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Amino-Alcohol Ligands: Synthesis and Structure of *N,N'*-bis(2-hydroxycyclopentyl)ethane-1,2-diamine and Its Salts, and an Assessment of Its Fitness and That of Related Ligands for Complexing Metal Ions

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The synthesis and solid state structure of the amino-alcohol ligand, (1*R*,2*R*,1'*S*,2'*S*)-*N,N'*-bis(2-hydroxycyclopentyl)ethane-1,2-diamine (Cyp$_2$en) obtained by the reaction of cyclopentene oxide with ethylenediamine, as well as its bromide, chloride, perchlorate, and nitrate salts, is reported. In all five structures, the Cyp$_2$en ligand sits on a center of inversion with the two amino groups and two hydroxyl groups of the cyclopentyl moieties trans to each other across that inversion center. Comparing this conformation to that of a density functional theory (DFT)-calculated structure of *cis*-$[Ni(Cyp_2en)(H_2O)_2]^{2+}$ suggests that the ligand is not well pre-organized for coordinating a metal ion. The likely solution structure of this ligand, and that of the related ligands bis(2-hydroxy)ethane-1,2-diamine (Bheen) and bis(2-hydroxycyclohexyl)ethane-1,2-diamine (Cy$_2$en), was explored using molecular mechanics modeling with the generalized AMBER force field. A Boltzmann distribution of the lowest energy conformations found shows that 36 conformations of Bheen each contribute more than 1% to the population at 300 K; this decreases to 27 conformations for Cyp$_2$en and to 12 for Cy$_2$en, and Cy$_2$en is the most rigid of the three ligands. The population-weighted root-mean-square deviation (rmsd) between these lowest energy conformations and the conformation required for coordinating a metal ion increased in the order Cy$_2$en < Cyp$_2$en < Bheen, while stability constants for coordinating Ni(II) decrease in the order Cy$_2$en > Bheen > Cyp$_2$en. The high pre-organization of Cy$_2$en is due to an intramolecular N$-$H$\cdots\cdot$O hydrogen bond, apparently missing in the other two ligands. Pre-organization is likely to be an important, but not the only factor, that controls the value of the stability constants of these ligands with metal ions.

Introduction

Pearson's concept of hard and soft acids and bases is extremely useful in deciding what donor atoms to incorporate in a ligand for a particular targeted metal ion[1,2] but several other parameters of ligand structure and topology have been developed toward this end.[3] For example, it has been demonstrated that the presence of neutral oxygen donors favors larger metal ions[4] while larger chelate rings favor smaller metal ions.[5] The replacement of ethylene bridges between donor atoms in amino and amino-alcohol ligands by, for example, cyclohexyl bridges leads to ligands that have been termed *reinforced*.[6] Interest in reinforced amino-alcohol ligands stems from the observation[4] that whereas a 2-hydroxyethyl group promotes selectivity for large metal ions, the presence of a cyclohexyl bridge between the N and O donors promotes selectivity for smaller metal ions. Being able to discriminate between metal ions based on their size is a key goal in ligand design. In brief, the selectivity is thought to arise from the relief of steric crowding on the periphery of the ligand as coordination to a small metal ion requires greater ligand curvature,[7,8] and short non-bonded H$-$H contacts between H atoms on the cyclohexyl bridges and those on the ethylene bridges of the ligand decrease as the curvature of the ligand increases.

These reinforced ligands are readily synthesized[9] by the reaction of a di- or triamine with a cycloalkene oxide. The reaction yields single substitution products that are crystalline, and consist of only diastereomeric pairs. It is thought that the high

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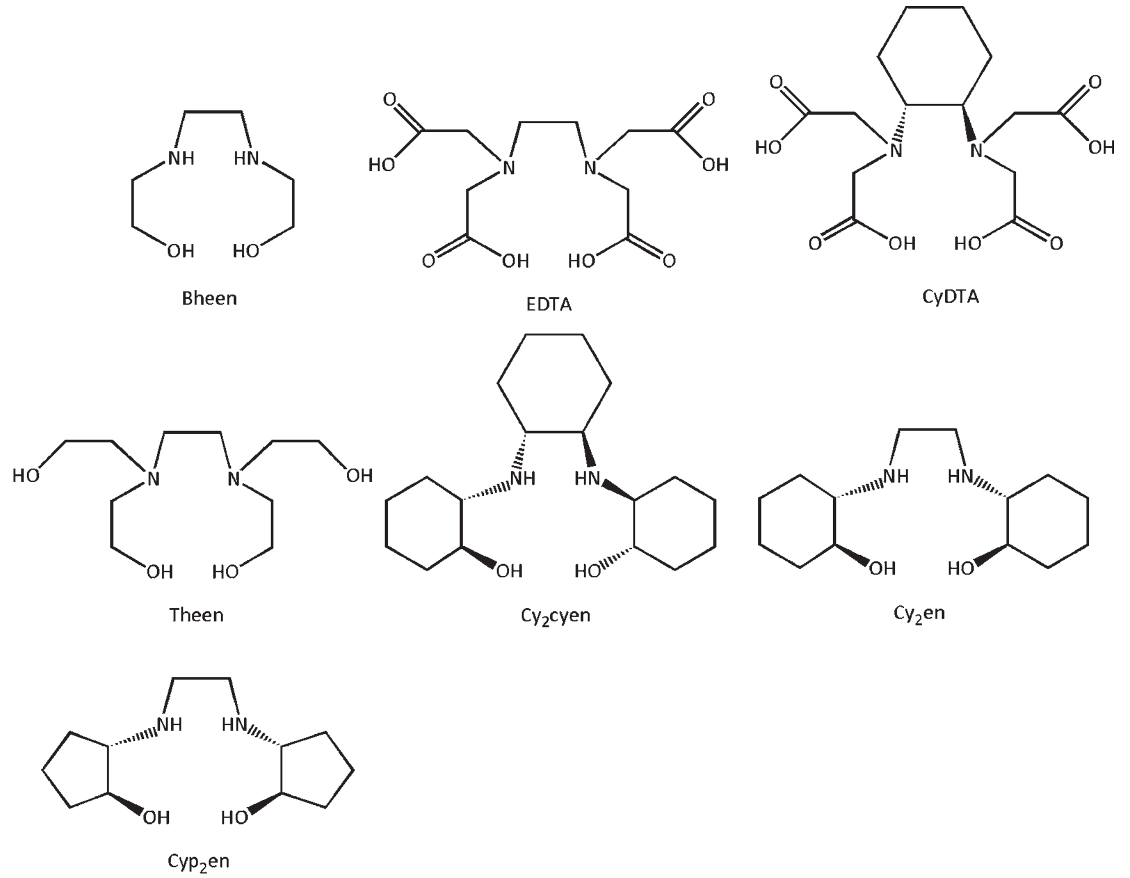

