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Lewis Acid Properties of Zinc(II) in Its Cyclen Complex. The Structure of [Zn(Cyclen)(S=C(NH$_2$)$_2$](ClO$_4$)$_2$ and the Bonding of Thiourea to Metal Ions. Some Implications for Zinc Metalloenzymes

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The structure of the complex [Zn(cyclen)Tu](NO$_3$)$_2$ (**1**) is reported (cyclen = 1,4,7,10-tetraazacyclododecane; Tu = thiourea): orthorhombic, space group $P2_12_12_1$, $a = 11.4170(11)$ Å, $b = 12.1995(11)$ Å, $c = 12.5299(12)$ Å, $Z = 4$, R = 0.0504. The coordination of the cyclen is the same as that found for other similar Zn^{II} complexes, with square pyramidal coordination around the Zn^{II} and mean Zn–N bond lengths of 2.16 Å. The coordinated Tu occupies the axial coordination site, with Zn–S = 2.31 Å. The Zn–S–C–N torsion angle, involving the coordinated Tu, of 75.4° is unusually large, because such torsion angles involving coordinated Tu are normally closer to 0°. The bonding between Zn and S is discussed in terms of overlap with the p orbitals on S, which favors the eclipsed (Zn–S–C–N torsion = 0°) mode of coordination of Tu. The energies of eclipsed and staggered modes (Zn–S–C–N = 90°) of coordination of Tu to metal ions are examined by means of ab initio calculations, using the STO-3G basis set. It is concluded that the rather low formation constant for the Tu complex with Zn^{II}/cyclen reported in this work was due to steric effects in **1**, which prevent the adoption of the lower energy eclipsed conformation. These steric effects, because of clashes that would occur between Tu in the eclipsed conformation and the cyclen ring, cause the coordination of Tu with a higher energy conformation, with Zn–S–C–N = 75.4°. The latter approaches the high energy staggered conformation that has Zn–S–C–N = 90°. log K_1 values for Cl$^-$, Br$^-$, I$^-$, and CN$^-$ are reported and shown to be consistent with the binding site on the Zn^{II} in the Zn^{II}/cyclen complex being softer in the hard and soft acids and bases (HSAB, Pearson 1997) sense than the Zn^{II} aqua ion, but not as soft as Zn^{II} in triaza macrocycles that promote tetrahedral coordination. The change in HSAB character from intermediate in the Zn^{II} aqua ion to softer in the cyclen complex, and softer still in tridentate N-donor ligands in model complexes, and in the Zn^{II} active site of carbonic anhydrase as representative of Zn^{II} metalloenzymes in general, is discussed in terms of the role of such effects in the functioning of metalloenzymes.

Introduction

Model complexes have played an important role[1,2] in understanding the catalytic properties of zinc(II) in metalloenzymes.[3] In particular, the complex [Zn([12]-ane-N$_3$)-H$_2$O]$^{2+}$ (see Figure 1 for the key to the ligand abbreviations) has been important as a model for enzymes where the Zn^{II} is bound in the active site of the enzyme by three nitrogens from histidine residues, such as carbonic anhydrase[4] (CA) or phosphate esterases.[4] A point of interest,[5,6] usually overlooked in discussions of Zn^{II} metalloenzymes, is that the chemistry of Zn^{II} in metalloenzymes is greatly altered[1,5,6,7] in the hard and soft acids and bases (HSAB) sense of Pearson.[8] Thus, in the classic study by Kimura et al.,[5] it was

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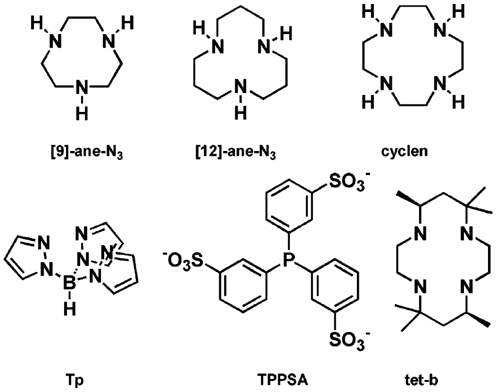

Figure 1. Ligands discussed in this paper.

Table 1. Formation Constants (log K_1) for Binding of Unidentate Ionic Ligands to Zn^{II} in Its Aqua Ion,[9] in[5] $[Zn([12]\text{-}aneN_3)H_2O]^{2+}$, and in Carbonic Anhydrase (CA)[10]

	log K_1						
Lewis acid	OH^-	F^-	Cl^-	Br^-	I^-	SCN^-	CN^-
Zn^{2+}(aq)	4.6	1.15	0.5	−0.1	−1.5	0.7	(5.1)
Zn^{II} in CA	6.2	−0.07	0.72	1.19	2.07	2.1	5.62
$[Zn([12]\text{-}aneN_3)H_2O]^{2+}$	6.5	0.8		1.5	1.6	2.4	

shown that zinc(II) in its [12]-ane-N_3 complex is “soft” in the HSAB sense, as compared to the Zn^{2+} aqua ion, which is classified[8] as “intermediate”. This change in the HSAB properties of Zn^{II} is indicated by the log K_1 values for halides replacing the water molecule on its axial binding site, as shown below, an effect that is also found for Zn^{II} in CA.[10] For the intermediate Zn^{2+} aqua ion, log K_1 values with halide ions vary, $F^- > Cl^- > Br^- > I^-$ (which is actually more consistent with hard behavior), whereas (Table 1) for the soft Zn^{II} in CA or the [12]-ane-N_3 complex, the order is $I^- > Br^- > Cl^- \gg F^-$. In the CA site itself, the change in softness is probably not relevant because CO_2 does not bind directly to Zn^{II}, but the behavior of CA with halide ions is representative of Zn^{II} in metalloenzymes in general.

