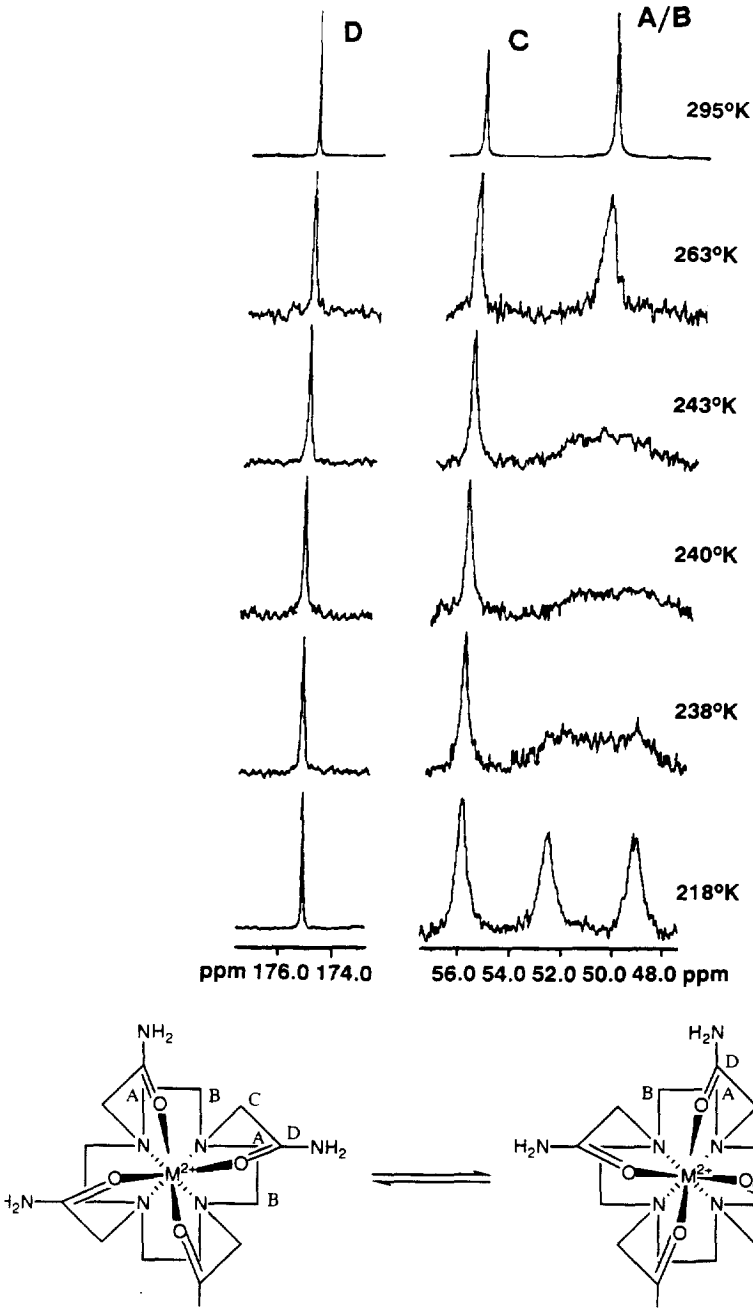


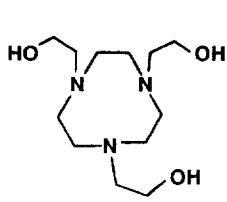

Fig. 19. (Above) $^{13}C$ NMR spectra [62] of the complex of Zn(II) with DOTAM at different temperatures in $D_7$-DMF solution. (Below) Diagram of the Zn(II) DOTAM complex showing the assignment of the peaks in the $^{13}C$ NMR spectra.

