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The neutral oxygen donor and macrocyclic chemistry

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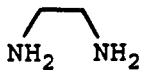
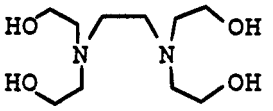
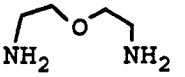
Abstract - The coordinating properties of neutral oxygen donors are discussed. The addition of neutral oxygen donors, whether as part of pendent donor groups, or a macrocyclic ring, leads to an increase in complex stability for large metal ions relative to small. This observation leads to a rule of ligand design, whose use in the design of the ligand 1,4,7,10-tetrakis(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane (THP-12-aneN_4) specifically for removing the heavy metal poison Cd(II) from the body is demonstrated. The reasons for the fact that neutral oxygen donors promote selectivity for large metal ions are explored, and it is suggested that the size selective properties of ligands containing neutral oxygen donors, including such ligands as crown ethers, are largely due to the presence of the neutral oxygen donors as part of five membered chelate rings. Five membered chelate rings have least steric strain with large metal ions of high coordination number, while six membered rings have least steric strain with small metal ions with tetrahedral coordination geometry.

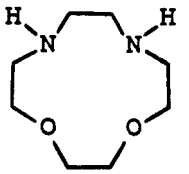
One of the unprecedented properties of the crown ethers when they were first discovered by Pedersen (ref. 1) was the fact that they complexed well with alkali and alkali earth metal ions, but not with transition metal ions. This fact is widely interpreted in terms of the idea of *size-match selectivity*, i.e. that a metal ion will form its most stable complex with that member of a series of macrocyclic ligands where the match between the size of the metal ion and the size of the macrocyclic ligand is closest (ref. 2). We have over the last few years (ref. 3) investigated the coordinating properties of the neutral oxygen donor in its own right as it occurs in non-macrocyclic ligands, and have come to rather different conclusions about the coordinating properties of the neutral oxygen donor, and therefore the crown ethers. An almost invariable effect on the formation constants of complexes of metal ions with ligands is that alteration of the ligand by addition of groups containing the neutral oxygen donor leads to greater stability of the complexes of large relative to small metal ions. The neutral oxygen donors can be added either as pendent alcoholic oxygens, as when EN is turned into THEEN, or as ethereal oxygens,

as when EN is turned into ODEN. The effect on complex stability is seen for the small Cu(II) ion and the large Pb(II) ion:







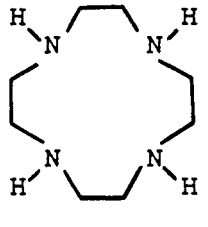


	EN	THEEN	ODEN	12-aneN$_2$O$_2$
logK_1				
Cu(II):	10.50	8.49	8.70	8.7
Pb(II):	5.04	7.2	6.10	6.3

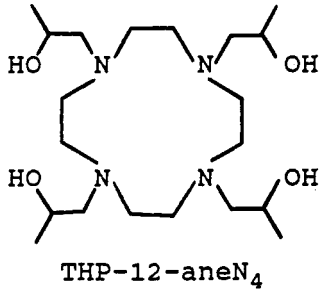
(Formation constant data from references 4 and 5).

One sees from these logK_1 values that the effect of neutral oxygen donors on complex stability is very similar, whether the oxygen donors are part of a macrocyclic ring or not. These observations lead (ref. 6) to a rule of ligand design: *Addition of groups containing neutral oxygen donor atoms to an existing ligand leads to an increase in selectivity of the ligand for large metal ions over small metal ions.*

This rule has proved useful in ligand design efforts aimed at removing heavy metal ions such as Cd(II) and Pb(II) from the body. Both of these ions are large, while metal ions that should not be removed from the body such as Cu(II) and Zn(II) are small. The Ca(II) ion should also not be complexed, which is a major drawback for use of EDTA in removing toxic metal ions, since EDTA has a relatively high affinity for Ca(II). One might try to take advantage of the low affinity of Ca(II) for nitrogen donor ligands by selecting 12-aneN$_4$ as the starting point for ligand design:



12-aneN$_4$



THP-12-aneN$_4$

	ionic radius(Å)	logK_1	logK_1	change in logK_1
Cd(II)	0.95	14.3	17.46	+3.1
Pb(II)	1.18	15.9	15.07	-0.8
Ca(II)	1.00	3.1	5.68	+2.6
Zn(II)	0.74	16.2	13.45	-2.7
Cu(II)	0.57	23.3	19.48	-3.8

(Formation constants from ref. 4 and 7; ionic radii from ref. 8; 1Å = 10^{-10}m).

One sees from the above formation constants that the effect on complex stability follows the rule on metal ion size, with the

apparent exception of the Pb(II) ion. In the case of Cd(II), the ligand THP-12-aneN$_4$ has good selectivity for Cd(II) over Zn(II) and Ca(II). The program ECCLES (ref. 9) can be used to model metal ion equilibria in the body, and calculates a PMI (Plasma Mobilizing Index), which is the ratio of the total concentration of the metal ion in blood plasma in the presence of a ligand, in this case THP-12-aneN$_4$, divided by its concentration in plasma without the ligand present. The PMI of THP-12-aneN$_4$ for Cd(II) is (ref. 10) much higher than for Cu(II), showing that the ligand will remove Cd(II) from the body much more strongly than Cu(II), which is also true for Zn(II) and Ca(II). Preliminary animal studies show (ref. 10) that this is exactly what is observed, with THP-12-aneN$_4$ being able to remove Cd(II) very effectively, without removing any Cu(II), Ca(II), or Zn(II).

The behaviour of Pb(II) with THP-12-aneN$_4$ is disappointing. One might have expected it to show a strong increase in logK_1 with THP-12-aneN$_4$ relative to 12-aneN$_4$, as was found for the other large metal ions Ca(II) and Cd(II). The origin of this problem appears to be (ref. 7) that the Pb(II) ion can have a stereochemically active lone pair of electrons, or a lone pair that is not stereochemically active. The consequences of this are (ref. 7) that when the lone pair becomes stereochemically active, the bonds from the Pb(II) to the donor atoms on the side of the complex away from the lone pair become shorter, by about 0.3 Å (Fig 1). The

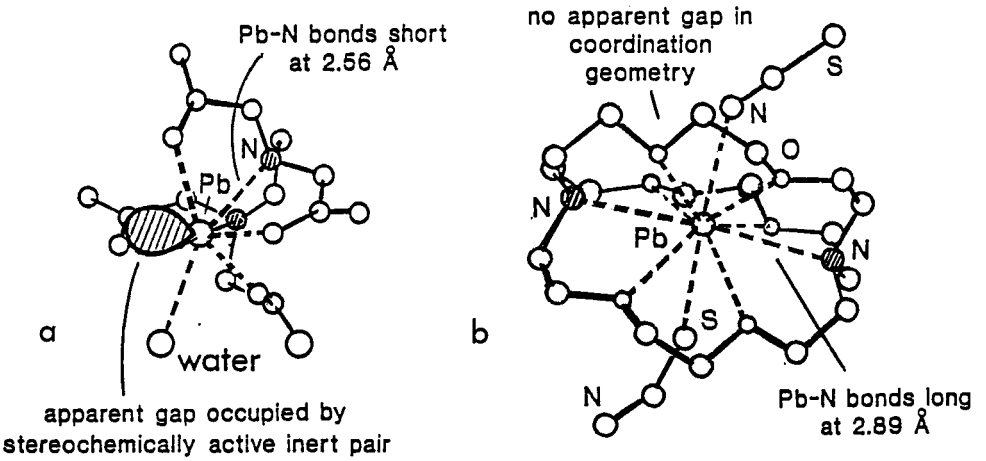
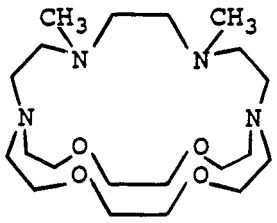