Nature utilizes only fairly hard metal ions from the first row of transition metals, such as Zn, Fe, Cu, Co, Mn, and Ni,[11] to effect elegant catalytic reactions, which are generally carried out in organometallic chemistry with very soft metal ions such as those of Rh or Ir. Only W and Mo, of the heavier transition metals, are so far known to be utilized, and that on a limited basis, in biochemistry.[11] The alteration of the HSAB properties of metal ions, particularly those of Zn^{II}, in metalloenzymes may, in some cases, be an important part of their functioning. For example, in liver alcohol dehydrogenase, the ability to bind alcohol strongly as an ethoxide ion to Zn^{II} is an important first step in the dehydrogenation reaction to produce acetaldehyde.[11] Ordinarily, alkoxides of metal ions such as Zn^{II} are hydrolyzed instantly in water. An important contribution to soft behavior may be[7] the steric aspects of the binding of ligands to metal ions, and steric hindrance of the bulky alkyl group of ethanol to a tetrahedral Zn^{II} ion may be less than that to a more crowded six-coordinate Zn^{II} aqua ion. The occurrence of soft behavior in Zn metalloenzymes may be particularly important in situations where soft thiolate groups bound to Zn^{II} are alkylated[12−14] to become soft-donor thioether groups. The strength of binding of these groups to Zn^{II} should be controlled so that the formation of the thioether is not energetically so unfavorable as to oppose the alkylation reaction, but the thioether also should not bind to the Zn^{II} so strongly as to be difficult to expel after the alkylation reaction is completed.

A majority of the known structures of Zn metalloenzymes that have a mononuclear Zn active site[4,15] have a four-coordinate tetrahedral Zn^{II}, usually held in place by three histidine nitrogens, and include a bound water on the fourth coordination site. In a few examples, a five coordinate Zn^{II} is present, such as in astacin[16] or adenosine deaminase,[17] including a water molecule that occupies the fifth coordination site. Perhaps more importantly, numerous studies[2] have suggested that the transition states in many of the reactions catalyzed by Zn metalloenzymes involve five-coordinate Zn^{II}.

It has been demonstrated by many examples[1,2] that an increase in the coordination number (CN) from 4 up to 6 causes a rise in the pK_a of the coordinated water molecule on Zn^{II}, as evidenced by model complexes of the Tp type,[2] from 6.5 (CN 4) to 8.0 (CN 5) and 9.5 (CN 6). In an attempt to see how a change of coordination number would affect the HSAB properties of bound Zn^{II}, we have studied the binding of small ligands such as halides to Zn^{II} in its complex with cyclen. Also included are ligands that are very soft, such as thiourea (Tu), the phosphine TPPSA (Figure 1), and cyanide. The binding of these unidentate ligands provides[18] an indication of the general bonding tendencies of a Lewis acid and an indication of how the factors contributing to HSAB behavior have been altered. The question of interest here is, how will an increase in coordination number to five in complexes of the type $[Zn(cyclen)H_2O]^{2+}$ affect the HSAB behavior. As it turned out, the log K_1 value for the Zn^{II}/cyclen complex with Tu was surprisingly low. The structure of $[Zn(cyclen)S{=}C(NH_2)_2](ClO_4)_2$ was determined in order to see whether some steric reason for this low stability could be determined and is reported here. Of particular interest is the suggestion[7] that the fact that many soft ligands such as Tu bind only very weakly with metal aqua ions is caused by a steric clash with the coordinated water molecules in an ion such as $[Zn(H_2O)_6]^{2+}$.

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Table 2. Crystal Data and Structure Refinement for $[Zn(cyclen)S{=}C(NH_2)_2](NO_3)_2$ (**1**)

empirical formula	$C_9H_{24}N_8O_6SZn$
M	437.79
T/K	110(2)
cryst syst	orthorhombic
space group	$P2_12_12_1$
unit cell dimensions	$a = 11.4170(11)$ Å $b = 12.1995(11)$ Å $c = 12.5299(12)$ Å
α/deg	90
β/deg	90
γ/deg	90
V/Å^3	1745.2(3)
Z	4
μ/mm^{-1}	1.573
reflns collected	15 987
independent reflns	3843 [R(int) = 0.0412]
final R indices [$I > 2\sigma(I)$]	R1 = 0.0504, wR2 = 0.1133
R indices (all data)	R1 = 0.0644, wR2 = 0.1217

Table 3. Bond Lengths and Angles for $[Zn(cyclen)S{=}C(NH_2)_2](NO_3)_2$ (**1**)[a]

Bond Lengths (Å)			
Zn(1)−N(3A)	2.084(6)	Zn(1)−S(1)	2.3128(11)
Zn(1)−N(1A)	2.233(6)	Zn(1)−N(2A)	2.191(6)
Zn(1)−N(4A)	2.136(7)	S(1)−C(9)	1.748(4)

Bond Angles (deg)			
N(3A)−Zn(1)−N(4A)	84.3(2)	N(1A)-Zn(1)−S(1)	114.09(16)
N(3A)−Zn(1)−N(2A)	82.3(2)	N(4A)-Zn(1)−N(2A)	135.8(2)
N(3A)−Zn(1)−N(1A)	134.3(2)	N(4A)-Zn(1)−N(1A)	80.4(2)
N(2A)−Zn(1)−N(1A)	79.5(2)	N(3A)-Zn(1)−S(1)	111.56(17)
N(4A)−Zn(1)−S(1)	107.58(17)	N(2A)-Zn(1)−S(1)	116.58(17)
C(9)−S(1)−Zn(1)	96.52(13)	C(6A)-N(3A)-Zn(1)	105.8(5)

[a] Note that these refer to one of the two disordered individuals centered on the Zn^{II} ion.