Figure 1. Ligands referred to in this paper.

degree of diastereoselectivity is effected by, first, the exclusive trans opening of the epoxide and second, hydrogen bonding of the second amino addition site to the first cyclic alcohol group added directs the second addition stereoselectively.[9,10]

The presence of a cyclohexyl bridge, it has been argued,[6] reinforces the ligand backbone, making it more rigid, and hence more *pre-organized* for the complexation of metal ions. The same effect has been achieved by addition of a second bridge between two donor atoms.[11,12] Pre-organization, in which ligand donor atoms are arranged in the orientation required for coordination to a metal ion, is an important aspect of ligand design.[13] Compared to ethylenediaminetetraacetic acid (EDTA), CyDTA (Figure 1) has formation constants (as log K_1 values) that are up to 5 orders of magnitude larger for a given metal ion[14] which has been attributed[15] to the greater pre-organization of the cyclohexyl-reinforced ligand. In Cy_2cyen[16] (Figure 1) all ethylene bridges of the simple amino-alcohol Bheen[17] are replaced with cyclohexyl bridges. This clearly favors the coordination of smaller 2+ metal ions: with 4-coordinate Cu^{2+}, $r = 0.57$ Å,[18] $\log K_1 = 11.50$; 6-coordinate Ni^{2+}, 0.69 Å, 6.84; Zn^{2+}, 0.74 Å, 4.77; Cd^{2+}, 0.95 Å, 4.08; and Pb^{2+}, 1.19 Å, 4.80.[6] The basicity of a neutral oxygen donor is increased by the inductive effect of alkyl substituents[3,9,19] so that, in principle, the pendent hydroxyl groups of Bheen and its derivatives (Figure 1) are viable ligands for metal ions in solution and are expected to compete successfully with solvent H_2O ligands for the coordination sites of the metal. It is not always clear that this is indeed the case. For example, the Bheen complex of Zn^{2+} crystallizes as an ML_2 complex, with 4-coordinate Zn^{2+} coordinated through the N-donors of the ligands and the hydroxyl groups forming at most very weak, long-range interactions with the metal.[17] The Cd^{2+} complex crystallizes as a dimer with bridging chloride ligands, and only one hydroxyl group of each ligand is coordinated to the metal ion;[17] the dimerization may be a consequence of the crystallization process, and electrospray ionization-mass spectrometry (ESI-MS) data suggest the presence of a complex mixture of monomeric and dimeric complexes in solution, in several of which not all OH moieties are coordinated to the metal ion. The Cu^{2+} complex of Theen (Figure 1) crystallizes as a dimer with bridging equatorial alkoxide ligands and axial hydroxyl ligands, with one OH moiety from each ligand uncoordinated.[20]

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Table 1. Experimental Data from the Crystal Structure Determination of Cyp_2en and Four of Its Salts

	Cyp_2en	$(Cyp_2en)(NO_3)_2$	$(Cyp_2en)(ClO_4)_2$	$(Cyp_2en)Cl_2$	$(Cyp_2en)Br_2$
CCDC	766041	766042	766043	766044	766045
empirical formula	$C_{12}H_{24}N_2O_2$	$C_{12}H_{26}N_4O_8$	$C_{12}H_{26}Cl_2N_2O_{10}$	$C_{12}H_{26}Cl_2N_2O_2$	$C_{12}H_{26}Br_2N_2O_2$
molecular mass	228.33	354.37	429.25	301.25	390.17
temperature/K	173(2)	173(2)	173(2)	173(2)	173(2)
wavelength /Å	0.71073	0.71073	0.71073	0.71073	0.71073
crystal system	monoclinic	monoclinic	triclinic	triclinic	triclinic
space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
unit cell dimensions					
a /Å	11.1351(3)	9.2917(14)	7.1544(2)	5.8335(3)	6.03780(10)
b /Å	7.7965(2)	8.4205(12)	7.4987(2)	7.1178(4)	7.23360(10)
c /Å	7.2759(2)	10.5946(15)	9.7346(2)	9.9264(4)	10.0217(2)
α /deg			99.026(2)	103.417(3)	103.4390(10)
β /deg	99.9880	94.578(3)	106.072(2)	94.390(3)	95.0420(10)
γ /deg			107.9320(10)	109.438(3)	108.4490(10)
volume /Å^3	622.08(3)	826.3(2)	460.41(2)	372.71(3)	397.604(12)
Z	2	2	1	1	1
density (calc.) /mg m^{-3}	1.219	1.424	1.548	1.342	1.629
absorption coefficient/mm^{-1}	0.083	0.119	0.407	0.433	5.095
$F(000)$	252	380	226	162	198
crystal dimensions/mm	0.34 × 0.30 × 0.11	0.39 × 0.39 × 0.09	0.42 × 0.39 × 0.13	0.39 × 0.30 × 0.05	0.36 × 0.17 × 0.04
θ range for data collection /deg	1.86 to 28.00	2.20 to 28.00	2.26 to 27.99	2.14 to 28.00	2.12 to 28.00
index ranges	$-14\leq h \leq 14$ $-10 \leq k \leq 10$ $-9 \leq l \leq 9$	$-10 \leq h \leq 12$ $-10 \leq k \leq 11$ $-13 \leq l \leq 13$	$-9 \leq h \leq 8$ $-9 \leq k \leq 9$ $-12 \leq l \leq 12$	$-7 \leq h \leq 7$ $-9 \leq k \leq 7$ $-13 \leq l \leq 13$	$-7 \leq h \leq 7$ $-9 \leq k \leq 9$ $-13 \leq l \leq 13$
reflections collected	11215	5847	4620	3923	6334
independent reflections	1498 [R(int) = 0.0381]	1994 [R(int) = 0.0394]	2218 [R(int) = 0.0512]	1796 [R(int) = 0.0465]	1918 [R(int) = 0.0374]
completeness to θ	100.0%	100.0%	99.9%	99.9%	100.0%
absorption correction	none	none	integration	integration	integration
max./min transmission	−0.9910 and 0.9724	0.9893 and 0.9550	0.9490 and 0.8476	0.9787 and 0.8492	0.8222 and 0.2613
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2
data/restraints/parameters	1498/0/81	1994/0/110	2218/0/119	1796/0/83	1918/0/83
goodness-of-fit on F^2	1.053	1.061	1.050	0.977	1.050
final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0400$ $wR_2 = 0.1091$	$R_1 = 0.0395$ $wR_2 = 0.1112$	$R_1 = 0.0418$ $wR_2 = 0.1125$	$R_1 = 0.0403$ $wR_2 = 0.0904$	$R_1 = 0.0241$ $wR_2 = 0.0601$
R indices (all data)	$R_1 = 0.0449$ $wR_2 = 0.1132$	$R_1 = 0.0554$ $wR_2 = 0.1176$	$R_1 = 0.0476$ $wR_2 = 0.1167$	$R_1 = 0.0569$ $wR_2 = 0.0963$	$R_1 = 0.0280$ $wR_2 = 0.0611$
largest diff. peak/hole/e Å^{-3}	0.297/−0.226	0.263 and −0.242	0.464 and −0.380	0.501 and −0.401	0.623 and −0.416

