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Bond Energies of Copper Ion−Ligand L Complexes CuL_2^+ Determined in the Gas Phase by Ion−Ligand Exchange Equilibria Measurements

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Abstract: The free energy changes, ΔG_2, for the reaction $CuL_2^+ = Cu^+ + 2L$ were obtained in the gas phase for some 23 different ligands L. These results were based on the determination of ligand exchange equilibria of the type CuA_2^+ 2B = CuB_2^+ 2A. The equilibria were observed in a gas-phase ion−molecule reaction chamber sampled with a mass spectrometer. The entropy changes ΔS_2° were determined by evaluation of the entropies S°, of the reactants from vibrational frequencies and moments of inertia obtained with HF/3-21G* basis sets. Combining ΔG_2° and ΔS_2° one obtained also the ΔH_2° values. The range of ΔH_2° values extended from 72 kcal/mol for the most weakly bonded ligand ethyl chloride to 135 kcal/mol for the most strongly bonding one, 1-methylimidazole. The results provide a partial confirmation of the Hard and Soft Acids and Bases (HSAB) principle. Comparison with available data for $M^+ = Li^+$ and Ag^+ show that soft bases such as Me_2S bond relatively more strongly to soft acids such as Cu^+ and Ag^+. However the actual bond energies ΔH_2° are affected also by other interactions such as electrostatic contributions due to ion−ligand dipole attractive forces. Several of the ligands used correspond quite closely to the functional groups present on peptide residues. Therefore, a partial scale of peptide residue bonding to Cu^+ can be established. Histidine is found to be the most strongly bonding residue.

Introduction

$Cu^{+/2+}$ complexes play an important role in chemistry and biochemistry and have been intensively studied in the condensed phase. An alternate approach is to study the thermochemistry of the complexes in the gas phase under conditions where solvent molecules and counterions are absent. It is under these conditions that the intrinsic bonding characteristics are most directly revealed. The differences in complexation energies between gas phase and solution indicate the role of the solvent. Much of the interest in Cu ligand complexes derives from the important role that Cu^+/Cu^{2+} complexes play in enzymes effecting redox and O_2 transport reactions. The environment of the protein near the Cu complex may be often hydrophobic, and the complexation energies under these conditions may be closer to those in the gas phase than those in solution.

For smaller ligands, the gas phase energies are also of interest because they are directly comparable with stabilization energies obtained by high level theoretical ab initio calculations, and such calculations are presently possible for smaller ligands.[1]

Jones and Staley[2] have provided the most extensive experimental gas phase study of the bond energies of CuL_2^+ complexes. This was based on the determination of ligand exchange equilibria

$$CuA_2^+ + B = CuAB^+ + A \qquad (1a)$$

$$CuAB + B = CuB_2^+ + A \qquad (1b)$$

$$CuA_2^+ + 2B = CuB_2^+ + A \qquad (1)$$

where A and B are two different ligands. Cu^+ was produced by laser pulses onto a copper wire target, and the studies were performed in an ion-cyclotron resonance (ICR) mass spectrometer. On the basis of exchange equilibria, eq 1, measurements involving 43 different ligands, these authors were able to obtain a scale of *relative* CuL_2 bond free energies ΔG_2° for the reaction; eq 2:

$$CuL_2^+ = Cu^+ + 2L \qquad (2)$$

Generally, such relative scales can be converted to absolute values for ΔG_2° by calibrating to the known value for one given ligand, when such a value is available in the literature due to determinations by some other method, see for example Taft *et al.*[3] Unfortunately, such an absolute value was not available for any of the ligands used by Jones and Staley.[1] Furthermore, the compounds used by Jones and Staley were relatively weakly bonding ligands which were mostly oxygen bases. The most strongly bonding CuL_2^+ complex had the ligand L = $(i\text{-}Pr)_2$-CO, diisopropyl ketone. More strongly bonding nitrogen bases such as NH_3, amines, amides, pyridine, and imidazole or thioethers such as Me_2S or alkyl nitriles such as CH_3CN were not determined. Yet, the bond energies of some of these strongly bonding ligands can be of special interest. A most important example is the participation of such ligands as

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[1] (a) Bauschlicher, C. W.; Langhoff, S. R.; Partridge, H. *J. Chem. Phys.* **1991**, *94*, 2068. (b) Bauschlicher, C. W.; Partridge, H.; Langhoff, S. R. *J. Phys. Chem.* **1992**, *96*, 3273. (c) Langhoff, S. R.; Bauschlicher, C. W.; Partridge, H.; Sodupe, M. *J. Phys. Chem.* **1991**, *95*, 10677.