Table 4. Binding Constants [log K_1(L)] for the Formation of Zn^{II}/Cyclen Complexes with the Unidentate Ligand L Bound to the Zn^{II}, Determined by Glass Electrode Potentiometry as Described in the Text, at 25 °C and $I = 0.1$ ($NaNO_3$), and Compared with Available Literature log K Values [log $K_{(lit)}$]

equilibrium	log K(L)	log $K_{(lit)}$	references
$H^+ + OH^- \Delta H_2O$		13.78	9
[Zn(cyclen)] + L Δ [Zn(cyclen)L]			
L = OH^-	6.1	6.0	this work, 22
L = Cl^-	1.6	1.5	this work, 22
L = Br^-	1.4		this work
L = I^-	1.1		this work
L = SCN^-		2.2	22
L = Tu	−0.2		this work
L = TPP	0.8		this work
L = CN^-	4.5		this work

Experimental Method

Materials. All of the chemicals and reagents used were of analytical grade, purchased from commercial sources, and used without further purification.

Synthesis of $[Zn(cyclen)S{=}C(NH_2)_2](NO_3)_2$ (1). Totals of 0.0152 g of thiourea, 0.0345 g of cyclen, and 0.0595 g of $Zn(NO_3)_2 \cdot 4H_2O$ were dissolved in 20 mL of ethanol. After the solution stood for a few days, colorless crystals of **1** were deposited. Anal. Calcd for $C_9H_{24}N_8O_6SZn$: C, 24.69; H, 5.53; N, 25.60. Found: C, 24.85; H, 5.48; N, 25.73.

Molecular Structure Determination. A mounted crystal of **1** was placed in a cold nitrogen stream (Siemens LT-2) maintained at 110 K. A Siemens P4 four-circle diffractometer was employed for crystal screening, unit cell determination, and data collection. The goniometer was controlled using the XSCANS software suite.[19] The structure was solved by Patterson synthesis and refined to convergence.[20] The cyclen ring was disordered as two separate individuals disordered about the Zn^{II} cation, each with 50% occupancy. The complex cation, showing one of the disordered cyclen individuals, is seen in Figure 1. Details of the structure determination are given in Table 2, and bond lengths and angles of interest are given in Table 3.

Potentiometric Titrations. All of the titrations were carried out under nitrogen at 25 ± 0.1 °C in a jacketed cell, with ionic strength $I = 0.10$ M ($NaNO_3$). The pH meter (VWR SR601C) was calibrated daily using a standard HNO_3 solution titrated with a standardized NaOH solution. The method of measuring the binding constants of the unidentate ligands to the axial binding site of $[Zn(cyclen)(H_2O)]^{2+}$ was that reported by Kimura et al.[5] Essentially, a solution containing a 1:1 ratio of Zn^{II} and cyclen (5×10^{-3} M) in 0.1 M $NaNO_3$ was allowed to equilibrate for 60 min to ensure the complete complexation of the Zn ion with the cyclen. This solution was then titrated with NaOH to obtain a value of log K for the reaction

$$[Zn(cyclen)(H_2O)]^{2+} + OH^- \rightleftarrows [Zn(cyclen)OH]^+ \qquad (1)$$

This titration gave a value of log K (Table 4) in reasonable agreement with the literature value. The formation constants for the binding of unidentate ligands (L) were then calculated from the displacement of this titration curve to higher pH by the binding of added concentrations of L to the Zn^{II}/cyclen complex, as in

$$[Zn(cyclen)L]^{n+} + OH^- \rightleftarrows [Zn(cyclen)OH]^+ + L^{(2-n)-} \qquad (2)$$

The binding of L to Zn causes a displacement of the OH^- uptake curve for the Zn^{II}/cyclen complex. The more strongly L binds, the more the OH^- uptake curve is displaced to higher pH. K_{exch} for the replacement of OH^- by L on the Zn^{II}/cyclen complex is given by eq 3:

$$K_{exch} = [Zn(cyclen)L][OH^-]/[Zn(cyclen)OH]\,[L] \qquad (3)$$

which gives[21] eq 4:

$$= \{1 - [1 - \bar{n}(OH)]\bar{n}(L)/\bar{n}(OH) - \bar{n}(L)\}[OH^-]/\bar{n}(L)[L] \qquad (4)$$

In eq 4, $\bar{n}$ is the ratio of the concentration of hydroxide bound to Zn^{II} to the total Zn^{II} concentration. $\bar{n}$(OH) refers to the titration carried out in the absence of added ligand L, whereas $\bar{n}$(L), in eq 4, is $\bar{n}$ at the same pH as that of $\bar{n}$(OH), but it refers to the titration carried out in the presence of added L. Clearly, if no complex forms, $\bar{n}(L) = \bar{n}(OH)$ and $K_{exch} = 0$. log K_1(L), which refers to eq 5:

$$[Zn(cyclen)H_2O]^{2+} + L^{n-} \rightleftarrows [Zn(cyclen)L]^{(2-n)+} + H_2O \qquad (5)$$

can be calculated from eq 6:

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(21) Equation 4 may be derived as follows: The ratio [Zn(cyclen)L]/[Zn(cyclen)OH] in eq 3 is equal to $\bar{n}(L)/\bar{n}(OH, L)$, where $\bar{n}$(OH, L) is $\bar{n}$ for the MLOH complex in the presence of added L. In the presence of added L, [Zn(cyclen)OH] may be substituted with $\bar{n}$(L), so that we only need to express [Zn(cyclen)L] in terms of $\bar{n}$ values. We consider that [Zn(cyclen)L] = [Zn^{II}(total)] − [$Zn(cyclen)^{2+}$] − [Zn(cyclen)OH]. Working with $\bar{n}$ values, $\bar{n}$ for [Zn^{II}(total)] = 1 and [Zn(cyclen)OH] = $\bar{n}$(L). Thus, all that is needed is to calculate $\bar{n}$ for [$Zn(cyclen)^{2+}$]. In both the presence and absence of added [L], the ratio of [$Zn(cyclen)^{2+}$]/[Zn(cyclen)OH] must be the same. In the absence of added L, this ratio is given by $[1 - \bar{n}(OH)]/\bar{n}(OH)$. In the presence of L, $\bar{n}$ for [$Zn(cyclen)^{2+}$] will be given by $[1 - \bar{n}(OH)]\,\bar{n}(L)/\bar{n}(OH)$. Making substitutions in eq 3 thus gives eq 4.

$$\log K_1(\mathrm{L}) = \Delta(\mathrm{pH}) + \log K_{\mathrm{exch}} \qquad (6)$$

In eq 6, Δ(pH) is, thus, the shift in pH of the titration curve at any given value of $\bar{n}$, from that obtained with no ligand present to that in the presence of the molarity ([L]) of competing ligand L. Note that, for shifts of the titration curve to a higher pH [Δ(pH)] of greater than one pH unit, eq 7 holds to a good approximation:

$$\log K_1(\mathrm{L}) = \Delta(\mathrm{pH}) - \log[\mathrm{L}] \qquad (7)$$

Values of log K_1(L) obtained by glass electrode titration for complexes of L binding to $[\mathrm{Zn(cyclen)H_2O}]^{2+}$ are given in Table 4.

Molecular Modeling. Molecular modeling on the coordination of Tu to metal ions was carried out with the program Hyperchem 7.5,[23] and ab initio calculations employing the STO-3G basis set[24] were carried out using the ab initio module built into Hyperchem.

Results and Discussion

The log K_1 values for unidentate ligands binding to the $\mathrm{Zn^{II}}$/cyclen complex show that the $\mathrm{Zn^{II}}$ in its cyclen complex is not soft in the HSAB sense, but intermediate. It is, however, softer than the $\mathrm{Zn^{2+}}$ aqua ion in that it still forms complexes of some stability with soft ligands such as $\mathrm{I^-}$. Thus, the five-coordinate $\mathrm{Zn^{II}}$/cyclen complex is a weaker Lewis acid than the four-coordinate [12]-ane$\mathrm{N_3}$ complex, and it is also harder. This type of effect has been observed[25,26] in the $\mathrm{Cu^{II}}$ complexes of tet-b, where the latter $\mathrm{Cu^{II}}$ complex is soft, whereas the $\mathrm{Cu^{2+}}$ aqua ion is intermediate, verging on hard. This is seen in the log K values shown in Table 5.

Table 5 shows that $\mathrm{Cu^{II}}$ in its tet-b complex has changed its metal complexing properties quite remarkably. This extends to the $\mathrm{SCN^-}$ complex $[\mathrm{Cu(tet\text{-}b)SCN}]^+$ in which the thiocyanate is S-bonded[27] to the $\mathrm{Cu^{II}}$, which may be regarded as a hallmark of soft behavior, with hard metal ions bonding to the harder N donor of the thiocyanate. This structure underlines one of the small inconsistencies that makes[28] HSAB somewhat unreliable in its predictions and ultimately leads to its failure to be expressed as a quantitative theory, particularly as far as its ability to predict formation constants is concerned. Thus, although $\mathrm{Cu^{II}}$ is classified as "intermediate" in the HSAB classification, it frequently forms S-bonded complexes with $\mathrm{SCN^-}$, whereas $\mathrm{Cd^{II}}$, which is "soft", almost never does,[27] unless the $\mathrm{SCN^-}$ is bridging between two $\mathrm{Cd^{II}}$ ions. Such effects have been proposed to be steric in origin,[29] with a possible contribution from solvational effects. The formation constants for Lewis acids interacting with Lewis bases in aqueous solution can be modeled[29] quantitatively using eq 8:

$$\log K_1 = E'_{\mathrm{a}}E'_{\mathrm{b}} + C'_{\mathrm{a}}C'_{\mathrm{b}} - D_{\mathrm{a}}D_{\mathrm{b}} \qquad (8)$$

In eq 8, log K_1 is the formation constant in water for the complex between a Lewis acid and any unidentate ligand, whereas E' and C' refer respectively to the ionic and covalent contributions to bonding in the Lewis acid "a" and base "b". The D_{a} and D_{b} contributions reflect solvational effects, which may be attributed to (1) steric effects due to clashes between the coordinating unidentate ligand and the adjacent coordinated water molecules and (2) hydrogen-bonding effects, where the covalent bonding of the incoming ligand reduces the charge on the metal ion and, hence, decreases its ability to hydrogen-bond with the solvent.

