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The role of donor group orientation as a factor in metal ion recognition by ligands

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Contents

Abstract

Factors that control the metal ion complementarity of ligand architectures are described. These include cavity size, metal ion topography, and donor group orientation. Attention focuses on the last factor with a detailed discussion of how molecular mechanics has been used to investigate the role of donor group orientation in polyamine and polyether ligands.

Keywords: Molecular mechanics; Metal ions; Ligand design; Amine; Ether; Complementarity; Preorganisation; Amide

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1. Introduction

Much has been done and written with respect to understanding the factors that control metal ion binding affinity with ligands [1–10]. A principal factor is the covalent or ionic nature of the M–L (M, metal, L, ligand donor atom) bonds formed in terms of the hard and soft acid and base (HSAB) classification of Pearson [1]. One points out here that a major theme of this review is steric effects and selectivity, so that we mention in passing that it has been suggested that there is a major steric component in generating HSAB behavior [6], in addition to the covalent and ionic contributions. Following closely on the primary consideration of correct choice of ligand donor atom type for complexing the target metal ion is ligand architecture.

Ligand design consists essentially of selecting appropriate donor atoms for the target metal ion, and then connecting that number of them appropriate for the coordination number of the metal ion in an architecture that satisfies the geometric requirements of the metal ion. Two general issues arise. The first issue is that of preorganization [9]. Preorganization can be viewed as an entropy effect [11]. The more conformational states that the ligand can be in, the less likely it is to be in the binding conformation required to coordinate to the metal ion. Conformational freedom of ligands can be readily investigated using molecular modeling techniques based on classical force fields (molecular mechanics (MM) or molecular dynamics (MD)). The influence of preorganization in terms of the chelate effect [2], the macrocyclic effect [3], and the cryptate effect [4] have been extensively reviewed elsewhere [12].

The second issue, the subject of this review, is complementarity [13], i.e. the degree of structural correspondence between the binding sites offered by a ligand structure and the binding sites required by a metal ion. Once we choose a ligand architecture to link our donor atoms together, they are constrained to certain regions in space defined by the conformational states of the ligand. After the binding conformation(s) of a ligand has been identified, the questions to be addressed are as follows.

- How well does this structure complement a given metal ion?
- What are the structural factors that give rise to complementarity?
- Given two structures with identical sets of donor atoms, how do we determine which one gives the best fit with the target metal ion?

2. Ligand cavity size

One of the criteria for optimal complementarity is that the metal ion be able to contact all the donor atoms of the ligand at an optimal M–L distance. If the cavity presented by an array of donor atoms is too large, then the possibility exists that not all of the donor atoms will be able to make contact. The converse is also true, that if the cavity is too small, then the metal ion cannot enter and cannot contact the donors at an optimal distance. The concept of matching size of ligand cavity to size of metal ion, i.e. size-match, has been in the past, and continues in the present to be, a major consideration in ligand design. However, the use of cavity size as the sole criteria for the design of complementary ligand architecture often fails to yield the desired result.

An example is provided by the ligand series 12-aneN_4 through 16-aneN_4. One might expect that the affinity of the tetra-azamacrocycles for a large metal ion such as Pb(II) would increase with increasing size of the macrocylic ring, and hence increasing cavity size. In fact, the exact opposite is observed [14]. As shown in Table 1, there is a steady decrease in Pb(II) affinity as size of the macrocyclic ring increases.

Despite many examples such as that above, it remains a common belief that size-match is the only important factor with respect to metal ion complementarity. This is the basis of the principle of size-match selectivity, i.e. the idea that a ligand will form the strongest complex with the metal ion that most closely matches the size of the ligand cavity. The principle of size-match selectivity was first proposed based on the behavior of 18-membered ether macrocycles such as 18-crown-6 [15]. However, subsequent studies have established this behavior to be anomalous since the smaller crown ethers 15-crown-5 and 12-crown-4 fail to exhibit the predicted selectivity for Na^+ and Li^+, respectively [16–19]. On the basis of these and other examples, it has been concluded that the size-match selectivity concept alone is not a particularly useful tool for rationalizing or predicting the metal ion selectivity of macrocyclic ligands [14,20]. There is some evidence that size-match selectivity can be achieved with more three-dimensional architectures. For example, size-match successfully predicts alkali cation affinities for a series of cryptands built up by successive addition of ethylene bridged ether donors [21]. However, we note that the size-match criteria fails to predict the observed behavior when ethylene bridges are substituted with propylene bridges to yield larger cryptand cavities [21].

Achieving optimal M–L distance is clearly an important factor in determining whether a ligand architecture is complementary for a given metal ion. The ligand scaffold must position the donor groups such that they can contact the metal ion without causing excessive strain in the complex. However, as the evidence presented above illustrates, size-match is a necessary, but not a sufficient condition for complementarity. There are at least two other structural factors that must be considered to account for the influence of ligand architecture on metal ion binding affinity and selectivity.