[2] Jones, R. W. and Staley, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 2296.

[3] Taft, R. W.; Anvia, F.; Gal, J. F.; Walsh, S.; Capon, M.; Holmes, M. C.; Hosn, K.; Olonmi, G.; Vasanwala, R.; Yazdani, S. *Pure Appl. Chem.* **1990**, *62*, 17.

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functional groups on the residues of amino acids in enzymes in which a Cu^+ ion is coordinated to such groups.[4] For example, residues and corresponding functional groups in brackets, histidine (imidazole), methionine ($-CH_2CH_2SCH_3$), and cysteine ($-CH_2SH$), are frequently involved[4] in Cu enzymes.

Cerda and Wesdemiotis[5] have obtained qualitative bond energy orders for Cu(I) amino acid complexes with the kinetic method based on mass spectrometric determinations of the dissociation yields of excited $CuAB^+$ which dissociate to the products $CuA^+ + B$ and $CuB^+ + A$. The determinations were very comprehensive, covering some 19 amino acids. While these results are valuable, the data obtained reflect the complete interaction, i.e., interaction with the amide group *and* the functional group of the amino acid residue. It is obviously desirable to have data for the bonding energies involving only the specific functional group of the residue.

In the present work we describe determinations of the exchange equilibria, eq 1, which were determined with a "high pressure" (10 Torr) reaction chamber and a mass spectrometer. The ligands L used to lead to more strongly bonding complexes than the ligands used by Jones and Staley. Fortunately, the scale ΔG_1° values obtained could also be converted to absolute ΔG_2° values by anchoring it to one absolute value available in the literature. Since the scale connected to the Jones and Staley scale of ligands, absolute values were obtained also for these compounds. The ΔG_2° values were combined with ΔS_2° values obtained computationally, see section (c) in Experimental and Calculations, so that ΔH_2° values were obtained also. The general significance of these data is considered in Results and Discussion where particular attention is given to the ligands involved in the Cu enzyme complexes.

The choice of the CuL_2^+ complexes rather than CuL_n^+ where $n \neq 2$, by Jones and Staley[2] and in the present work, is partially based on experimental convenience. Cu^+ (and Ag^+) forms very strongly bonded dicoordinated linear complexes. These very strong bonds have been attributed[1] to the presence of sdσ hybridization of the metal orbital. Since the interaction with the ligands is mostly electrostatic, the sdσ orbital allows the two ligands to approach the ion with minimum electronic repulsion.[1] The first two bond energies M^+-L and ML^+-L are approximately equal and much higher than those observed with additional ligands. The special stability of CuL_2^+ facilitates the measurements of the exchange equilibria, eq 1. While these results may be considered restricted, they are nevertheless very significant because they deal with the first two strongest bonding interactions.

Experimental and Computational Methods

(a) Apparatus. The apparatus used has been described in detail previously,[6] and therefore only a brief account will be given here. Ion-ligand complexes $Cu(CH_3CN)_2^+$ were produced by electrospray.[7] The gas-phase ions carried in pure N_2 gas were introduced via a capillary into the reaction chamber. A mixture of carrier gas N_2 (10 Torr) and ligand vapors A and B at pressures in the 10−100 mTorr range flowed through the reaction chamber. The exchange equilibria, eq 1, established in the reaction chamber and the relative concentrations of the ion ligand complexes CuA_2^+, $CuAB^+$, and CuB_2^+ at equilibrium were sampled by continuously bleeding a very small sample of the gas into an evacuated chamber containing a triple quadrupole mass spectrometer. The relative intensities of the three ions CuA_2^+, $CuAB^+$, and CuB_2^+ were determined with the mass spectrometer. The relative intensities were assumed to correspond to the relative concentrations of the ions in the equilibration chamber.

(b) Methods of Equilibria Measurements. The methods used to determine the equilibria, eq 1, involving CuL_2^+ complexes were the same as those described recently in detail which involved the same type of exchange equilibria but with the silver ion, Ag^+, as the core ion.[8] Therefore only a brief account will be given here. Kinetic[8] investigations of the reactions, eq 2, indicated that equilibria will be reached at ligand gas pressures considerably above 2 mTorr, since the residence time of the ions in the reaction chamber is only ~100 μs. The equilibria 2 were determined using ligand pressures up to 100 mTorr. The equilibrium expressions, K_{1a} and K_{1b}