Table 5. Formation Constants[25,26] for Complexes of $[\mathrm{Cu(tet\text{-}b)}]^{2+}$ with Small Unidentate Ligands, Compared with Those for the Aqua Ion[a] [9]

	log K_1					
Lewis acid	$\mathrm{Cl^-}$	$\mathrm{Br^-}$	$\mathrm{I^-}$	NH3	$\mathrm{CH_3CH_2NH_2}$	$\mathrm{N(CH_3)_3}$
$\mathrm{Cu^{2+}(aq)}$	0.4	−0.03	<−1	4.04	~3	no complex
$[\mathrm{Cu(tet\text{-}b)}]^{2+}$	1.19	1.26	1.35	1.95	2.84	2.69

[a] Note the ability of $\mathrm{Cu^{II}}$/tet-b to complex strongly with sterically hindering ligands such as $\mathrm{(CH_3)_3N}$, which the aqua cannot do.

In relation to point 1, an examination of the Cambridge Structural Database[30] (CSD) reveals that thiocyanate is frequently S-bonded to $\mathrm{Cu^{II}}$, but when it does so, it almost always occupies the axial coordination site, with long Cu−S bonds in the vicinity of 2.8 Å, as compared to expected in-plane Cu−S bonds of 2.3 Å (expected on the basis of typical[30] in-plane $\mathrm{Cu^{II}}$−S bonds in complexes of other S-donor ligands such as thioethers). One can demonstrate the predictive power of eq 8 for the $[\mathrm{Zn(cyclen)}]^{2+}$ complex, as well as for $[\mathrm{Cu(tet\text{-}b)}]^{2+}$, as seen in Table 6.

A major point of interest in the changes in HSAB produced in metal ion complexes such as $[\mathrm{Cu(tet\text{-}b)}]^{2+}$ as compared to those of the free $\mathrm{Cu^{2+}}$ ion, or those of $\mathrm{Zn^{II}}$ in its [9]-ane-$\mathrm{N_3}$ or [12]-ane-$\mathrm{N_4}$ complex compared to those of the free $\mathrm{Zn^{2+}(aq)}$ ion, is the origin of the changes. Clearly, the same controlling factors may be operating in changing the HSAB properties of $\mathrm{Zn^{II}}$ in metalloenzymes such as CA,[10] so that understanding this type of effect could be of some importance in understanding the operation of metalloenzymes. The ratio between E'_{a} and C'_{a} has been proposed[18] as a measure of the hardness of the metal M, but more simply, it may be regarded[7] as a measure of the ionicity of the M−L bond. If one examines the $\mathrm{E'_a/C'_a}$ ratios for the Lewis acids of interest here, one sees that there is a change in the ionicity of bonding in passing from $\mathrm{Zn^{2+}(aq)}$ to the $\mathrm{Zn^{II}}$/cyclen complex, but there is also a decrease in the D_{a} parameter (see Table 7). The changes in covalence in the $\mathrm{Zn^{II}}$ and $\mathrm{Cu^{II}}$ complexes on passing from the aqua ions to the complexes with N-donor macrocycles, evidenced by the changed $E'_{\mathrm{a}}/C'_{\mathrm{a}}$ ratios, seem likely to originate in the drop in coordination number, as well as in the binding to the less electronegative N donors of the ligand instead of the O donors of water. The changes in the D_{a} parameters suggest that the alteration in affinity for ligands with large donor atoms such as Cl or S comes from changes in the steric and solvational factors

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Table 6. Formation Constants for Complexes between Unidentate Ligands and the Lewis Acids $[Zn(H_2O)_6]^{2+}$, $[Zn(cyclen)H_2O]^{2+}$, $[Cu(tet\text{-}b)(H_2O)]^{2+}$, and $[Zn([12]\text{-}ane\text{-}N_3)(H_2O)]^{2+}$, Calculated[a] Using Eq 8 and Observed (parentheses)[b]

	Lewis acid			
	$[Zn(H_2O)_6]^{2+}$ log K_1	$[Zn(cyclen)H_2O]^{2+}$ log K_1	$[Cu(tet\text{-}b)(H_2O)]^{2+}$ log K_1	$[Zn([12]\text{-}ane\text{-}N_3)(H_2O)]^{2+}$ log K_1
OH^-	4.4	6.1	2.70	5.9
	(4.6)	(6.1)	(2.71)	(6.4)
F^-	1.43	1.8	0.4	1.0
	(1.3)			
Cl^-	0.8	1.9	1.2	2.6
	(0.5)	(1.6)	(1.2)	
Br^-	−0.3	1.4	1.2	2.5
	(−0.1)	(1.4)	(1.3)	(1.5)
I^-	−1.5	1.0	1.4	2.5
	(−1.5)	(1.1)	(1.4)	(1.6)
SCN^-	1.2	2.4	1.5	2.8
	(1.3)	(2.2)	(2.2)	(2.4)
CN^-	2.3	4.5	3.7	7.2
	(?)[c]	(4.5)	(3.5)	