Table 1
Aqueous formation constants for tetraazamacrocycles with Pb(II) [14]

Macrocycle	12-aneN_4	13-aneN_4	14-aneN_4	15-aneN_4	16-aneN_4
log K_1	16.0	13.6	10.8	10.2	9.6

Table 2
Aqueous formation constants for dien and 9-aneN3 with transition metal ions [27]

Metal ion:	Ni(II)	Cu(II)	Zn(II)
log K_1 (dien)	10.7	15.9	8.8
log K_1 (9-aneN_3)	16.2	15.5	11.6

3. Metal ion topography

Much is presently known about packing of donor atoms about metal ions. In many cases, the polyhedra that are observed can be rationalized in terms of simple points-on-a sphere (POS) models [22–26]. The structures that we observe are those that would be expected on the basis of ligands spreading out to minimize steric repulsion. If we are designing for a POS type of metal ion, e.g. Group 1A and 2A metals, trivalent lanthanides and actinides, then it does not matter so much where we locate the donor atoms, as long as the criteria of correct cavity size and correct orientation of the donor group with respect to the metal ion, discussed below, are satisfied. Idealized polyhedra are not necessary. For example, the POS model predicts that the best packing for six donor atoms is an octahedron. Yet, potassium coordinates 18-crown-6 in a planar D_{3d} conformation that places the six oxygen atoms in a nearly planar array that does not correspond to a stable POS arrangement.

Certain metal ions do exhibit bonding directionality and in these cases, the position of the donor atoms in the coordination sphere can have a marked effect on complex stability. The effect of ligands that are constrained in such a way that they cannot meet the steric requirements of the metal ion is seen, for example, in complexes of Cu(II) with 9-aneN_3. The tridentate 9-aneN_3 is constrained to coordinate to one face of an octahedron. The square-planar coordination geometry preferred by Cu(II) cannot accommodate this geometry. As a result, one sees that in the series of complexes formed with dien as compared with 9-aneN_3, for example, there is not the large increase in complex stability at the Cu(II) complex with 9-aneN_3 that might be expected [27]. In fact, 9-aneN_3 is one of the few ligands that forms a complex with Ni(II) that is more stable than the Cu(II) analog (see Table 2)

Of particular interest are the post-transition metal ions such as Pb(II) and Bi(III) that may display a stereochemically active lone pair of electrons, which is apparent in crystal structures as a gap in the coordination sphere which is presumed to be occupied by the lone pair. This is illustrated in Fig. 1 where the crystal structure of a $[Pb(II)(en)(acetate)_2]$ is displayed [28]. The lone pair has the effect that M–L lengths become shorter on the side of the metal ion away from the lone pair, and lengthen as they are closer to the lone pair. This is an effect that would create interesting steric requirements in designing ligands specific for Pb(II) or Bi(III).

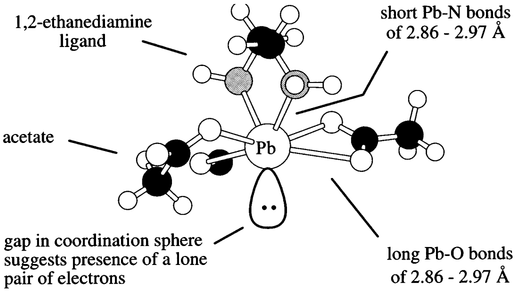

Fig. 1. Crystal structure of [Pb(II)(en)(acetate)$_2$] showing the effect of the lone pair of electrons on the structure [28].

4. Donor atom orientation

Given the popularity of concepts such as size-match and metal ion topology match, the importance of the orientation of the donor atoms is an often-overlooked aspect of complementarity. It is a simple fact that to obtain the maximum interaction with the metal ion, the donor group must have the proper orientation with respect to the metal ion. It is often incorrectly concluded that maximum complementarity is achieved when the architecture of a ligand places the donor atoms at the optimal distance from the metal center, and when the topology of the complex satisfies metal ion bond directionality. Examples of this would be the M–O distances in 18-crown-6 satisfying the requirements of the K^+ ion, or the ligand cyclam allowing for the square planar geometric requirements of the Cu^{2+} ion [7]. With attention focused on the metal center, targeting cavity size and idealized polyhedra, a third important factor is overlooked. There must be a proper orientation of the donor atom with respect to the metal ion.

In M–L bonds that are regarded as covalent, there must be a correct alignment of donor atom orbitals and metal orbitals in order to achieve the strongest covalent bonds. Similarly, in ionic M–L bonds the orientation of the ligand dipoles towards the metal ion must be such as to achieve optimum electrostatic interaction. In the case of coordination of saturated nitrogens to metal ions, as in the complex of Cu^{2+} with dien [7], the ideal orientation of the nitrogen towards the Cu^{2+} ion requires a Cu–N–C bond angle of 109.5°, and a Cu–N–C–C dihedral angle of ± 60 or 180° (see Fig. 2). For K^+ complexes with ethers, the geometry around the oxygen coordinated to the K^+ should be planar [10], with K–O–C bond angles of 123.5°, and K–O–C–C torsion angles of 0 or $\pm 120°$ (see Fig. 6).