We report here the synthesis and structure of a new reinforced amino-alcohol ligand, (1*R*,2*R*,1′*S*,2′*S*)-*N*,*N*′-bis(2-hydroxycyclopentyl)ethane-1,2-diamine (Cyp_2en, Figure 1) obtained by the reaction of cyclopentene oxide with ethylenediamine. Stability constants of this ligand with Ni(II) are available.[21] To determine whether the identity of the counterion had any effect on the conformation of the ligand, we also crystallized its bromide, chloride, perchlorate, and nitrate salts, and report their structures. Using molecular mechanics modeling, we compare and contrast the pre-organization of Cyp_2en, Cy_2en, and Bheen for coordinating metal ions in an effort to assess their relative fitness for this purpose.

Results and Discussion

Structures. Cyp_2en crystallizes in the $P2_1/c$ space group with the molecule located at a center of inversion (see Table 1 for experimental details). The cyclopentyl rings are in an envelope conformation, with all but the carbon atom bonded to the amino group very nearly coplanar (average absolute displacement from the mean plane is 0.020(5) Å). Bond lengths and bond angles are listed in the Supporting Information, Table S1; they are all within the ranges expected from data available in the Cambridge Structural Database (CSD,[22] see the Supporting Information, Tables S2 and S3).

Molecules of Cyp_2en arrange in sheets, in which the mean plane of the molecules are parallel to [1 0 0] (Supporting Information, Figure S1), held together by hydrogen bonds between N1 and O1 from a neighboring molecule (see Figure 2 for atom labeling scheme). There is no intramolecular hydrogen bonding.

The nitrate salt $(H_2Cyp_2en)(NO_3)_2$ crystallizes as colorless plates in the monoclinic space group $P2_1/c$. Each $H_2Cyp_2en^{2+}$ cation is located on a center of inversion. As with Cyp_2en itself, the cyclopentyl rings are in an envelope conformation. The compound packs in layers parallel to [0 1 0] (Figure 3) with hydrogen bonding between the organic cations and the NO_3^- counterions both within each layer, and between the layers (Supporting Information, Figure S2, Table S4). O1−H1A forms hydrogen bonds with O3 (2.19 Å) and O2 (2.29 Å) of NO_3^- while there is a close contact between H1A and N2 (2.56 Å). In similar fashion, N1−H1B hydrogen bonds to O4 (1.94 Å)

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(22) *Cambridge Structural Database*, 5.30 (updated to Sept 2009); CSD: Cambridge, U.K., 2008.