[a] The E'_a, C'_a, and D_a parameters are, respectively, for the Lewis acids: $[Zn(H_2O)_6]^{2+}$, 1.43, 0.312, 2.5; $[Zn(cyclen)H_2O]^{2+}$, 1.8, 0.437, 2.0; $[Cu(tet\text{-}b)(H_2O)]^{2+}$, 0.4, 0.193, 0.9; $[Zn([12]\text{-}ane\text{-}N_3)(H_2O)]^{2+}$, 1.1, 0.42, 1.1. The E'_b, C'_b, and D_b parameters for the ligands are: OH^-, 0, 14.0, 0; F^-, 1.0, 0, 0; Cl^-, −1.04, 10.4, 0.6; Br^-, −1.54, 14.2, 1.0; I^-, −2.43, 20.0, 1.7; SCN^- (N-bonded), −0.76, 9.3, 0.4; CN^-, −4.43, 30.0, 0.3. [b] The equilibrium for each Lewis acid involves the replacement of a water molecule from the coordination sphere by the Lewis acid indicated. Formation constants for $[Zn(H_2O)_6]^{2+}$ are from ref 9; for $[Zn(cyclen)H_2O]^{2+}$, they are from this work; for $[Cu(tet\text{-}b)(H_2O)]^{2+}$, they are from refs 22 and 23; for $[Zn([12]\text{-}ane\text{-}N_3)(H_2O)]^{2+}$, they are from ref 5. [c] There is considerable disagreement on log K_1 for the Zn^{II} cyanide complex. Some authors[9] claim to detect a first complex with log $K_1 \sim 5$, while other authors[31] suggest that no mono complex is detectable and the first complex formed is the dicyano complex. This would imply that log $K_1 \ll$ log K_2 for the Zn^{II} cyanide system, consistent with a change in structure, possibly from octahedral to tetrahedral with the simultaneous addition of two CN^- to the Zn^{II}. The predicted value of log K_1 for Zn^{II}/CN^- here would refer to octahedral Zn^{II} and would be consistent with the nonobservation of a mono complex in light of the generally agreed-upon value[9] of log β_2 for this system of 10.7.

Table 7

Lewis acid	$Zn^{2+}(aq)$	$[Zn(cyclen)]^{2+}$	$[Zn([12]\text{-}ane\text{-}N_3)]^{2+}$	$[Cu(tet\text{-}b)]^{2+}$	$Cu^{2+}(aq)$
E'_a/C'_a	4.58	4.12	2.62	2.07	2.68
D_a	2.5	2.0	0.9	0.9	6.0

at the binding site. By extension, one would expect a similar role for steric and solvational factors in the binding site of a metalloenzyme such as CA. The E', C', and D parameters discussed here have considerable predictive power and generally predict log K_1 values for complexes of $M^{n+}(aq)$ ions with unidentate ligands to within 0.2 log units. However, the interpretation of the significance of these parameters is largely based on a comparison with HSAB ideas and needs a stronger theoretical foundation. A start on this has been made[32] with density functional theory calculations that allow for the prediction of log $K_1(NH_3)$ values for $M^{n+}(aq)$ ions, which agree remarkably well with both experimentally known[9] values and the values predicted by eq 8, which cannot be determined experimentally because of hydrolysis to yield only hydroxides in the presence of ammonia. An important aim is to understand the nature of the D_a parameters. Preliminary results indicate that the D_a parameters reflect largely solvational effects. In simple terms, coordination of the base to the Lewis acid decreases the charge on the Lewis acid more strongly as the M−L bond becomes more covalent. This, in turn, decreases the strength of solvation of the metal ion, which leads to unfavorable energetic effects. This is well illustrated by the fact[32] that $(CH_3)_2S$ is a stronger proton base in the gas phase than $(CH_3)_2O$, but this effect is reversed on solvating the proton in the gas phase with a second water molecule in each case.

Equation 8 predicts a value of log K_1 for the Zn^{II}/cyclen complex with Tu of 2.8, which is much higher than the value determined here of −0.2. The structure of **1**, shown in Figure 2, may suggest the reason for this. It is seen that Zn^{II} in **1** has a structure similar to those of other reported structures of Zn^{II} complexes of cyclen,[34−36] with square pyramidal

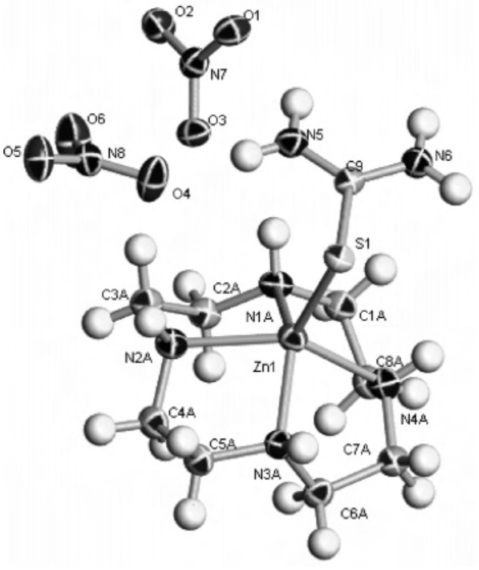

Figure 2. Structure of $[Zn(cyclen)(Tu)](NO_3)_2]$, showing the atomic numbering scheme. Note the orientation of the coordinated thiourea (Tu), where the Zn does not lie close to the plane containing the Tu, as is most commonly found for complexes of Tu, but adopts a "staggered" conformation (see Figure 4).