To evaluate the consequences of donor group orientation on the complementarity of a multidentate ligand, it is first necessary to understand the structural requirements for optimal interaction between the metal ion and each of the donor groups present in the system. That is to say, we must know the geometry that defines the optimal orientation of a donor group, usually defined in terms of M–L–X angles and M–L–X–X dihedral angles (where X is usually but not always a C atom), as well as the energetic cost of distortion away from this geometry. In what follows we will present the optimal orientation for several types of donor groups, and discuss how ligand architecture impacts donor orientation in multidentate ligands. We employ a useful device for visualizing donor orientation. To each donor atom we attach a vector (set at 5 Å in length) emanating at the optimal M–L–X angle and M–L–X–X dihedral angle. The strongest interaction with each donor group will occur when the metal ion lies on the vector attached to that donor group. Optimum complementarity in a multidentate ligand requires that all the donor group vectors intersect on the point where the metal ion is located.

4.1. Amine donor atoms

The importance of donor group orientation was first realized in studies of amine complexes [6]. The geometry leading to optimal interaction with the amine nitrogen is shown in Fig. 2. For this tetrahedral nitrogen donor atom, the lone electron pair points directly at the metal ion yielding an M–N–C bond angle of 109.5°. In addition, the metal ion must be located such that it is in a staggered configuration with respect to the substituents on carbon, i.e. with an M–N–C–X dihedral angle of ±60 or 180°. Failure to achieve this orientation weakens the interaction. For example, using the structure in Fig. 2, a 10° compression of the M–N–C angle with accompanying 5° increases in the M–N–H bond angles weakens the bonding interaction by 0.7 kcal mol^{-1} (with a 0.2 mdyn Å rad^{-2} force constant for M–N–X angle distortion [6]).

Fig. 2. The optimal orientation for the amine donor group with transition metal ions. The strongest covalent interaction with a tetrahedral nitrogen donor occurs when M–N–X has a value of 109.5° and the M–N–C–X torsion angle has a value of ±60 or 180°.

The architecture of a multidentate amine ligand can prevent the donor groups from achieving an optimal orientation to the metal ion. This phenomenon is observed even in simple bidentate amines [6–8]. Fig. 3 illustrates the three-dimensional structures of 1,2-ethanediamine (en) and 1,3-propanediamine (tn), each in a binding conformation. Vectors to the nitrogen atoms show the optimal orientation of a metal ion with respect to each of the two donor groups. Examination of en reveals that these vectors do not intersect at any distance from the ligand, i.e. with respect to donor orientation this architecture is not strictly complementary for any size metal ion. Distortion of the ligand structure is required to bring the vectors into convergence. In terms of energy, bond rotations are the least costly, and with rotations of 10–15° about the C–N and C–C bonds of en the vectors intersect at a distance of ~2.7 Å from the nitrogen donors. Thus, the ethylene linkage constrains the donor groups in an orientation that is most complementary for large metal ions. Another way of stating this is that at an M–N distance of 2.7 Å, we obtain the best

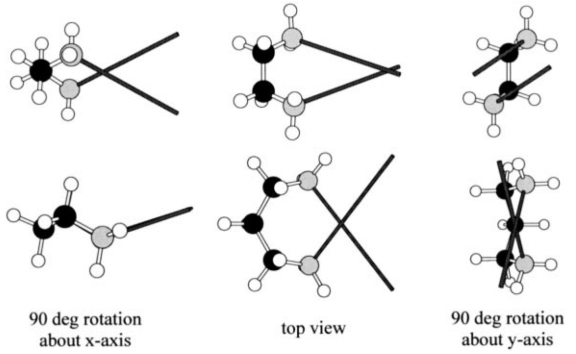

Fig. 3. Three views of 1,2-ethanediamine (en) (top) and 1,3-propanediamine (tn) (bottom). The 5 Å vector attached to each nitrogen illustrates the optimal line of approach for the metal ion to overlap with the lone pair on the nitrogen donor atom.

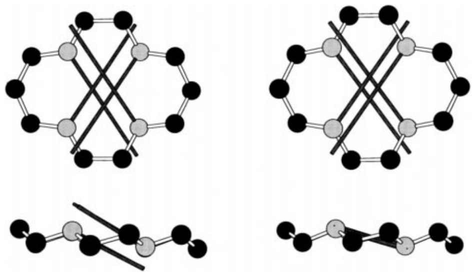

Fig. 4. Donor group orientation vectors in the + + − − conformer of 14-aneN_4 before (left) and after (right) coordination to Ni(II).

nitrogen atom orientation possible (M–N–X, 109.5°; M–N–X–X, between 40 and 50°, or between 160 and 170°), with the least amount of steric distortion to the ligand. Examination of tn reveals a different picture. Here the vectors intersect at a distance of ~2.0 Å from the nitrogen atoms without requiring any distortion of the ligand. Thus, the propyl linkage in tn constrains the donor groups in an orientation that is perfectly complementary for an M–N–X distance of 2.0 Å.

We note that the M–N distances of 2.7 and 2.0 Å presented herein for the en and tn rings were calculated with the MM3 force field and therefore differ somewhat from values of 2.5 Å for en rings and 1.6 Å for tn rings reported previously by one of the present authors [8,29]. Possibly more detailed studies might pin down the ideal M–N bond length for these chelate rings, but this will require a consideration of the likely variation in M–N–X and M–N–X–X parameters as the metal ion size is varied (see Section 5).