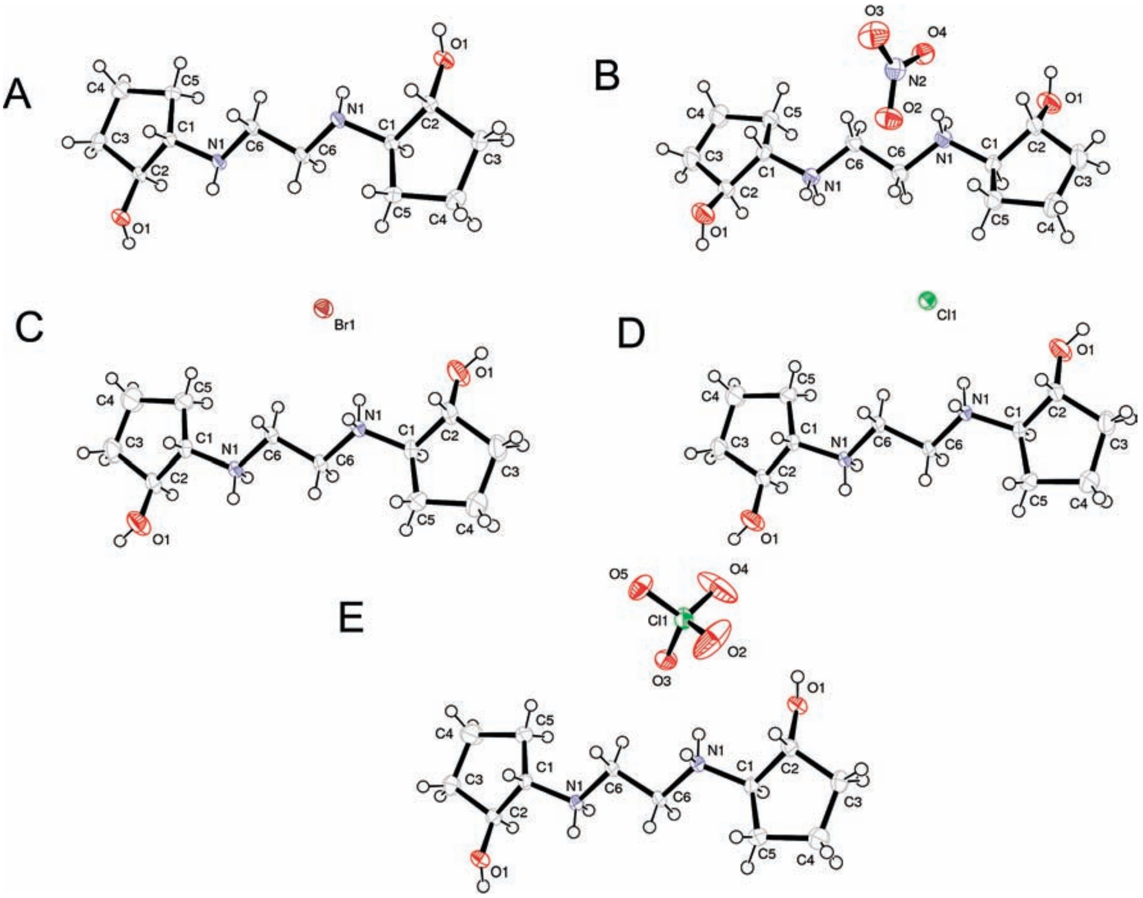

Figure 2. ORTEP3 diagrams of the molecular structure (50% probability level) and atom labeling of A, Cyp_2en; B, $(H_2Cyp_2en)(NO_3)_2$; C, $(H_2Cyp_2en)(Br)_2$; D, $(H_2Cyp_2en)(Cl)_2$; and E, $(H_2Cyp_2en)(ClO_4)_2$.

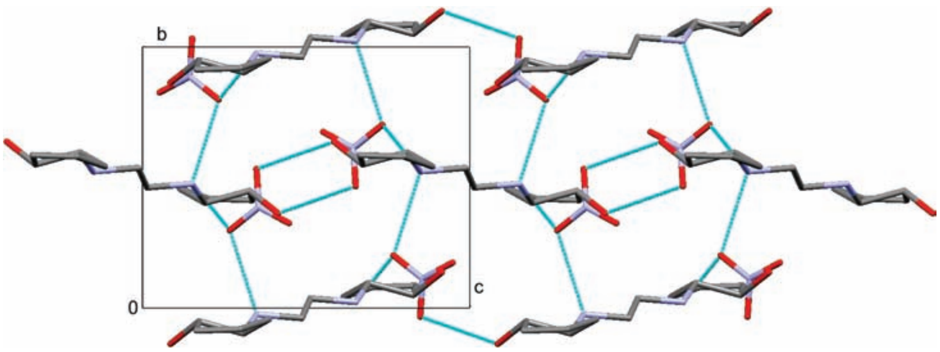

Figure 3. Packing of $(H_2Cyp_2en)(NO_3)_2$ viewed along the *a* axis. Hydrogen atoms are omitted for clarity, and only the strongest hydrogen bonds are shown.

and O2 (2.52 Å) and makes a close contact with N2 (2.59 Å), while N1−H1C hydrogen bonds O4 (1.95 Å) and O3 (2.48 Å) and contacts N2 (2.53 Å) of a different anion.

There are several C−H···O weak interactions and a C−H···H−C interaction, where the H···O and H···H distances are shorter than the sum of the van der Waals radii of the two interacting atoms (see Supporting Information, Figure S3). We have recently reported similar C−H···O and H−H bonds in the crystal structure of $\Lambda-\delta\delta\delta$ $[Ni(en)_3](NO_3)_2$ (en = ethylenediamine).[23]

Protonation of the amino groups has a small effect on the structural metrics of the complex. The C1—N1 bond (see Supporting Information, Table S2) increases from 1.466(1) Å in the free base to 1.499(2) Å in the nitrate salt while the C6—N1 bond increases from 1.471(1) to 1.488(2) Å. All other bond lengths are within 0.007 Å or less in the two compounds, with the exception of the C3—C4 bond which is 0.022 Å longer in the free base. All valence angles are within 2.2° in the two compounds. In particular, the C1—N1—C6 and N1—C6—C6 angles are only 1.5 and 1.1° larger and smaller, respectively, in the protonated and free base amino-alcohol. In this, and the other salts, the difference between the value of all bond lengths and bond angles observed in these structures is within 2σ of the means of the CSD data.

The perchlorate salt $(H_2Cyp_2en)(ClO_4)_2$ crystallizes as colorless triangular crystals in the $P\bar{1}$ space group with the

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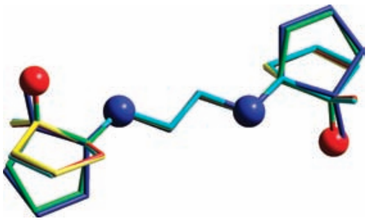

Figure 4. Conformation of the five structures of Cyp_2en, in its neutral (green) and protonated forms overlaid at the N−C−C−N backbone. The four ligand donor atoms of neutral Cyp_2en are shown as red (oxygen) and blue (nitrogen) spheres.

cation again located at a center of inversion. Two molecules, related by a center of inversion, are hydrogen bonded to each other through N1−H1C····O1 hydrogen bonds (Supporting Information, Figure S4A). This creates a ribbon of H-bonded molecules running down the *a* axis (Supporting Information, Figure S4B). Molecules in these ribbons hydrogen bond to perchlorate ions between the ribbons (Supporting Information, Figure S4C), creating a H-bonded sheet of alternating perchlorate and cation molecules parallel to [0 0 1]. Weak interactions are evident between C6−H6A and O3, C6−H6B and O2, and C5-H5B and O5, and there may be a very weak C−H····H−C interaction between C5-H5A of one molecule and C5-H5A of another (Supporting Information, Figure S5).

The structures of the chloride and bromide salts are isomorphous and crystallize as colorless plates in the $P\bar{1}$ space group with a single molecule in the unit cell located at a center of inversion (Supporting Information, Figure S6). The unit cells of the two salts are very similar, as is the pattern of hydrogen bonds (Supporting Information, Figure S7). As in the nitrate structure, and in contrast to the structures of the free base and the perchlorate salt, the molecules do not hydrogen bond directly to each other. N1−H1B is hydrogen bonded to a X^- ion from a neighboring unit cell (2.18 Å when $X = Cl^-$, 2.37 Å when $X = Br^-$), while N1−H1C hydrogen bonds to an anion in the same unit cell (2.40 Å when $X = Cl^-$ and 2.61 Å when $X = Br^-$) as well as to an hydroxyl group of the organic cation from a neighboring unit cell (2.78 Å in the chloride salt, 2.53 Å in the bromide salt). There is a hydrogen bond between O1−H(1A) and a neighboring X^- (2.32 and 2.44 Å for $X = Cl^-$ and Br^-, respectively). As with the other structures reported in this work, there are several weak interactions (Supporting Information, Figure S9). In particular, the van der Waals radii of C1−H1 and Cl1 overlap by 0.18 Å; in the case of Br^-, the overlap decreases to 0.14 Å.