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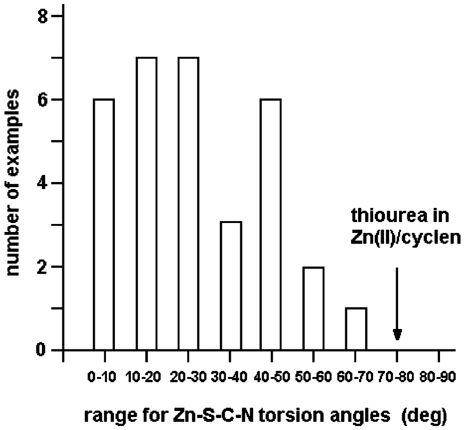

Figure 3. Range of Zn−C−S−N torsion angles (deg) found in the CSD[30] for Zn^{II}/ thiourea (Tu) complexes. Because Tu is essentially planar, there will be two Zn−S−C−N torsion angles for each coordinated thiourea, one less than 90° and the other larger than 90° by an equal amount. Here, only the smaller of each of the two Zn−S−C−N torsion angles is considered. The arrow shows the Zn−S−C−N torsion angle for the coordinated thiourea in the Zn^{II}/cyclen complex (**1**) studied here to be rather large at 75.4°. Only structures with $R < 0.05$ were used in constructing the diagram.

coordination around the Zn^{II} and the coordinated small ligand (CO_3,[2−34] CH_3CH_2OH,[34] deoxythymidine,[35] and nitrophenyl phosphate[36]) occupying the axial coordination sites. What is significant is that, in **1**, the Tu coordinates to Zn^{II} in such a way that the Zn−S−C−N torsion angle is unusually large at 75.4°, which means that the Zn^{II} ion is well out of the plane occupied by the Tu ligand. An inspection of the structures of Zn^{II} complexes reported in the CSD[30] (only structures with $R < 0.05$ were examined) shows that, in most cases, the Tu ligand coordinates such that the Zn−S−C−N torsion angle is closer to zero, what might be referred to as the eclipsed conformation. This is summarized in Figure 3, where the numbers of examples of Zn^{II} complexes with Tu with Zn−S−C−N torsion angles in given ranges are indicated. Figure 3 suggests that a predominant mode of coordination for Tu with Zn^{II} is the eclipsed mode. Where large Zn−S−C−N torsion angles occur (the staggered conformation), an inspection of the structures[30] suggests that steric effects are present. In the case of linear $[M(Tu)_2]^{n+}$ complexes (M = Au^{I}, Ag^{I}, Hg^{II}), where steric effects will be minimal, the structures all have the Tu coordinated in, or close to, an eclipsed fashion.[30]

The eclipsed structure for M^{n+}/Tu complexes would be expected on a simple qualitative molecular orbital basis. The lone pairs on sulfur that would form a bond to a metal ion should lie in the plane of the ligand. Ab initio calculations at the STO-3G level[23,24] were carried out on the linear [AgTuCl] complexes, where steric effects on the coordinated Tu should be at a minimum. The Tu ligand in these calculations was constrained to be in the eclipsed conformation in one case and staggered in the other. These structures are seen in Figure 4a, together with their calculated energies. It is seen that the eclipsed structure for [AgTuCl] is calculated to be 4.75 kcal mol^{-1} lower in energy than the staggered form. This energy difference is consistent with the apparent preference for coordination with Tu in the eclipsed mode found for metal ions in the CSD.[30] However, as an energy difference, it is not large, and it accounts for the ability of steric effects to distort the coordination in the direction of the staggered form. At the simple STO-3G level employed here, the energy differences are only suggestive of what more accurate calculations might indicate, but they do serve to show that the staggered form of the coordinated Tu ligand is not at a very much higher energy than the eclipsed form. Hence, the particular steric situation in complex **1**, shown in Figure 2, is likely to lead to a drop in energy of a few kcal mol^{-1}. If the coordinated Tu in **1** is rotated into the eclipsed mode of coordination, it is found that a serious steric

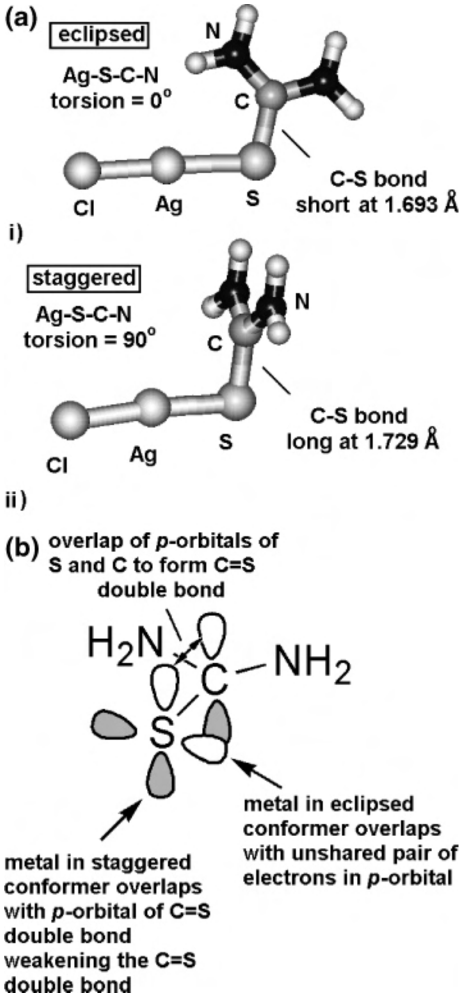

Figure 4. (a) Eclipsed (i) and staggered (ii) forms of the complex [Ag(Tu)Cl], generated using an STO-3G basis set in the program Hyperchem.[23,24] The calculated energy difference between the two structures suggests that the eclipsed form is energetically stabilized relative to the staggered form by 4.75 kcal mol^{-1}. Note that the calculated S−C bond length of Tu is longer in the staggered form than in the eclipsed form. (b) Diagrammatic representation of the bonding of a metal ion to the S of thiourea (Tu). In the eclipsed form, the metal ion overlaps with the p orbital involved in the lone pairs on S, while in the staggered form, the overlap is with the p orbital on S that is involved in the π overlap in the C=S double bond, weakening the latter bond.