The geometric constraints imposed by ethylene and propylene linkages are not restricted to simple diamine ligands. Similar structural interactions are present when these linkages occur in multidentate ligand systems, and as a consequence, similar constraints on donor atom orientation are imposed. Fig. 4 shows 14-aneN_4 in the

$++--$ conformation before and after coordination to Ni(II). Prior to metal complexation, the donor atoms in this tetradentate ligand exhibit the same geometries seen in the bidentate ligands (Fig. 3). Vectors from each pair of propylene-bridged nitrogens converge in the same way as those in tn, and vectors from each pair of ethylene-bridged nitrogens diverge in the same way as those in en. On coordination to Ni(II), a metal ion with an M–N distance complementary to this cavity, structural changes to the ligand occur as the amine groups attempt to attain their optimal orientation. Although the structural changes do improve the convergence of the four vectors, it is not possible for all four nitrogens to simultaneously achieve the optimal geometry with respect to the metal ion.

The preceding example serves to illustrate an important point. The possible orientations of two adjacent donor groups are largely controlled by the structure linking them together. This observation provided the motivation for detailed study of steric effects [8,29] in isolated diamine chelate rings. Molecular mechanics calculations were used to examine the strain five-membered and six-membered chelate rings formed by diamine metal complexes as a function of both M–N distance and N–M–N angle. The results confirm that the five membered chelate ring formed by en has an intrinsic preference for larger metal ions. The six-membered ring formed by tn has an intrinsic preference for small metal ions. Calculations show that size mismatches can lead to increases in strain energy of the chelate ring of as much as 6 kcal mol^{-1}. These calculations lead to the formulation [8] of a rule of ligand design, *The complexes of large metal ions are destabilized more than those of small metal ions by an increase in chelate ring size from five to six membered.*

A large body of experimental evidence supports these findings [7,8,12,14,29–32]. Replacing five-membered chelate rings with six-membered chelate rings often results in a dramatic increase in selectivity for smaller metal ions. This effect is illustrated in Fig. 5. The effect of adding two methylene groups to 12-aneN$_4$ to obtain 14-aneN$_4$, is measured by the difference in log K values for forming each complex. The resulting $\Delta\log K$ corresponds to log K for the reaction:

$$[\mathrm{M(12\text{-}aneN_4)}]^{n+} + \mathrm{14\text{-}aneN_4} \rightarrow [\mathrm{M(14\text{-}aneN_4)}]^{n+} + \mathrm{12\text{-}aneN_4}.$$

Similarly, the effect of adding one methylene group to EDTA to obtain TMDTA is measured by the $\Delta\log K$ for this system. Fig. 5 shows plots of the $\Delta\log K$ values for these systems versus the ionic radius of the metal ion. What one sees in Fig. 5 is that the response of $\Delta\log K$ for both the EDTA/TMDTA pair of ligands and the 12-aneN$_4$/14-aneN$_4$ pair of ligands, are very similar. One interprets this as evidence that changes in the amine donor orientation associated with the chelate ring size are governing $\Delta\log K$. In both the pairs of ligands, chelate ring sizes are increasing from five- to six-membered, and the increase in ring size favors complex formation with smaller metal ions. Fig. 5 demonstrates how closely complex stability is tied to chelate ring size and demonstrates how the effect of chelate ring size on metal ion selectivity of ligands is observed for both open chain and macrocyclic ligands. In the latter case, where the cavity size is thought to be increasing in passing from 12-aneN$_4$ to 14-aneN$_4$, the changes in complex stability are exactly the opposite of what would be predicted from size-match selectivity. The answer as to why a large

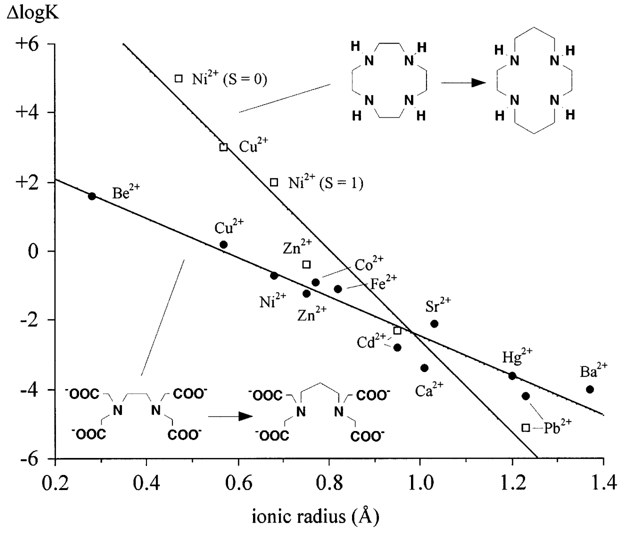

Fig. 5. Illustration of the effect of change of chelate ring size from five- to six-membered on the complex stability of analogous pairs of ligands differing only in chelate ring size. The value of $\Delta \log K$ is the constant for the reaction $ML + L' = ML' + L$. For the two ligand pairs shown on the diagram, L and L′ are the pair of analogous ligands with the first member of the pair form all five-membered chelate rings, while the second member of the pair forms at least one six-membered chelate ring.

metal ion such as Pb(II) would prefer to complex with 12-aneN_4 with its smaller cavity than 14-aneN_4 lies in (1) the flexibility of macrocycles, and (2) the intrinsic complementarity of ethylene-bridged amine donors for larger metal ions.