Fig. 1. Drawing of (a) the Pb(II) EDTA complex where the inert pair is stereochemically active (ref. 13), and (b) the Pb(II) complex with cryptand-2,2,2 where the inert pair is (ref. 14) stereochemically inactive.

evidence suggests (ref. 7) that the lone pair in the [Pb(12-aneN$_4$)(H$_2$O)$_x$]$^{2+}$ complex is stereochemically active. We are thus dealing here with a much smaller metal ion than would be suggested by the octahedral ionic radius, and the rules for ligand design concerning the use of groups containing neutral oxygen donors do not apply in any simple way to Pb(II) complexes where the lone pair is sterochemically active. The tendency for the lone pair on Pb(II) to become stereochemically active appears (ref. 7) to become stronger as the tendency of the donor atoms on the ligand to form more covalent metal-ligand bonds increases. This creates a problem because, in order to achieve the high complexing power necessary to

remove Pb(II) from the body, one would naturally tend to use more strongly coordinating groups, which will most likely lead to a stereochemically active lone pair on Pb(II), and hence problems in applying the rule regarding neutral oxygen donors and complex stability to ligand design for Pb(II). A way out here might be to apply ligand *preorganisation* as a means of increasing complex stability without necessarily increasing the covalence of the M-L bond. Preorganisation is a term coined by Cram (ref. 11) which is the extent to which the free ligand is fixed in the conformation required for complexing the target metal ion. The increases in complex stability associated with the chelate and macrocyclic effects would be (ref. 12) an example of preorganisation.

It is interesting to compare the ligand THP-12-aneN_4 with cryptand-2,2,(N-CH_3)$_2$. Both ligands have the same donor set, namely an N_4O_4 donor set, so any differences must be due to ligand architecture.



cryptand-2,2,(N-CH_3)$_2$

With all metal ions smaller than Pb(II), the ligand THP-12-aneN_4 forms more stable complexes (refs. 4,7) than does cryptand-2,2,(N-CH_3)$_2$. This behaviour is very strongly related to metal ion radius, and in Figure 2 is shown a plot of the difference in logK_1 between the THP-12-aneN_4 and cryptand-2,2,(N-CH_3)$_2$ complexes versus the ionic radii (ref. 8) of the metal ions. It is seen that the larger the metal ion, the more it favours the cryptand, while the smaller it is the more it favours the pendent donor macrocycle.

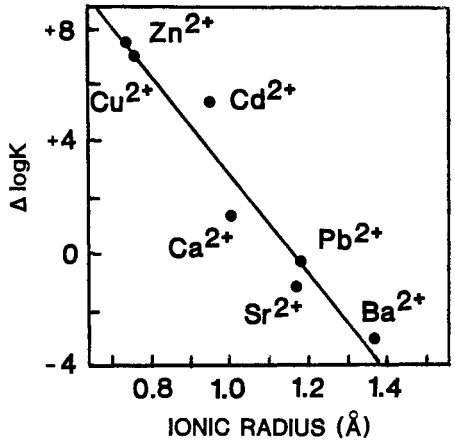


Fig. 2. Relationship between Δlog$K$ and metal ion radius. Δlog$K$ values are logK_1 for THP-12-aneN_4 minus logK_1 for cryptand-2,2,(N-CH_3)$_2$. Ionic radii from ref. 8, formation constants from refs. 4 and 7.