$$K_{1a} = \frac{I(CuAB^+)P_A}{I(CuA_2^+)P_B} \tag{3}$$

$$K_{1b} = \frac{I(CuB_2^+)P_A}{I(CuAB^+)P_B} \tag{4}$$

were evaluated from the observed ion intensities when a reaction mixture containing a given *constant* ratio of ligand partial pressures P_B/P_A flowed through the reaction chamber. On the basis of preliminary experiments, the ligand that led to weaker bonding was determined, and then in the actual measurement, the pressure of that ligand was set higher so as to obtain, at equilibrium, ion intensities which did not differ by very large factors. As the partial pressure of the ligands was increased, the system reached equilibrium, and the equilibrium quotients became invariant with pressure and equal to the equilibrium constant. To check that equilibrium was truly achieved, experiments with different constant P_B/P_A ratios were used, and these were found to lead to the same equilibrium constant.

(c) Production of CuL_2^+ Ions by Electrospray. Solvent Dependence of Cu^+/Cu^{2+} Redox Equilibrium. In previous work involving ion-equilibria measurements[6,8] with electrospray produced ions, we have generally used methanol or water−methanol mixtures as solvent and 10^{-4} mol/L concentrations of the salt which contains the needed cation. Under these conditions for a singly charged cation M^+ and a salt MX (where X generally equaled Cl or NO_3), the gas-phase ions produced by electrospray were $M(MeOH)_n^+$, when neat methanol was the solvent, and $M(MeOH)_x(H_2O)_y^+$, when methanol−water solvent mixtures were used.[6,7b,8] However, the corresponding Cu^+ ions were not observed when Cu(I) salts such as CuCl were used. CuCl, whose solubility product in water is $K_{sp} = 10^{-6}$, is sufficiently soluble to provide the needed Cu^+ concentration. The absence of observable Cu^+ ions is probably closely related to the redox reaction

$$2Cu^+ = Cu^0 + Cu^{2+} \quad K_5 = \frac{[Cu^{+2}]}{[Cu^+]^2} = 10^6 \tag{5}$$

which is known to occur in water and other solvents which are oxygen bases.[9] In qualitative agreement with the predictions of eq 5, abundant Cu^{2+} ions solvated by methanol and/or water were observed when 10^{-4} mol/L solutions of CuCl were electrosprayed. The complete absence of Cu^+ ions in the electrospray mass spectrum still appears surprising since the equilibrium constant $K_5 = 10^6$ (for aqueous solutions) and initial concentrations of [CuCl] = 10^{-4} M should lead to an expected ratio of $[Cu^+]/Cu^{2+}] \approx 0.1$ at equilibrium, indicating that Cu^+ ions should have been detected. However, the actual ratio of gas-phase ions

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[6] (a) Klassen, J. S.; Blades, A. T.; Kebarle, P. *J. Phys. Chem.* **1995**, *99*, 15509. (b) Blades, A. T.; Klassen, J. S.; Kebarle, P. *J. Am. Chem. Soc.* **1996**, *118*, 12437.

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[9] Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*; Interscience Publ.: 1996; p 895.

depends on a number of additional factors.[7b,10] The concentrations of solutes present in the droplets which lead to the gas-phase ions are much higher than the original concentration due to solvent evaporation. Estimates indicate solute concentrations that are about 100 times higher.[10] Under such conditions, if equilibrium eq 5 is maintained in the evaporating droplets, the ratio in the droplets can be predicted to be closer to $[Cu^+]/Cu^{2+}] \approx 0.01$. This very low relative concentration for Cu^+ is closer to the experimental observations.

The redox equilibrium eq 5 is shifted toward Cu^{2+} ions because these are relatively much better solvated by H_2O than is Cu^+. Other solvents which lead to stronger solvation of Cu^+ shift the equilibrium toward the Cu^+ ion. Electrospray with different solvents was tried, and best results were obtained with acetonitrile, MeCN. Abundant $Cu(MeCN)_n^+$ ions were obtained with this solvent and CuCl as solute, while Cu^{2+} ions were absent. The solvent dependence of the Cu^+, Cu^{2+} yield was confirmed also in the reverse sense. Thus, solutions of $CuCl_2$ in MeCN led to gas-phase ions dominated by Cu^+ ions. The ligand bonding energies determined in the present work, *vide intra*, provide an illustration of the very much stronger bonding of Cu^+ to MeCN relative to H_2O and MeOH.

The $Cu(MeCN)_2^+$ ions desired for the equilibrium measurements in the reaction chamber were obtained from the $Cu(MeCN)_x^+$ delivered by the electrospray by controlling the temperature of the reaction chamber. Good yields of $Cu(MeCN)_2^+$ were obtained at 120 °C, and the equilibria measurements were performed at this temperature.