4.2. Ether donor atoms

The effect of donor group orientation on metal ion complementarity has been studied in detail for ether complexes with the alkali and alkaline-earth metal ions [10,33–38]. Fig. 6 shows the geometry leading to optimal interaction with the ether oxygen. The strongest interaction is obtained when the metal ion aligns with the ether dipole yielding a trigonal planar oxygen. The M–O–C angles are 123.5° and the metal ion lies in the plane of the C–O–C moiety, giving rise to M–O–C–X torsion angles of 0 and ± 120°. As with amines, failure to achieve this orientation can significantly weaken the interaction. For example, a 30° displacement of Na^+

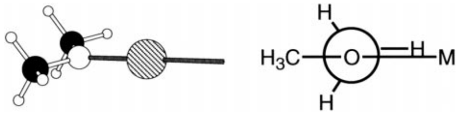

Fig. 6. The optimal orientation for the ether donor group with alkali and alkaline earth metal ions. The strongest electrostatic interaction with the oxygen occurs when the metal approaches along the dipole moment of the ligand to give M–O–C angles of 123.5° and M–O–C–X dihedral angles of 0 and ± 120°.

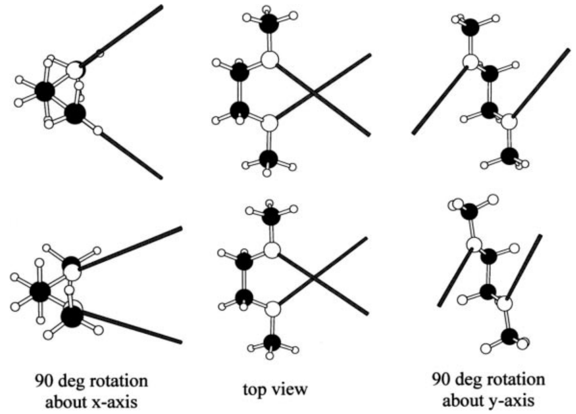

Fig. 7. Three views of 1,2-dimethoxyethane (dme) before (top) and after (bottom) Na^+ complexation. The 5 Å vector attached to each oxygen illustrates the optimal line of approach for the metal ion.

from the C–O–C plane, a distortion commonly seen in crystal structures of crown ether complexes, is accompanied by a loss in energy of 1.0 kcal mol^{-1} [34].

The ethylene group is a common linkage for two ether donor atoms. Fig. 7 illustrates the three-dimensional structure of a metal ion binding conformation of 1,2-dimethoxyethane (dme). Vectors to the oxygen atoms show the optimal orientation of a metal ion with respect to each of the two donor groups. Like en (Fig. 3), we observe that the vectors do not intersect at any distance from the ligand. However, the divergence is much more pronounced than in the diamine case and, as a result, much larger C–C and C–O rotations, 45–50°, are required to have the vectors intersect. Thus, in comparison to the ethylene-bridged tetrahedral nitrogen atoms, ethylene-bridged trigonal planar oxygen atoms yield a structure of significantly lower complementarity [35]. When a metal ion coordinates with dme, structural changes to the ligand occur as the ether groups attempt to attain their optimal orientation. However, as shown in Fig. 7, the ethylene linkage prevents this from occurring.

Molecular mechanics calculations have been used to examine the five-membered chelate rings formed by diether metal complexes as a function of both M–O distance and metal ion charge [34–36]. The results reveal that the five-membered chelate ring formed by dme has an intrinsic steric preference for large, low charged metal ions. This finding is completely congruent with the observation that metal ions that complex well with crown ethers all have ionic radii above 1.0 Å and cationic charges of two or less [39].

Molecular mechanics calculations also have been performed on five-membered ether chelate rings to examine the effect of alkyl substitution on metal ion complementarity [36]. The calculated degree of complementarity afforded by different linkages was found to correlate with experimental changes in complex stability caused by alkyl substitution of crown ether macrocycles. For example, the analysis revealed that relative to the unsubstituted ethylene linkage, *cis*-cyclohexyl substitution has almost no effect on complementarity whereas *trans*-cyclohexyl substitution significantly decreases complementarity. This result explains, in part, the experimental result that when two *cis*-cyclohexyl substituents are added to 18-crown-6, binding affinities for potassium decrease by a factor of two whereas when *trans*-cyclohexyl groups are added to 18-crown-6, binding affinities decrease by a factor of 250 (MeOH, 25°C).