Fitness of Cyp_2en As a Ligand. In all five structures of Cyp_2en reported in this work, the ligand, either as the free base or as a diprotonated cation, assumes a very similar conformation in the solid state (Figure 4). The molecules are in the meso 1*R*,2*R*,1′*S*,2′*S* form with the center of the C6−C6 bond on a center of inversion. Thus, the N donors are trans to each other across the center of inversion, as are the two O donors.

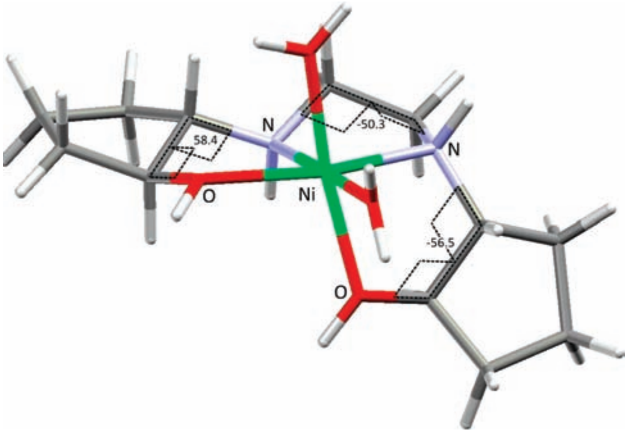

Figure 5. X3LYP/6-31+G(d,p) structure of *cis*-$[Ni(Cyp_2en)(H_2O)_2]^{2+}$. See text. The folding of the ligand for coordination to the metal can be quantified by three torsions of the chelate rings.

Table 2. Formation Constants of Selected Amino-Alcohol Ligands with Ni(II)[a]

ligand	pK_a	log *K*	conditions/ temp (°C), μ (M)	reference
Bheen	9.32, 6.52	6.67	25, 0.5	43,44
Cy_2en	9.66, 6.62	7.77	25, 0.1	8
Cyp_2en	9.48, 6.45	3.79	25, 0.1	21

[a] See Figure 1 for ligand structure.

We have recently found[24] in a X3LYP/6-31+G(d,p) study that both in the gas phase and in solvent (CPCM-UAKS model) the structure of the cis isomer of $[Ni(Cyp_2en)(H_2O)_2]^{2+}$ is over 8 kcal mol^{-1} more stable than the trans isomer; therefore the cis isomer (Figure 5) is expected to be the predominant isomer in solution. For the ligand to coordinate the metal ion in the manner of Figure 5 requires that it adopt a very different conformation to that seen in the solid state (Figure 4, for the neutral ligand and four of its salts); one might argue that Cyp_2en is not well pre-organized for coordination to a metal ion and so expect, assuming that the solid state structure is representative of the structure of the ligand in solution, that log *K* values for the coordination of a metal, such as Ni(II), by Cyp_2en, would be low. However, we have also found[25] that both Bheen itself[17] and Cy_2en crystallize in a very similar conformation to Cyp_2en (Supporting Information, Figure S10) and that these too, are not pre-organized ligands.

From the formation constant data available (Table 2) it is clear that even though their Lewis basicities toward H^+ are not very different, the three ligands have rather different affinities for Ni(II). In a density functional theory (DFT) exploration of the structure of Cy_2en and Cyp_2en[26] it was recently shown that the electron density and its Laplacian at the ring critical point of the cycloalkyl moiety in Cyp_2en is twice as large as that in Cy_2en. In Cy_2en there is an intramolecular N−H···O interaction between each cyclohexanol and its nearest amino group, as well as a C−H···H−C interaction between a methylene group on the cyclohexyl ring and a ligand backbone methylene group; the analogous interactions in Cyp_2en are considerably weaker, as gauged from a Natural Bond Orbital analysis of the second-order perturbation lowering energy $E^{(2)}$ that arises from charge transfer between the O-atom and the N−H antibonding orbital. This led to

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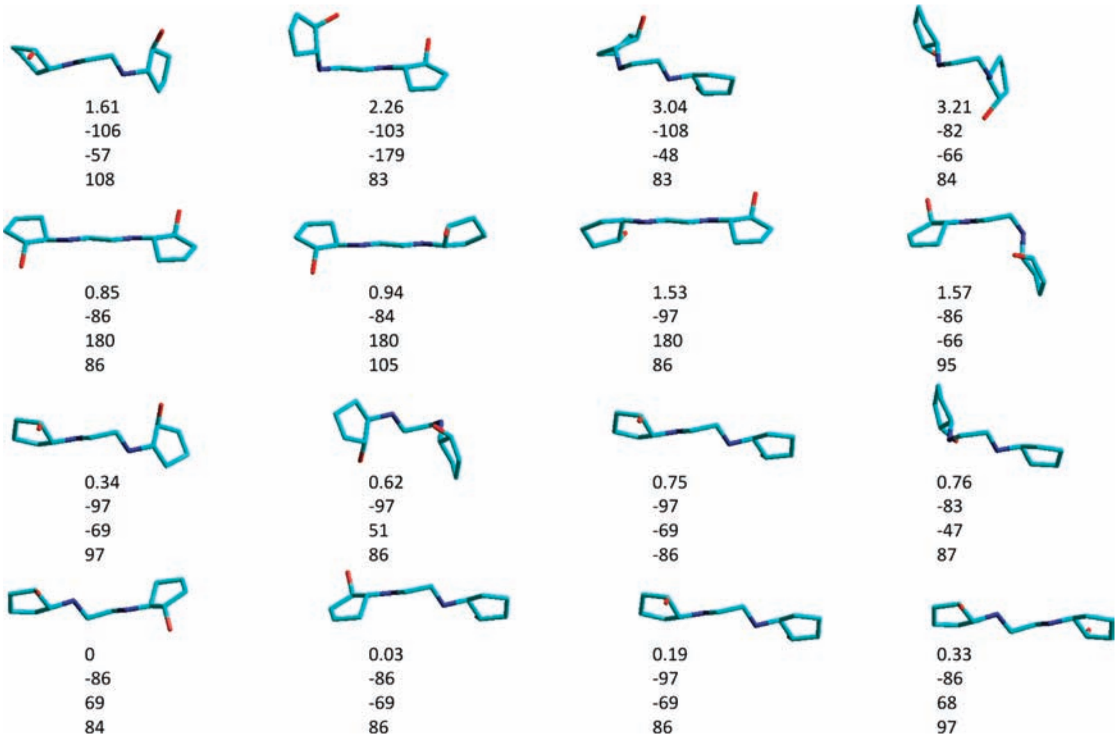