The necessity, dictated by the chemistry in solution, to produce a primary reagent ion CuL_2^+ where L = MeCN is a strongly bonding ligand, has a drawback because the scale to be obtained by the exchange equilibria eq 1 is limited to ligands which are of nearly equal bonding strength or are more strongly bonding. To illustrate this restriction we consider the general exchange reaction: $MA_2^+ + 2B = MB_2^+ + 2A$, where A and B are ligands other than MeCN. When A and B are more strongly bonding their presence in the reaction chamber always leads to rapid replacement of the primary reagent ion $M(MeCN)_2^+$ with MA_2^+ and MB_2^+ ion even when the pressure of the ligands A and B is quite low. On the other hand, when A and B are much more weakly bonding, they must be added at very much higher pressures to overcome the slow kinetics of the endergonic exchange of MeCN with A and B ligands. However, the upper ligand pressure that can be used is limited (∼100 mTorr for the present apparatus),[11] and, therefore, the extension of the scale to ligands which are more weakly bonding than MeCN is limited to a few kcal/mol free energy difference between MeCN and these ligands.

The ΔG_1° values obtained were used to establish a scale of free energy changes, shown in Figure 1. To obtain also the enthalpy changes ΔH_1° from experimental measurements one needs to measure the equilibria eq 1 at different temperatures over a temperature range which is as wide as possible. However, at temperatures lower than 120 °C the formation of higher coordination CuL_n^+ complexes interferes with the measurements. Determinations at temperatures above 120 °C would have been possible. However the present apparatus has an upper temperature limit of 200 °C due to the cryopumping used.[6] Therefore, ΔS_2° values were obtained by calculation, and ΔH_2 values were then obtained from the equation $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$, as described in the next section.

Results

Thermochemical data for $CuL_2^+ = Cu^+ + 2L$. The free energies for the exchange reactions 1, ΔG_{1a}°, ΔG_{1b}° and ΔG_1° obtained from the equilibria are given in Table 1. While the primary interest is in the complete exchange, ΔG_1°, the values for the partial exchanges, ΔG_{1a}° and ΔG_{1b}°, also provide some interesting information. The first exchange, ΔG_{1a}°, is in practically all cases much more exergonic than the second exchange, ΔG_{1b}°. When the complete exchange ΔG_1° is of low exergonicity, the second exchange can be even endergonic.

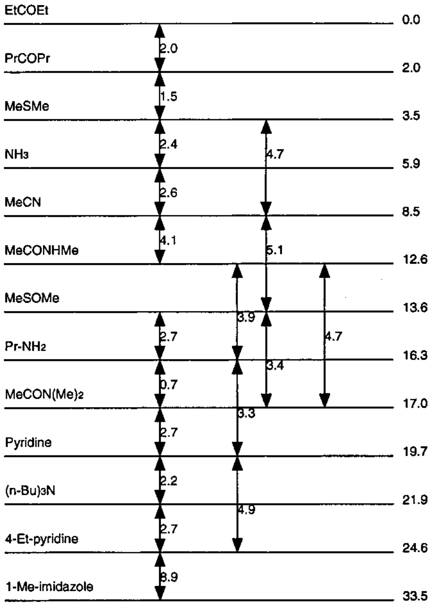

Figure 1. Scale of relative dissociation free energies, ΔG_2°, for reactions $CuL_2^+ = Cu^+ + 2L$, based on measured free energies ΔG_1° for exchange reactions $CuA_2^+ + 2B = CuB_2^+ + 2A$. Temperature 393 K. Values in kcal/mol. Double arrows connect CuL_2^+ pairs for which exchange equilibria were determined.

Table 1. Free Energy Changes for Reactions: $CuA_2^+ + B = CuAB + A$, $CuAB^+ + B = CuB_2 + A$ and $CuA_2^+ + 2B = CuB_2^+ + 2A$