As is the case with amine donors, the geometric constraints imposed by the ethylene linkage are not restricted to dme. Similar effects are present in macrocyclic ethers in which the oxygens are connected by ethylene linkages [34]. Fig. 8 shows 18-crown-6 in the D_{3d} conformation before and after coordination to K^+. Although it is widely believed that this architecture is ideally organized for potassium coordination when judged by M–O distance, examination of the orientation vectors again reveals that the ethylene linkages preclude optimal M–O–C and M–O–C–X torsion angles. Instead, three vectors intersect at a point above the cavity and three vectors intersect at a point below the cavity, with the intersections at a distance of 3.9 Å from the oxygen atoms. Thus, with respect to donor group orientation this conformation of 18-crown-6 provides two tridentate binding sites that are perfectly complementarity for an M–O bond length of 3.9 Å. Coordination of the potassium ion within the center of the cavity results in an unsuccessful attempt to align the dipoles with the metal ion. Structural changes within each chelate ring are almost identical to those observed in an isolated dme chelate ring (Fig. 6) [34]. The dipole misalignment destabilizes the potassium complex. Thus, although this ligand exhibits a log *K* of 6.1 for K^+ complexation in methanol, it has been estimated that ligand architectures offering an optimal alignment of the six ether donor groups could increase the log *K* value by three orders of magnitude in this solvent [40].

15-Crown-5 provides an even more striking example of non-complementary ether oxygen orientation. The ligand conformer that most readily binds with Na^+ has been identified [41]. Fig. 9 shows this 15-crown-5 conformer before and after

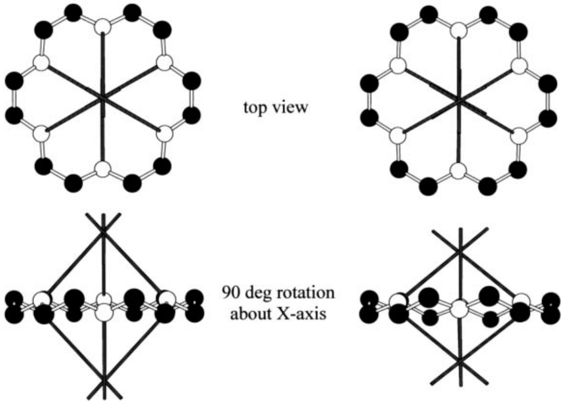

Fig. 8. Donor group orientation vectors in the D_{3d} conformer of 18-crown-6 before (left) and after (right) K^+ coordination.

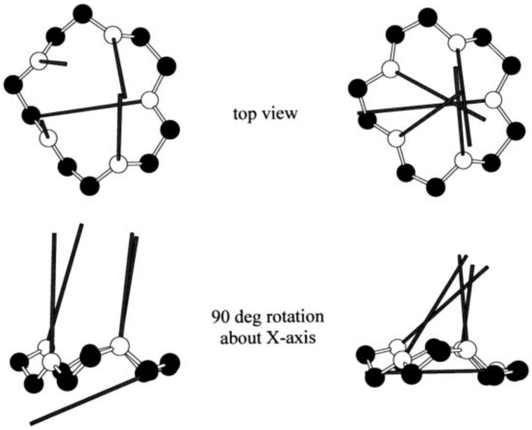

Fig. 9. Donor group orientation vectors in the Na^+ binding conformer of 15-crown-5 before (left) and after (right) Na^+ coordination.

coordination to Na^+. Prior to Na^+ complexation, the vectors are pointing above and below the plane of the cavity defined by the five oxygens. In no case is an oxygen atom oriented to place a metal ion within the center of this cavity at an optimal position. Thus, what initially appears to be an architecture ideally sized for Na^+ complexation when judged by M–O distance, on closer inspection turns out to be an architecture without a cavity when judged by O-orientation. As with 18-crown-6, metal ion coordination results in structural distortion to the ligand due to attempts to align the dipoles with the metal ion. The poor degree of Na^+ complementarity provides a steric explanation for the failure of this macrocycle to obey the size-match rule (vide supra).

A similar argument explains why 12-crown-4, with a cavity size diameter of 4.06 Å, coordinates only very weakly to ‘suitably sized’ cations such as Li^+ and Mg^{2+}. Almost without exception, 12-crown-4 adopts a C_4 symmetry conformation when coordinated with the alkali and alkaline earth cations. Fig. 10 shows this 12-crown-4 conformer before and after coordination to Li^+. We observe that none of the oxygen atoms are oriented to place a metal ion in the center of the cavity at an optimal position. Instead, the vectors are nearly perpendicular to the plane of the oxygens and they do not intersect at any distance from the cavity. Thus, what initially appears to be an architecture ideally sized for Li^+ when judged by M–O distance, again turns out to be an architecture without a cavity when judged by oxygen orientation.

Linear correlations between metal ion binding affinity (e.g. log K values or extraction constants) and molecular mechanics strain energies have been reported for a number of complexes with macrocyclic polyethers [33,34,36,40,42–44]. In almost all the cases that have been examined in these studies, the molecular mechanics model indicates that once the ligand has adopted its binding conformation, the primary structural factor leading to steric strain in these complexes is a failure to meet donor orientation requirements rather than a failure to meet M–O distance requirements.

A final example of the importance of donor group orientation is provided by recent theoretical studies of a hexadentate starand [45,46]. This rigid architecture, shown in Fig. 11, offers a cavity diameter of 3.81 Å from X-ray data and, on the basis of size-match criteria, it appeared to be a promising ionophore for Li^+. However, HF/6-31G* calculations revealed that the Li^+ complex was actually 12.7 kcal mol^{-1} more stable when the metal ion was coordinated to three oxygens outside the cavity than when the metal ion was coordinated to six oxygens inside the cavity. This behavior is readily understood on examination of the orientation of the oxygen donors. Fig. 11 reveals that, like 18-crown-6, three of the vectors intersect at a point above the cavity and three of the vectors intersect at a point below the cavity. In this instance, the intersections are at a distance of 5.0 Å from the oxygen atoms to yield an architecture that provides two tridentate binding sites that are perfectly complementary for an M–O bond length of 5.0 Å.