Figure 6. Sixteen unique conformations of Cyp_2en discovered by 30 MD/SA calculations. Hydrogen atoms are omitted for clarity. The first entry under each structure is the energy (kcal mol^{-1}) relative to the lowest energy conformation found (bottom left). The next three entries are the O−C−C−N, N−C−C−N, and N−C−C−O torsions (degrees). The ideal conformation for coordinating a metal ion like Ni(II) would require values of −57, −50, and 58°, respectively (see Figure 5).

the suggestions that (i) the increased electron density within the cyclopentyl rings is responsible for the much smaller intramolecular interactions observed in Cyp_2en and contributes to its lower affinity for metal ions and (ii) that the ability of the ligand to transfer charge between orbitals, as described by $E^{(2)}$, is a factor that influences the ligand's ability to form complexes. What insight is to be gained into the relative ability of these amino-alcohols to act as ligands toward a metal such as Ni(II) from a DFT examination of the structure of the metal−ligand complexes is currently under investigation[24] and will be reported elsewhere. Here we address another aspect of this problem: the a priori fitness of each ligand to coordinate a metal ion.

As outlined briefly in the Introduction, fitness depends on a number of factors, among them the nature of the donor atoms and the level of pre-organization of a ligand for complexing a metal ion. The first is constant for the ligands Bheen, Cy_2en, and Cyp_2en, and attention is here focused on the latter.

Bheen,[17] Cy_2en,[25] and Cyp_2en (this work) all crystallize in a similar conformation, unsuited for coordination of a metal ion (Supporting Information, Figure S10) and require rearrangement before chelation of the metal is possible. There is no guarantee that solid state structures are good representations of the solution structure, and of course it is the structure of the latter that is important insofar as the coordination chemistry of these ligands is concerned. We have therefore used molecular mechanics modeling with the Generalized AMBER force field (GAFF) of Kollman and co-workers[27,28] in an attempt to assess the likely solution structure of these ligands (see Supporting Information for details).

We began our examination of the possible structure of Cyp_2en outside the confines of the solid state by performing molecular dynamics simulations in the gas phase (300, 400, 600, and 1000 K; 500 ps and 1000 ps) and Langevin dynamics (with a frictional coefficient of 58 ps^{-1} to simulate water,[29] similar temperatures and duration). We found both techniques to be relatively uninformative. Fairly quickly (for example, by about 50 ps of simulation at 300 K, 100 ps at 500 K and 125 ps at 1000 K) the molecule would settle into one particular conformation and the energy supplied was used to effect bond and angle deformations, and rotation of the molecule, but virtually never a change in its torsions. Repeating the simulation would typically give rise to similar behavior, but with the molecule in a different conformation.

We then performed a series of molecular dynamics/simulated annealing (MD/SA) calculations. Thirty repeats of the procedure (see Experimental Section for details) yielded 16 unique conformations (Figure 6) within 3.2 kcal mol^{-1} of each other. Undoubtedly further repeats of the procedure would yield yet more conformations within this energy range. None of these conformations is particularly close to the conformation the ligand would need to adopt to coordinate a metal such as Ni(II) (Figure 5). Therefore, it would appear that Cyp_2en is not particularly well pre-organized for coordinating a metal ion.

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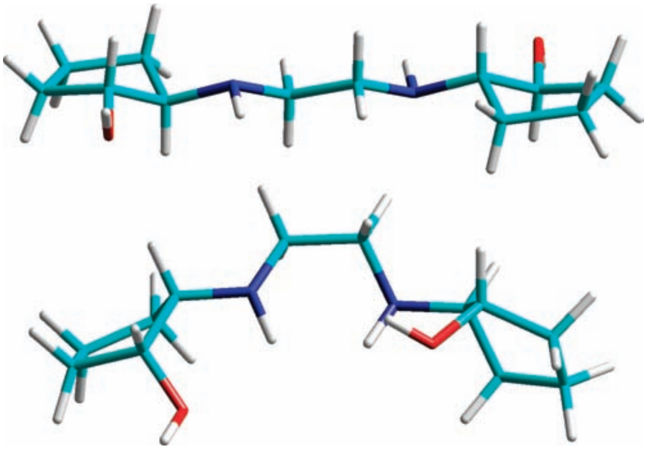

Figure 7. Comparison of the crystal structure (above) and the lowest energy structure found for Cyp_2en (below), which is 4.6 kcal mol^{-1} lower in energy and better pre-organized for coordinating a metal ion.

We are mindful that this conclusion is based on what is very likely an inadequate sampling of the ligand's conformational space and that the procedure might have to be repeated many hundreds of times before a more definitive conclusion could be reached; this is impractical. We therefore explored the ligand's conformational space using the conformational search facility[30] in HYPERCHEM[31] in which all torsions within the molecule, not involving hydrogen atoms, are altered at random followed by full energy minimization. We performed 5000 such simulations on Cyp_2en, and retained at most 100 conformations which were at most within 5 kcal mol^{-1} of the lowest energy conformation found. For Cyp_2en the conformation of the lowest energy structure found by this procedure (Figure 7) is different to that in the crystal structure and, indeed, seems more pre-organized for coordinating a metal ion. The O−C−C−N, N−C−C−N, and N−C−C−O torsions are −42, 62, and 45°, respectively, reasonably close to the ideal values of −57, −50, and 58°, respectively (see Figure 5) required for coordinating Ni(II), especially as inversion of configuration at an amino group is facile (amines readily invert through a planar structure with an energy barrier of only about 6 kcal mol^{-1}[32]). We repeated this exercise for Bheen and for Cy_2en.