	$-\Delta G_{393}$ (kcal/mol)		
A/B	$CuA_2^+ \rightarrow CuAB^+$	$CuAB^+ \rightarrow CuB_2^+$	$CuA_2^+ \rightarrow CuB_2^+$
$Et_2CO/(n\text{-}Pr)_2CO$	1.55	0.43	1.98
$(n\text{-}Pr)_2CO/Me_2S$	2.36	−0.85	1.51
Me_2S/NH_3	1.70	0.65	2.35
Me_2S/MeCN	2.89	1.85	4.74
NH_3/MeCN	2.1	0.54	2.64
MeCN/MeCONHMe	3.29	0.79	4.08
MeCONHMe/$n\text{-}PrNH_2$	2.78	1.09	3.87
MeCONHMe/$MeCONMe_2$	2.95	1.77	4.72
MeCN/Me_2SO	3.85	1.21	5.06
$Me_2SO/MeCONMe_2$	2.38	1.07	3.45
$Me_2SO/n\text{-}PrNH_2$	2.33	0.38	2.71
$n\text{-}PrNH_2/MeCONMe_2$	1.65	−0.96	0.69
$n\text{-}PrNH_2/C_5H_5N$	2.24	1.07	3.31
$MeCONMe_2/C_5H_5N$	2.37	0.30	2.67
$C_5H_5N/(n\text{-}Bu)_3N$	1.91	0.29	2.20
C_5H_5N/EtC_5H_5N	3.04	1.85	4.89
$(n\text{-}Br)_3N/EtC_5H_5N$	2.23	0.50	2.73
$EtC_6H_5N/MeC_3H_3N_2$	4.0	4.9	8.9

The scale of ΔG_1° values obtained at 393 K shown in Figure 1 was converted to absolute values of ΔG_2°, ΔH_2° and ΔS_2° at 298° for the dissociation reaction eq 2

$$CuL_2^+ = Cu^+ + 2L \qquad (2)$$

by the following procedures.

Bauschlicher *et al.*[1c] using high level theoretical calculations have determined the dissociation energies, $D_o(Cu^+{-}NH_3) = 51.8$ kcal/mol and $D_o(CuNH_3^+{-}NH_3) = 51.6$ kcal/mol, leading

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[10] Kebarle, P.; Ho, Y. On the Mechanism of Electrospray Mass Spectrometry. In *Electrospray Ionization Mass Spectrometry*; Cole, R. B., Ed.; John Wiley & Sons, Inc.: 1997.

[11] The use of ligand pressures higher than 100 mTorr may lead to nonequilibrium growth of the ion−ligand complex in the gas expansion zone which occurs past the sampling orifice leading to the vacuum chamber and mass spectrometer. Due to the adiabatic gas expansion in this region, the gas temperatures are much lower, and at high ligand pressures association reactions can occur in this region.

Table 2. Third Law Entropies of Reactants CuL_2^+ and L[a]

L	S°_{298}(L) (cal/K mol)[b]	$S^\circ_{298}(CuL_2)$ (cal/K mol)
EtCl	65.6 (65.9)	124.6
H_2O	45.1 (45.1)	72.4
EtBr	68.1 (68.7)	126.9
MeOH	56.6 (57.3)	93.8
i-PrBr	74.2 (75.5)	139.4
EtOH	64.1 (67.5)	106.5
MeSH	60.7 (60.9)	106.1
MeCOOMe	75.6	125.4
MeCOMe	71.1 (70.5)	127.3
MeCOMe	84.7 (88.4)	154.6
MeOMe	79.5 (81.9)	136.4
NH_3	48.2 (46.0)	76.8
MeCN	59.3 (58.2)	106.4
MeSMe	69.6 (68.3)	123.9
MeCONH(Me)	75.8	134.9
MeSOMe	75.7	132.6
$MeCON(Me)_2$	83.0	148.0
n-$PrNH_2$	71.9 (77.5)	124.5
C_5H_5N[c]	67.4 (67.6)	117.8
Me-$C_3H_3N_2$[d]	73.4	121.3

[a] Evaluated on the basis of HF/3-21G* basis set calculations for L and CuL_2^+. [b] Data in parentheses are experimental determinations from *The Chemical Thermodynamics of Organic Compounds*; Stull, D. R., Westrum, E. F., Jr., Sinke, G. C., Eds.; John Wiley & Sons, Inc.: New York, 1969. [c] Pyridine. [d] 1-Me imidazole.

to a sum of energies of 103.4 kcal/mol. This value corresponds to the energy change ΔE_2° at 0 K. The value $D_o(Cu^+{-}NH_3) = 51.8$ kcal/mol is supported by a very recent large basis set calculation by Luna *et al.*[12] which leads to $D_o(Cu{-}NH_3) = 52.3$ kcal/mol. The $\Delta E_2^\circ = 103.4$ kcal/mol at 0 K due to Bauschlicher[1c] can be converted to ΔH_2° at 298 K by evaluating the change of ΔE_2 with temperature (0.8 kcal/mol)[13] and the volume expansion work, $2RT = 1.2$ kcal/mol, which leads to $\Delta H_2^\circ = 105.4$ kcal/mol. Bauschlicher *et al.*[1c] estimate the error in the two D_o values as 3 kcal/mol each, which leads by the chain rule to a combined error for ΔH_2° of $\approx \pm 4.2$ kcal/mol.