The donor orientation of the starand architecture (Fig. 11) contrasts sharply with that of another hexadentate ether architecture, the hexa-anisole spherand shown in Fig. 12. Like the starand, the spherand structure is constrained to one conformation and exhibits a cavity diameter that is appropriately sized for Li^+. Unlike the

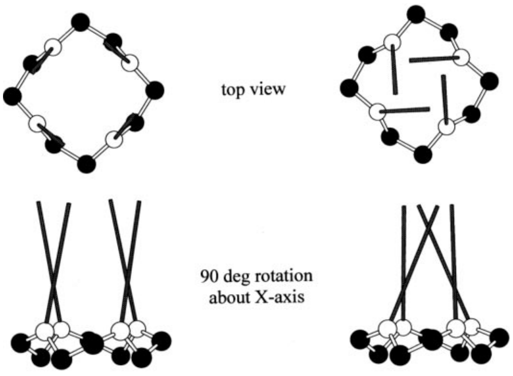

Fig. 10. Donor group orientation vectors in the C_4 conformer of 12-crown-4 before (left) and after (right) Li^+ coordination.

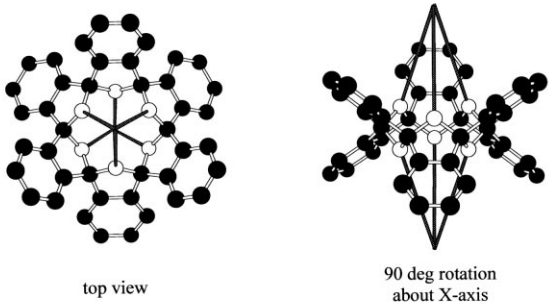

Fig. 11. Donor group orientation vectors in the starand before metal ion coordination.

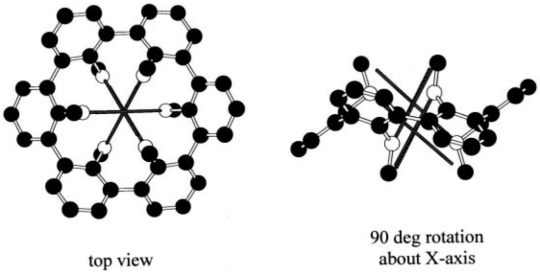

Fig. 12. Donor group orientation vectors in the spherand before metal ion coordination.

starand, however, the spherand architecture orients all six of the oxygen donors such that the vectors converge to two points within the cavity. Thus, whereas theory predicts that Li^+ will not enter the starand cavity, experiment has shown that Li^+ enters the spherand cavity to form the most stable Li^+ complex known for a hexadentate ether [47].

5. Concluding remarks

We have discussed three factors that must be considered in assessing the degree of metal ion complementarity that is offered by a given ligand architecture. These are the cavity size, the spatial distribution of donor atoms about the metal ion, and the orientation of the donor groups. Because of the way that traditional molecular mechanics models partition the steric energy into stretching, bending, and torsional interactions, such models are ideally suited to evaluate these factors [8,48–50]. The effect of cavity size mismatch can be gauged by strain in M–L bond interactions. With the proper choice of model, e.g. explicit definition of L–M–L angles for metal centers that exhibit directional bonding, the effect of topography mismatch can be gauged by the strain in L–M–L bending interactions. Finally, the effect of donor group orientation can be gauged by the strain in M–L–X and M–L–X–X torsional interactions. The total increase in molecular mechanics strain energy caused by metal ion complexation provides a convenient way to measure the degree of metal ion complementarity offered by a given architecture [7,36,40].

In this review, we have stressed how donor group orientation plays a critical role in defining the complementarity of the ligand architecture and, thus, in determining the stability of metal complexes. It is important to note, however, that compared with our general knowledge of M–L distance and L–M–L angle requirements, relatively little is known about the donor group orientation. This statement is readily appreciated by practitioners of MM where the assignment of parameters for M–L–X bending and M–L–X–X torsional interactions is a recurring issue. A common approach is to assume an idealized geometry at the donor atom, e.g. tetrahedral or trigonal planar, and to assign metal-independent bending force constants and rotational barriers, often by comparison with values used for analogous interactions within organic molecules. Such generic orientation parameters are then applied over a wide range of metal size and charge, e.g. in metal-size scans of macrocyclic ligands. There is growing evidence to suggest, however, that this approach is flawed.