Fig. 2 is interesting in that it shows that the monocyclic THP-12-aneN_4 forms more stable complexes than the bicyclic cryptand-2,2,(N-CH_3)$_2$ with metal ions smaller than Pb(II). The interpretation that would be put on this at this stage is that THP-12-aneN_4 is much less sterically demanding than the cryptand, where only Ba(II) Pb(II) and Sr(II) fit well. Looking at the two ligands, it would appear that the main effect of the cryptand structure is to suppress complex stability in the majority of metal ions relative to THP-12-aneN_4. The cryptand shows stronger selectivities than does the monomacrocycle, but the selectivities of the latter are, as shown by animal studies (ref. 10) in any case satisfactory, and the much stronger complexing abilities of THP-12-aneN_4 make it a better ligand for removing large toxic metal ions of the size of Cd(II).

The upward deviation of the point for Cd(II) in Figure 2 suggests that the Cd(II) complex of THP-12-aneN$_4$ is of particular stability. Eight coordinate Cd(II) has an ionic radius (ref. 8) of 1.10 Å, suggesting a Cd-O bond length of 2.47 Å, close to the ideal M-L of 2.50 Å required (ref. 15) for coordination in five membered chelate rings. In Fig. 3 are the ideal metal ion sizes and geometries for coordinating in five and six membered rings. Five membered rings coordinate best with large metal ions with high coordination numbers, which give smaller L-M-L angles, while six membered chelate rings fit best onto small metal ions of low coordination number, which gives large L-M-L angles. Also in Fig. 3 is the MM generated structure of [Cd(THP-12-aneN$_4$]$^{2+}$, showing how the geometry of the chelate rings, which are all five membered, approaches quite well the ideal geometry for five membered chelate rings. The Cd-O and Cd-N bonds in [Cd(THP-12-aneN$_4$]$^{2+}$ are somewhat stretched by non-bonded repulsions between the pendent donor groups, which problem would be even worse for smaller metal ions.

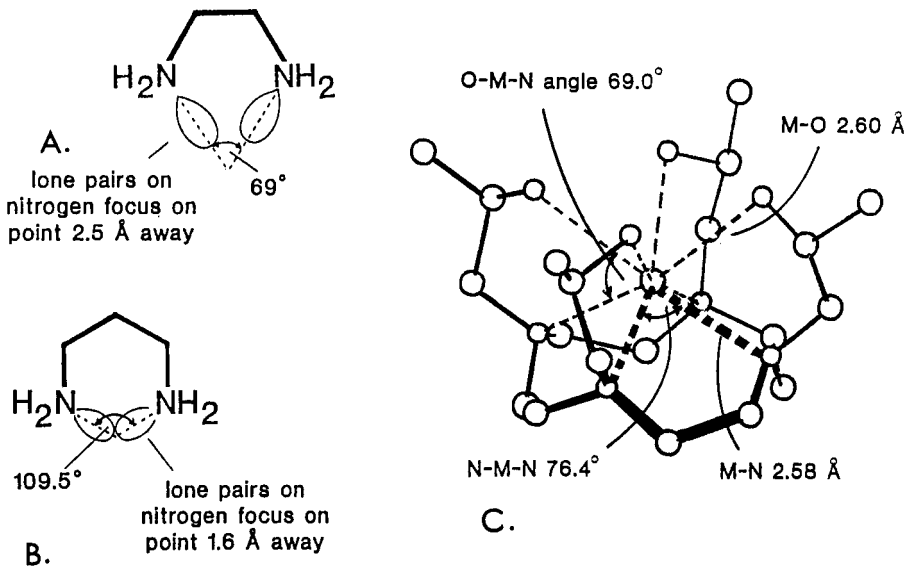


Fig. 3. Ideal size metal ion for coordination in (A) five membered chelate ring and (B) six membered chelate ring. At (C) is shown the molecular mechanics generated structure of [Cd(THP-12-aneN$_4$)]$^{2+}$.

The work reported here points the way to the use of neutral oxygen donors in pendent groups as useful ways of controlling complex stability based on metal ion size. Pendent oxygen donors also offer such advantages as synthetic simplicity in the generation of ligands useful in areas such as medicine or the environment.

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