Experimental determinations of the bond energies of Cu^+ to NH_3 are not available; however, comparisons of experimental results for other related systems with calculated values by Bauschlicher et al. generally lead to agreement within ±5 kcal/mol. See, for example, comparisons of theoretical results by Bauschlicher[1] with experimental results[14−16] for $Cu(H_2O)$ and experimental results for $M^+(H_2O)_n{}^+$ and $M(NH_3)_n$ where M^+ are first row transition metals such as Mn^+, Fe^+, Co^+, and Ni^+.

The value $\Delta H_2^\circ(NH_3) = 105.4 \pm 5$ kcal/mol based on the Bauschlicher data is used to reference the relative scale given in Figure 1 and to obtain ΔH_2° and ΔG_2° data. To complete the referencing, ΔS_2° data also are required. These were obtained from theoretically evaluated third law entropies: S° of the reactants. $S^\circ(CuL_2^+)$ and S°(L) were obtained from the vibrational frequencies, leading to S°_{vib} and moments of inertia leading to S°_{rot}, which were combined with evaluated translational entropies. The vibrational frequencies and moments of inertia of each reactant were obtained in this work by ab initio calculations with HF/3-21G* basis sets of Gaussian 94. The resulting entropy values for S°(L) and $S^\circ(CuL_2^+)$ at 298 K are given in Table 2. ΔS_2° values obtained with these data and the (translational) entropy of Cu^+, $S^\circ(Cu^+) = 38.3$ cal/degree mol, are shown in Table 3. A calculation of the ΔS_2° value based on reactant entropies evaluated at 393 K was found to be within 1 cal/deg mol of the 298 K result. Therefore ΔS_2° was assumed constant in the 298−393 K range.

Table 3. Thermochemical Data for Reaction: $CuL_2^+ = Cu^+ + 2L$

L	(η)[a]	ΔG°_{393}	ΔG°_{298}	ΔS° [b] (cal/K mol)	ΔH° (kcal/mol)
Me-$C_3H_3N_2$[h]		110.3	116.4	63.8	135.4
Et-C_5H_5N[i]		101.4			
$(n\text{-Bu})_3N$		98.7			
C_5H_5N	(5)	96.5	101.8	55.3	118.2
$MeCON(Me)_2$	(5.5)[f]	93.8	99.2	56.4	116.0
$Pr{-}NH_2$		93.1	98.6	57.7	115.8
Me_2SO		90.4	95.8	57.1	112.8
MeCONH(Me)		89.4	94.6	55.0	111.0
MeCN	(7.5)	85.3	90.9	59.3	108.6
NH_3	(8.2)	82.7	88.2	57.8	(105.4)[c]
MeSMe	(6)	80.4	85.5	53.5	101.4
Pr_2CO		78.8			
Et_2CO		76.9	81.9	53.2	97.8
Me_2CO[d]	(5.6)	74.2	79.3	53.2	95.2
$MeCO_2Me$[d]		71.1	77.7	64.2	96.3
Et_2O[d]	(∼7)[g]	71.7	77.5	60.9	95.6
MeSH[d]		70.9	76.0	53.6	92.0
EtOH[d]		64.6	70.3	60.1	88.2
i-PrBr[d]		62.2	66.7	47.3	80.8
MeOH[d]		61.1	66.6	57.9	83.8
EtBr[d]		57.8	62.3	47.7	76.5
H_2O[e]	(9.5)	53.9	59.3	56.2	76.0[e]
EtCl[d]		54.4	58.7	44.8	72.1

[a] Value of absolute hardness η of ligand L, obtained with equation: $\eta \approx (I - A)/2$, where I = ionization energy of L, A = electron affinity of L. Data for η from Pearson.[19d] See also Pearson *et al.*[19c,e,f] [b] Obtained from S° values of reactants which were based on vibrational and rotational constants of reactants with HF/3-21G* basis sets of Gaussian 94. [c] Based on theoretical calculations by Bauschlicher *et al.*[1c] This value is used to obtain absolute values from ΔG_1° experimental results for all other ligands. [d] From relative scale of ΔG° values obtained by Jones and Staley[2] and referenced to absolute scale and evaluated ΔS° changes of present work. [e] Based on average of experimental determination of Magnera *et al.*[13] (74 kcal/mol) and theoretical calculations by Bauschlicher *et al.*[1a] (78.2 kcal/mol) ΔG° values obtained with calculated ΔS°, present work. [f] Estimated value based on $\eta = 5.8$ for dimethylformamide.[19d] [g] Estimated value based on $\eta = 8$ for Me_2O.[19d] [h] 1-Methylimidazole. [i] 4-Et pyridine.