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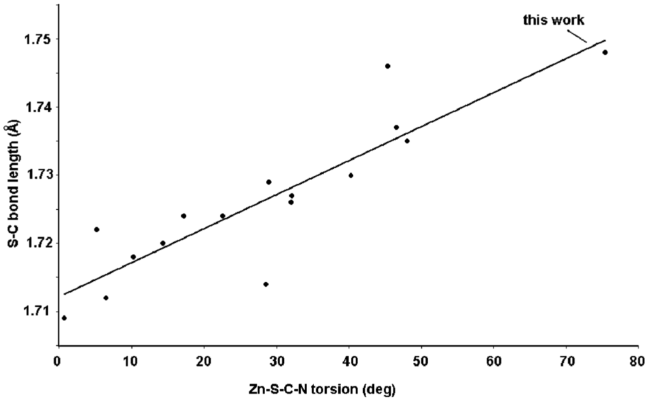

Figure 5. Relationship between the S−C bond length (Å) in coordinated thiourea (Tu) in complexes of Zn^{II} and the Zn−S−C−N torsion angle (deg). All of the data is from ref 30, except for the point labeled "this work", which refers to structure **1** reported here. The line is a least-squares fit, which has a correlation coefficient of 0.80. Note that the S−C length in the coordinated Tu in **1** is the longest reported S−C length for thiourea coordinated to Zn^{II} and is accompanied by a very large Zn−S−C−N torsion angle.

interaction with the cyclen occurs, with H− −H nonbonded separations of as little as 1.7 Å. The difference in energy between the eclipsed and staggered forms of Tu calculated for the [Ag(Tu)Cl] complex is consistent with a steric destabilization of the Zn^{II}cyclen/thiourea complex of a few kcal mol^{-1}, accounting for the smaller than expected log K value for the binding of Tu to the Zn^{II}/cyclen complex noted above.

What is of particular interest here is the nature of the bonding of Tu to metal ions when bonded in the staggered conformation. As mentioned above, in the eclipsed conformation, M−S bonding should involve the p orbital involved in the formation of the lone pairs on the S-donor atom (Figure 4b). Note that participation of the s orbital on the S-donor in the expected sp^2 hybrid is probably quite small, as evidenced by C−S−Zn angles in Zn^{II} complexes of Tu that are[30] closer to 90° (no s orbital participation) than 109.5° (full participation of the s orbital in the sp^2 hybrid). In the staggered Zn^{II}/Tu conformer, the bonding will most likely involve an overlap of the empty Zn orbitals with the p orbital on S that is involved in the formation of a C═S π bond. In support of this idea, its is seen that the STO-3G calculations on [Ag(Tu)Cl] show a lengthened C−S bond in the staggered form as compared to that of the eclipsed form. The same trend can be seen for Zn^{II} complexes of Tu in Figure 5, where there is a reasonable correlation between the Zn−S−C−N torsion angle and the C−S bond length. Because these changes in bond length are quite small, for the requisite accuracy, only structures[30] with $R < 0.05$ were considered in constructing Figure 5. The least-squares fit line in Figure 5 has a correlation coefficient of 0.80, showing a reasonable correlation between the C−S bond length and the Zn−S−C−N torsion angle. The latter correlation is in reasonable agreement with the simple model of bonding of the metal to the S donor of Tu, in that, as the metal moves from the eclipsed to the staggered form, the C−S bond lengthens. This is consistent with the idea that, in the staggered form, the Zn is overlapping with the p orbital on S that participates in the C═S double bond and the latter bond is weakened by overlap with Zn. The point for the coordinated Tu in **1** is included in Figure 5, and as expected from the bonding model presented here, the very large Zn−S−C−N torsion angle in **1** is accompanied by a longer C−S bond in the coordinated Tu. These results are also consistent with the idea that the Zn^{II}/cyclen complex with Tu is destabilized sterically by the inability of the Tu to coordinate to the Zn in the eclipsed mode.

Conclusions

This study has shown the following: (1) The five-coordinate Zn^{II} in the Zn^{II}/cyclen complex is softer than the Zn^{II} aqua ion but harder than the four-coordinate Zn^{II} in the [12]-ane-N_3 complex, as evidenced by the log K_1 values with halide ions. (2) An empirical equation based on E', C', and D parameters accounts adequately for the log K_1 values of the complexes of Zn^{II}/cyclen complexes of sterically less-demanding ligands such as halides, SCN^-, or CN^-. (3) The Tu complex of the Zn^{II}/cyclen complex is of lower stability than that predicted by the latter equation. This can be related to steric effects of the cyclen ligand, which prevents the coordinated Tu from adopting the eclipsed conformation (Zn−S−C−N torsion angle = 0°), which is calculated to be lower in energy than the staggered conformation (Zn−S−C−N torsion angle = 90°). The latter steric effect appears to cause the lower than expected log K_1 value for the Zn^{II}/cyclen complex with Tu. These results support the observation[37] that an understanding of the stability of the complexes requires more than a simple consideration of whether M−L bonds are of the appropriate length. Rather, selectivity is also strongly controlled by bond angles involving the metal ion, and as demonstrated here, torsion angles can be highly important. The Zn^{II}/cyclen complex shows how a steric aspect of the complex, in this the case the cyclen ligand itself, can control selectivity for small ligands such as Tu. (4) These steric effects point to how metal ions such as Zn^{II} in the active site of a metalloenzyme may control selectivity for substrate ligands. In considering the latter, it is important to consider both the bond and torsion angles involving the coordinated ligand and the metal ion as an approach to understanding selectivity in the active site.

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