From a Boltzmann distribution we calculated what percentage of the population at 300 K would be found in a particular conformation. The results are listed in Supporting Information, Table S10. At 300 K, there are 36 conformations of Bheen that each contributes more than 1% to the population; this decreases to 27 for Cyp_2en and to 12 for Cy_2en. We conclude, unsurprisingly, that Bheen is considerably more flexible than Cyp_2en which is in turn more flexible than Cy_2en; moreover, a cycloalkyl reinforcement does indeed increase ligand rigidity.

To better quantify the closeness of a ligand conformation to the conformation required to coordinate a metal ion we began from our X3LYP/6-31+G(d,p) (vide supra) structure of each Ni(II)-amino-alcohol complex and deleted the metal ion; this gives the conformation of each ligand ideally suited for coordination to Ni(II) (Supporting Information, Figure S11). We took the 12 Cy_2en and 27 Cyp_2en structures that each contribute >1% to the population, and (for practical purposes) the 13 Bheen structures that each contribute >2% of the population, and overlaid them at the 2 O and 2 N donor atoms with the ideal conformation of each ligand. From this we obtained a root-mean-square deviation (rmsd) of each fit. The rmsd values were then weighted by population to give final population-weighted rmsd's between the donor atoms in the ligand population and in the conformation required for coordinating the metal ion. The values obtained are a measure of distance between the expected solution conformation of the ligands and the conformation required for complexing Ni(II), so the smaller the rmsd value of the ligand, the more suited the ligand for coordinating a metal ion. We obtained rmsd values of 2.38 Å for Bheen, 1.43 Å for Cyp_2en, and 0.92 Å for Cy_2en, and of these three amino-alcohols Cy_2en is best pre-organized for coordinating metal ions (Figure 8).

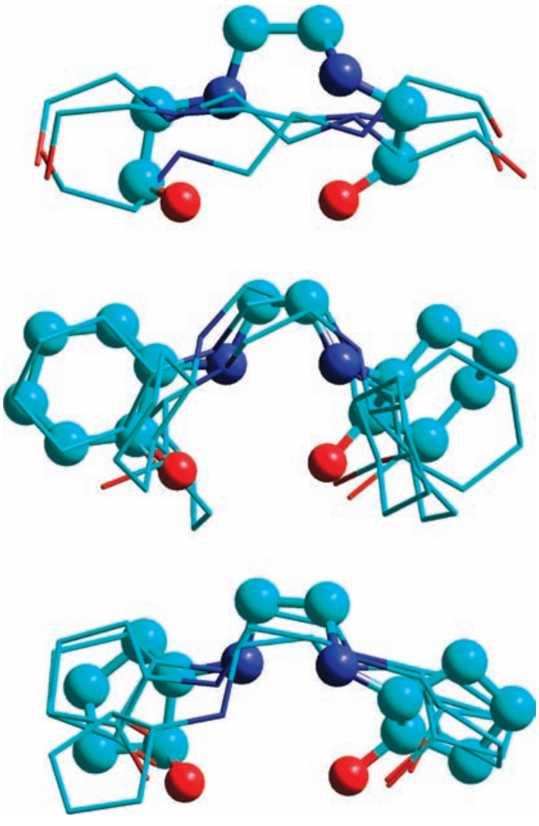

Figure 8. Overlay at the four atoms of the conformation of each amino-alcohol ligand in its complex with Ni(II) (from DFT modeling, balls and sticks) with the three lowest energy conformations (tubes) discovered by conformational searching constituting for Bheen (top) 18% of the population, for Cy_2en (middle) 52% of the population, and for Cyp_2en (bottom) 20% of the population.

A noteworthy feature of 9 of the 12 lowest energy structures of Cy_2en is the presence of an intramolecular hydrogen bond between an amino group and the furthest alcohol moiety to produce an **S**1,1(8) string motif (Figure 9). This motif, which is absent in the lower energy structures of Bheen and Cyp_2en we found, folds the ligand into a conformation suitable for coordinating a metal ion. The formation of these intramolecular rings, which causes ligands to fold into suitable conformations for coordinating metal ions, is known in a number of amino-alcohols in the solid state, including two **S**1,1(8) motifs in the related Cy_2cyen[16]

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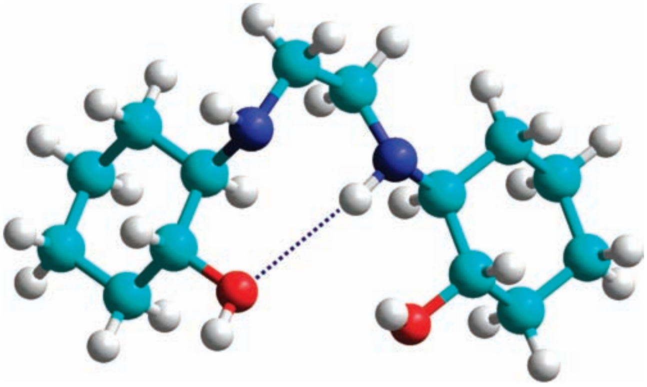

Figure 9. Pre-organization of Cy_2en for coordinating a metal ion is due to an intramolecular hydrogen bond. This hydrogen bond is absent in Bheen and Cyp_2en.

(Figure 1) and a **S**1,1(15) motif in bis-glucoamidocyclohexane;[33] and, through O−H····O interactions, in several ethanolamine derivatives.[34,35]

This pre-organization is likely to be a factor contributing to the relatively large log K value for coordination of Ni(II) by Cy_2en. It is, of course, unlikely to be the only factor. We note that Bheen is the least well pre-organized ligand yet has a log K value for complex formation with Ni(II) that is only 1.1 log units smaller than Cy_2en and nearly 3 log units larger than Cyp_2en. We suspect there are issues around the geometry of the final metal−ligand complex that might account for these differences; we are exploring these using DFT methods and will report our findings elsewhere.

Finally, we note that it is unfortunate that detailed thermodynamic data for the coordination of metal ions by these ligands are not available. We would expect, given the different level of flexibility of the ligands and the different level of pre-organization that our modeling suggests, to see significant differences in ΔS values for complex formation by these three amino-alcohols. We are also addressing this.