With the available $\Delta H_2^\circ(NH_3)$ from Banschlicher[1] and the evaluated $\Delta S_2^\circ(NH_3)$, one obtains $\Delta G_2^\circ(NH_3)$ for eq 2 for L = NH_3, at 393 K. The relative ΔG° scale, Figure 1, was referenced to this value.

From the ΔG_2° data for the other ligands L obtained after the referencing and the available ΔS_2° values, ΔH_2° results for all ligands as well as ΔG_2° values at 298 K were calculated with the equation $\Delta G = \Delta H - T\Delta S$. These are summarized in Table 3.

It is well-known that ab initio calculations with small basis sets such as the HF/3-21G*, which was used in the present work, provide only poor estimates of the bond energies. On the other hand, the predicted frequencies are sufficiently accurate, Sceger *et al.*,[17a] to be used for evaluation of vibrational entropies. The S°(L) entropies for the ligands L evaluated[17b] with the HF/3-21G* data can be compared with entropies S°(L) obtained by experimental measurements (see Table 2). The agreement is generally within less than 2 cal/deg mol. The $S^\circ(CuL_2^+)$ values are probably less reliable, and we arbitrarily assume an error of 5.4 cal/deg mol to a combined error (evaluated with the chain rule) of which leads to a combined error of 5 cal/deg mol, for

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(12) Luna, L.; Amekraz, B.; Tortajada, J. *Chem. Phys. Lett.* **1997**, *266*, 31.

(13) The evaluation of ΔE_2° at 298 K from ΔE_2° at 0 K, was obtained from vibrational frequencies of the reactants evaluated with HF/3-21G*, Gaussian 96 method (see entropy evaluations, this work) and the rotational and translational heat capacity change.

(14) Magnera, T. F.; Stulik, D. D.; Orth, R. G.; Jonkman, H. T.; Michl, J. *J. Am. Chem. Soc.* **1989**, *111*, 5036.

(15) Holland, P. M.; Castleman, A. W. *J. Chem. Phys.* **1982**, *76*, 4195.

(16) Clemmer, D. E.; Armentrout, P. B. *J. Phys. Chem.* **1991**, *95*, 3084.

the ΔS_2° value or an estimated error in $T\Delta S$ of 1.5 kcal/mol at $T = 298$ K. Combining this error with the ±5 kcal/mol error for the primary standard $\Delta H_2^\circ(NH_3)$ one obtains with the chain rule an error of 5.2 kcal/mol, for the ΔH_2° values of CuL_2^+ complexes which are near the anchoring ligand NH_3. We estimate errors in the order of 6 kcal/mol for complexes located much above or below $L = NH_3$ in the scale (Figure 1) due to cumulative errors in the ΔG_1° measurements.

As discussed in the Experimental Section, section d, the primary reagent ions produced by electrospray $Cu(MeCN)_2^+$ are relatively strongly bonded, and exchange equilibria, eq 1, cannot be determined with much more weakly bonding ligands. Fortunately, the earlier work by Jones and Staley[2] focused on weakly bonding ligands. The weakest bonding ligand complex with $L = Et_2CO$ in the present determinations, see Figure 1 and Table 1, was part of the Jones and Staley relative scale, and, therefore, we were able to convert the Jones and Staley relative scale to an absolute scale. For some of the compounds determined by Jones and Staley we have evaluated the entropy changes ΔS_2°, by the method described above. The ΔG_2°, ΔS_2° and ΔH_2° results obtained for these complexes are included in Table 3. With this addition, the bonding range extends from the weakest bonding ligand, ethyl bromide, EtBr, $\Delta H_2^\circ = 76.5$ kcal/mol, to the strongest, 1-Me imidazole, with $\Delta H_2^\circ = 135.4$ kcal/mol.