Table 3
The difference in M–O bond lengths between the shorter pair of M–O bonds and the longer pair for different metal ions in their DOTAM complexes, and the free energy of activation of helicity interchange from NMR spectra

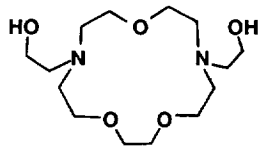
| Metal ion | Mean M–O length[a] | | Difference (Å) | $\Delta G^{+}$ for rate of helicity interchange[b] (kcal $mol^{-1}$) |
|---|---|---|---|---|
| | Shorter (Å) | Longer (Å) | | |
| Zn(II) | 2.19 | 3.23 | 1.04 | 11.2 |
| Hg(II) | 2.41 | 2.78 | 0.37 | 13.5 |
| Cd(II) | 2.34 | 2.64 | 0.30 | 13.7 |
| Ca(II) | 2.40 | 2.42 | 0.02 | 14.5 |
| Pb(II) | | | (0.00)[c] | 15.3 |

[a] M–O lengths from Refs. [56,61,62]. [b] Ref. [56].

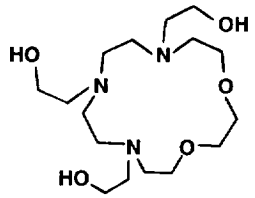
from 9-ane$N_3$ [64] and macrocycles such as 15-ane$N_2O_3$ [65] and 15-ane$N_3O_2$ [27] by addition of 2-hydroxyalkyl pendent donor groups. The ligands of interest are shown here.




THE-9aneN$_3$




DHP-15-aneN$_2$O$_3$




THP-15-aneN$_3$O$_2$

The ligand THE-9-ane$N_3$ behaves much as expected from the rules regarding addition of pendent groups containing neutral oxygen donors, with larger metal ions showing larger stabilizations [64]. The same is true for DHP-15-ane$N_2O_3$ and THP-15-ane$N_3O_2$ [27,65]. If one compares the stability of DHP-15-ane$N_2O_3$ complexes with those of the eighteen-membered macrocyclic ring DHP-K22, it is seen that the fifteen-membered chelate ring favors complexation of smaller metal ions (Table 4).

The magnitude of $\Delta$ log $K$ for passing from DHP-K22 to DHP-15-ane$N_2O_3$ is probably largely explainable in terms of the effect of the extra oxygen donor on DHP-K22.

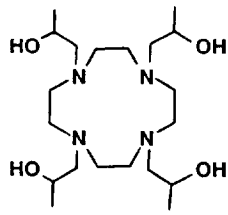
## 7. Ligand design using pendent neutral oxygen donors

A trend in ligand design that is discernible over the last 50 or so years is towards ever more highly preorganized ligands [66]. Thus, study of monodentate ligands gave way to the study of chelates, with the greater stability due to the chelate effect [67], followed by the more preorganized macrocyclic crown ethers [2] and cryptands

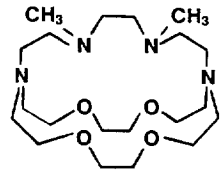
Table 4
Formation constants from Refs. [27,65]; octahedral ionic radii from Ref. [14]

| | Ionic radius (Å) | log $K_1$ DHP-15-ane$N_2O_3$ | log $K_1$ DHP-K22 | Δ log $K$ |
|---|---|---|---|---|
| $Zn^{2+}$ | 0.74 | 6.50 | 3.0 | −3.5 |
| $Cu^{2+}$ | 0.75 | 7.88 | 5.97 | −1.9 |
| $Cd^{2+}$ | 0.95 | 7.13 | 7.64 | +0.5 |
| $Ca^{2+}$ | 1.00 | 3.86 | 3.59 | −0.3 |
| $Sr^{2+}$ | 1.18 | 3.46 | 4.05 | +0.6 |
| $Pb^{2+}$ | 1.19 | 8.26 | 8.57 | +0.3 |
| $Ba^{2+}$ | 1.35 | 3.19 | 4.65 | +1.5 |

[3]. Macrocycles with pendent donor groups are half-way in level of preorganization between simple macrocycles and cryptands. It is instructive, however, to compare a cryptand and a pendent-donor macrocycle which have exactly the same donor set, to see how this affects complex stability and metal-ion selectivity. Both THP-cyclen and cryptand-22-N2 below have a donor set consisting of four saturated nitrogen donors and four saturated oxygen donors. The stability constants of these complexes, arranged in order of increasing metal ion radius [14], are shown here.