Conclusion

The solid structure of the amino-alcohol ligand Cyp_2en and four of its salts reveals an invariance in the solid state conformation that makes the disposition of the 2N2O donor atoms unsuitable for coordinating a metal ion, as assessed, for example, from the DFT-X3LYP/6-31+G(d,p) structure of its Ni(II) complex, *cis*-$[Ni(Cyp_2en)(H_2O)_2]^{2+}$. The likely conformation of the ligand in solution was explored by molecular dynamics/simulated annealing calculations and showed that the ligand, and the closely related ligands Bheen and Cy_2en, are not well pre-organized for complexing a metal ion. This was confirmed from a more thorough examination of the conformation space of each of these three ligands, achieved by randomly altering all torsions in the ligands and energy-minimizing 5000 structures, and retaining those that contribute $>1\%$ to the ligand population at 300 K. The population-weighted rmsd between these conformations and the conformation required for coordinating a metal ion increased in the order $Cy_2en < Cyp_2en <$ Bheen, while stability constants for coordinating Ni(II) decrease in the order $Cy_2en >$ Bheen $> Cyp_2en$. We found that the high pre-organization of Cy_2en is due to an intramolecular N−H····O hydrogen bond which is missing in the other two ligands. This may explain the larger log K value for coordination of Ni(II) by Cy_2en. However, it is clear that while pre-organization is likely to be an important factor it cannot be the principal factor that controls the value of the stability constants of these ligands with metal ions

Experimental Section

Synthesis. To a solution of cyclopentene oxide (6.1 g, 73 mmol) in absolute ethanol (60 mL) was added neat ethylenediamine (2.0 g, 33 mmol). The resulting solution was refluxed for 24 h. The solution was allowed to cool to room temperature, resulting in the precipitation of a white solid. The precipitate was filtered and washed with cold ethanol. Recrystallization of the compound from water afforded colorless, X-ray-quality crystals in 34% yield. ^1H NMR (300 MHz, 293 K, D_2O): $\delta = 1.39$ (m, 2H), 1.59−1.72 (m, 6H), 2.04 (m, 4H), 2.80 (s, 4H), 2.95 (m, 2H), 4.01 (m, 2H). ^{13}C [^1H] NMR (75.6 MHz, 293 K, $CDCl_3$): $\delta = 19.95$, 20.26, 30.12, 30.52, 32.23, 32.60, 42.04, 48.39, 50.82, 66.95, 67.00, 78.07, 78.42. ESI mass spectrum: $m/z = 229$ $[M-H]^+$. IR (cm^{-1}): 3255 (N−H str), 3079 (O−H str), 2958 (C−H str), 1573 (N−H bend), 1466 (C−H deformations), 1075 (C−O str). Melting point (uncorrected), 187−188 °C. The bromide, chloride, nitrate, and perchlorate salts of the amino-alcohol were prepared by treating it with 2 equiv of the appropriate acid and allowing slow evaporation over several weeks from aqueous solution.

X-ray Diffraction Data Collection. Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 kV, 30 mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the program SAINT+[36] and the data further processed with the program SADABS.[37]

The crystal structures were solved by direct methods using SHELXTL.[38] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using SHELXTL. All H atoms were positioned geometrically and allowed to ride on their parent atoms, with C−H bond lengths of 0.99 and 1.00 Å for CH_2 and CH respectively, N−H bond lengths of 0.92 Å, O−H bond lengths of 0.84 Å, and with $U_{iso}(H) = 1.2$ for CH_2 and CH, 1.2 for NH, and 1.5 for OH times U_{eq}(parent). MERCURY,[39] ORTEP-3,[40] and HYPERCHEM[31] were used to produce publication materials. The experimental data for the crystal structure determination are given in Table 1.

Modeling. All modeling described in this work was performed using the AMBER force field as implemented in HYPERCHEM[31] but with the Generalized AMBER Force Field parameters of Kollman and co-workers.[27,28] Energy minimization was performed with the Pollak−Ribiere algorithm and a convergence criterion of 0.001 kcal mol^{-1} $Å^{-1}$ in the energy gradient.

Molecular dynamics (MD) and molecular dynamics/simulated annealing (MD/SA) calculations were performed by integrating Newton's equations of motion using the leapfrog algorithm[41] with a time step of 1 fs. The temperature was

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controlled by coupling the system to a simulated heat bath[42] with a bath relaxation time of 0.1 ps. All atoms in the starting structure were assigned random initial velocities before MD or MD/SA calculations were performed. A typical MD simulation began with an initial heating phase of 5 ps from 0 K to the desired temperature. The run phase was then set at 500 or 1000 ps. In MD/SA simulations, the run phase was set between 1 and 30 ps at 600 K with annealing to 0 K over 20 ps followed by full energy minimization. Langevin dynamics were performed with similar methods but included a frictional coefficient of 58 ps^{-1} to simulate the effect of solvent.[29]

Conformational searching was performed by varying a random number (between 1 and 8) of torsions not involving H atoms simultaneously using a random walk method. Acyclic torsions were varied randomly between 30 and 150° while torsions involving rings were varied between 30 and 60°. A conformation was accepted and stored if it was < 5 kcal mol^{-1} higher in energy than the best conformation found, with a maximum of 100 conformations stored per search. Prior to minimization, a conformation was rejected if (i) the rmsd of all heavy atoms between it and the previous conformation < 0.5 Å or (ii) the torsions were within 15° or (iii) there was a change of chirality at the stereogenic centers. After minimization (with a convergence criterion of 0.001 kcal mol^{-1} $\mathrm{Å}^{-1}$ in the energy gradient, or 2000 iterations) a conformation was considered to be a duplicate of a stored conformation, and rejected, if its energy was within 0.05 kcal mol^{-1} and the rmsd between all heavy atoms was < 0.25 Å. The procedure was initiated by a random number generated from the computer's clock. A total of 5000 conformations were explored per search. Three repeats of this procedure for $\mathrm{Cyp_2en}$ yielded exactly the same lowest energy conformation and essentially similar low energy conformations.

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Supporting Information Available: Tabulation of the structural metrics in $\mathrm{Cyp_2en}$ and their comparison with available crystallographic data; illustrations and tabulations of hydrogen bonds in the structures of $\mathrm{Cyp_2en}$ and its salts; pictorial comparison of the solid state structures of $\mathrm{Cyp_2en}$, $\mathrm{Cy_2en}$, and Bheen; quantification of the population-weighted distance between the four donor atoms of each ligand and the conformation needed to complex a metal ion; description of the Generalized AMBER Force Field (GAFF) modeling of the three amino alcohols, and a comparison of the crystal structures and molecular mechanics structures of the three ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

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