One piece of evidence comes from the studies on aliphatic ether donors. Electronic structure calculations were used to determine geometries and potential energy surfaces for the orientation of the ether donor group with respect to the alkali and alkaline earth metal ions [34]. Although all metal ions examined yielded the same orientations in terms of M–O–C angle and M–O–C–X dihedral angle (Fig. 6), the energetic cost of distortion from this orientation varies greatly with the size and the charge of the metal ion. If either the size of the metal ion increased or the charge on the metal ion decreased, then it becomes easier to distort from the preferred geometry. In other words, as the M–O interaction becomes weaker, the orientation preferences also become weaker. For example, displacing the cesium cation (Cs–O distance 3.1 Å) 30° from the C–O–C plane costs 0.3 kcal mol^{-1}, whereas performing the same displacement on the magnesium dication (Mg–O distance 2.1 Å) costs 3.0 kcal mol^{-1}. Thus, although the assignment of the same geometries, i.e. M–O–C angles and M–O–C–X torsion angles, would be correct for all these metal ions, the assignment of invariant bending force constants and rotational barriers would not be.

In addition, we note that not all-metal ions will necessarily adopt the planar geometry found for ethers with the alkali and alkaline earth metal ions. Thus, unpublished work by the present authors suggests that metal ions that form more covalent M–O bonds will prefer to coordinate with sp^3 oxygen donors utilizing only one lone pair. Thus, in Fig. 13, the authors show the structures of $[Li(H_2O)_4]^+$ and $BH_3 \cdot H_2O$ generated by ab initio calculation at the HF/6-31 G** level [51]. One sees that while the water coordinates to the Li^+ cation as would be expected from the work of Hay on coordinated ethers, the water coordinates to boron as might be expected if only one lone pair on water was being used in forming the bond. Thus, the B–O–H angle at 110.7° is very close to what would be expected for regular tetrahedral geometry around the coordinated oxygen, including the non-bonded

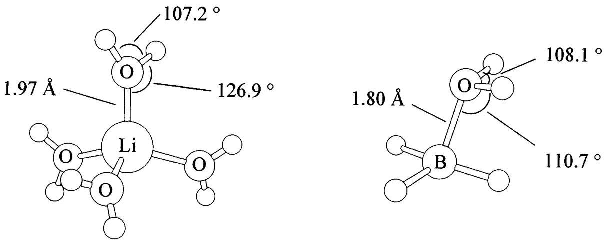

Fig. 13. Structures of $[Li(H_2O)_4]^+$ (left) and $BH_3 \cdot H_2O$ (right) generated by ab initio calculation at the HF/6-31G** level [51]. Note that in the lithium complex the water molecules are coordinated so as to give trigonal planar coordination around the oxygen atom, typical of the alkali and alkaline earth metal ions. In the boron complex the much lower cationic charge and higher covalence in the B–O bond is accompanied by trigonal pyramidal coordination around the oxygen atoms.

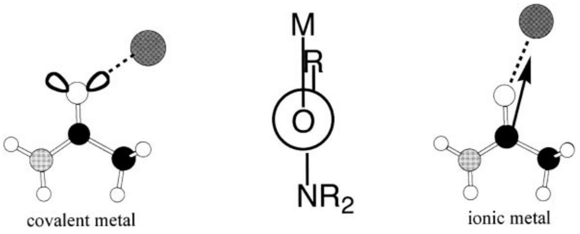

Fig. 14. The optimal orientation for the amide oxygen donor group. Predicted M–O–C angles based on ideal geometries for a pure covalent interaction (left) and a pure ionic interaction (right). Arrow on the right depicts the orientation of the acetamide dipole moment.

lone pair as a coordination site. It is not totally clear at this stage what factors will be important in determining whether water, alcohols, and ethers coordinate to metal ions in a trigonal planar or trigonal pyramidal fashion. The work done so far suggests that increased covalence and lower charge on the metal ion will promote trigonal pyramidal coordination. For example, the hydronium ion represents the most covalent interaction between a monovalent cation and water. In this case, the oxygen exhibits a trigonal pyramidal geometry with H–O–H angles of 111.8° [52]. Other factors such as electrostatic interaction between the positively charged protons on water, and other parts of the complex also appear to be important. Thus, attraction between the protons on water and negatively charged donor groups on the metal ion appear to promote trigonal pyramidal coordination.

A recent study of the amide oxygen donor suggests that both the preferred donor group orientation and the cost of distortion from this orientation change as the metal ion is varied [53,54]. The geometric features of the coordinated amide oxygen are shown in Fig. 14. With all metal ions the strongest interaction is obtained when the metal ion lies in the plane of the amide giving rise to M–O–C–X angles of 0 and 180°. However, the optimal M–O–C angle ranges between 120 and 154°. These limiting behaviors can be rationalized in terms of expected ideal geometries for a pure covalent or pure ionic interaction. In the idealized covalent case, optimal overlap between a metal centered orbital with a sp^2 oxygen orbital occurs at an M–O–C angle near 120°. In the idealized ionic case, the optimal interaction occurs when the metal aligns with the dipole moment of the ligand, an angle of 154° at an M–O distance of 2.5 Å. A set of empirical relationships was derived to assign MM3 force field parameters as a function of the metal ion size, charge, and electronegativity [54]. As with the ether donor example given above, significant differences are found as the properties of the metal ion vary. For example, the ideal M–O–C angle, bending force constant, and 2-fold M–O–C–X rotational barrier for Ni(II) are 126°, 0.17 mdyn Å rad^{-2}, and 1.0 kcal mol^{-1} whereas for U(IV) the corresponding values are 146°, 0.07 mdyn Å rad^{-2}, and 0.07 kcal mol^{-1}.

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