THP-cyclen




Cryptand-22-N2

| Metal ion | $r^+$ | log $K_1$ | log $K_1$ | Δ log $K$ |
|---|---|---|---|---|
| $Cu^{2+}$ | 0.57 | 19.48 | 12.7 | -6.8 |
| $Zn^{2+}$ | 0.74 | 13.45 | 6.0 | -7.5 |
| $Cd^{2+}$ | 0.95 | 17.46 | 12.0 | -5.5 |
| $Ca^{2+}$ | 1.00 | 5.68 | 4.3 | -1.4 |
| $Pb^{2+}$ | 1.18 | 15.07 | 15.3 | +0.2 |
| $Ba^{2+}$ | 1.35 | 3.74 | 6.7 | +3.0 |

These results suggest that the principal effect of the cryptand type of structure is to depress the stability of complexes of smaller metal ions. Only for the very large Ba(II) ion does the cryptand structure lead to a significant increase in complex stability. For metal ions of biomedical interest with $r^+$ values close to 1.0 Å, such as Pb(II), Cd(II), Hg(II), Gd(III), Y(III), In(III), Bi(III), and Sm(III), the cyclen structure with pendent donors may offer adequate complex stability and selectivity, with advantages such as greater synthetic simplicity and lower cost.

Table 5
Formation constants from Refs. [33,56], ionic radii from Ref. [14]

| Metal ion | $r^+$(Å) | Cyclen | THP-cyclen | DOTAM | DOTA |
|---|---|---|---|---|---|
| $Cu^{2+}$ | 0.57 | 23.4 | 19.48 | 16.3 | 22.2 |
| $Zn^{2+}$ | 0.74 | 16.2 | 13.45 | 10.47 | 21.1 |
| $Gd^{2+}$ | 0.94 | (~8) | — | 10.05 | 24.0 |
| $Cd^{2+}$ | 0.95 | 14.3 | 17.46 | >19 | 21.3 |
| $Ca^{2+}$ | 1.00 | 3.12 | 5.68 | 7.54 | 16.4 |
| $La^{3+}$ | 1.03 | (~7) | — | 10.35 | 21.7 |
| $Sr^{2+}$ | 1.18 | — | 5.02 | 6.67 | 14.4 |
| $Pb^{2+}$ | 1.19 | 15.9 | 15.07 | >19 | 22.7 |
| $Ba^{2+}$ | 1.35 | — | 3.74 | 5.35 | |

The design approach used in developing the ligand THP-cyclen for use in treating cadmium intoxication has already been discussed [1,35]. Evidence suggests [66] that the metal ion present in the body that competes with at least Gd(III) for coordination in ligands that are being used to sequester metal ions being used in biomedical applications is the Zn(II) ion. One sees from the table in Scheme 11 that the selectivity displayed by THP-cyclen for Pb(II) over Zn(II) is rather small. The use of amide donors in place of alcoholic donors, mentioned above, derives from the greater donor strength of the amide oxygen donor. Thus, the formation constants for the ligand DOTAM compared to THP-cyclen and DOTA are shown in Table 5.

It is seen that the electron-withdrawing effect of the amide groups has lowered the basicity of the nitrogens of the cyclen ring of DOTAM, which has depressed the log $K_1$ values for small metal ions such as Cu(II) and Zn(II) that derive their complex stability chiefly from bonding to the nitrogen part of the ligand. For larger metal ions such as Cd(II) or Pb(II) that are able to achieve the eight-coordination required by the octadentate DOTAM, stability can be very high. In this review we have attempted to demonstrate how useful neutral oxygen donors can be in designing ligands for the coordination of larger metal ions, and it is hoped that the principles outlined here will be useful in the development of new ligands for use in biomedical applications and the environment.

## Acknowledgements

The authors thank the University of the Witwatersrand and the Foundation for Research Development for generous financial support for this work.

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