Except for NH_3, there are no thermochemical data in the literature with which the results of Table 3 can be compared. There is only one indirect comparison. For $L = H_2O$, there are both experimental, $\Delta H = 74$ kcal/mol (Magnera *et al.*[13]), and theoretical, $\Delta H = 78.2$ kcal/mol (Bauschlicher *et al.*[1a]) values. Unfortunately $L = H_2O$ was not part of the experimental equilibria scale.[2] The value for H_2O given in Table 3 is not from equilibria but based on the above literature data.[1a,13] H_2O is expected to be more weakly bonding than MeOH, which is part of the scale. For AgL_2^+ complexes,[8] MeOH bonds more strongly by 8 kcal/mol. Assuming[18] the same difference also for the CuL_2^+ complexes and taking the average of the experimental[13] and theoretical[1a] value for $Cu(H_2O)$, a $\Delta H_2^\circ \approx 84$ kcal/mol is predicted for Cu(MeOH), which is very close to the value of 83.8 kcal/mol obtained in Table 3.

Discussion of Results

(a) Correlation of Bond Energies with Predictions of the Hard and Soft Acid and Base Theory (HSAB). Enthalpies ΔH_2° for the dissociation, $ML = M^+ + 2L$, are shown in Figure 2 where ΔH_2° values for AgL_2^+ are shown plotted versus the values for CuL_2. A second plot shows the $\Delta H_{1,0}$ values for the dissociation $LiL^+ = Li^+ + L$ versus the ΔH_2° for CuL_2^+. The AgL_2^+ values are taken from previous work from this laboratory,[8] while the LiL^+ data are from Taft *et al.*[3] Approximate straight lines can be drawn through the data for the oxygen bases in both plots. The experimental points for the other bases such as MeCN, NH_3, and particularly Me_2S show large deviations from linearity. Significantly, these bases show relatively *stronger* interactions for AgL_2^+ in the AgL_2^+ vs CuL_2^+ plot and relatively *weaker* interactions in the LiL^+ vs CuL_2^+ plot. These results are in qualitative agreement with the HSAB principle,[19] which states that hard acids bond more strongly to hard bases. The hardness of the metal ion acid decreases in the order $Li^+ \gg Cu^+ > Ag^+$. The oxygen bases can be considered as harder bases than the nitrogen bases (NH_3 and amines and pyridine), and some of the nitrogen bases (NH_3) are harder bases than the sulfur bases, $R-CH_2-SH$ and Me_2S. In the plot of LiL^+ versus CuL_2^+, the softer bases and particularly MeCN, NH_3, pyridine, and Me_2S deviate from the oxygen bases by showing relatively stronger bonding to the softer base Cu^+. Conversely, in the plot of AgL_2^+ vs CuL_2^+, the softer bases, particularly NH_3 and Me_2S, deviate from the line by exhibiting stronger bonding with the acid Ag^+ which is softer than Cu^+.

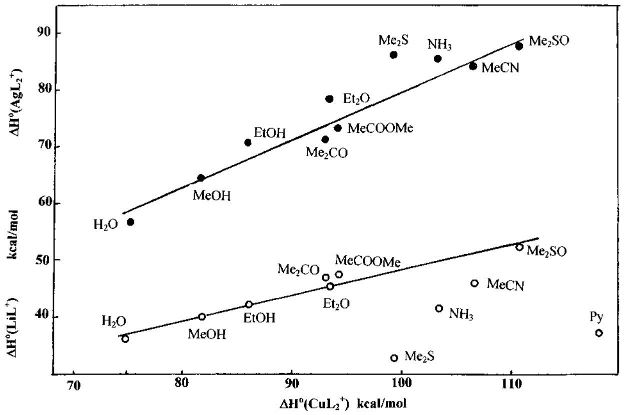

Figure 2. Upper plot: Plot of bond dissociation enthalpies for AgL_2^+ versus CuL_2^+. Straight line represents fit through oxygen bases. The softer bases Me_2S and NH_3 are found to lead to relatively stronger bonding with the softer acid Ag^+. Lower plot: Dissociation enthalpies for LiL^+ versus those for CuL_2^+. Straight line represents best fit through oxygen bases. The softer bases Me_2S, NH_3, MeCN, and Py lead to relatively stronger bonding with the softer acid Cu^+. The differences are more pronounced in this plot because Cu^+ is very much softer than Li^+, while in the upper plot Ag^+ is only somewhat softer than Cu^+.

Jones and Staley[2] have made very similar observations in a plot of binding energies for LiL^+ versus CuL, where the bases L were oxygen bases and the softer bases were HCN, MeSH, and EtSH (see Figures 4 and 5 in ref 2). The data of these authors did not include nitrogen bases and dialkylsulfides.

The "absolute hardness" η of the ligands can be evaluated with the expression[19c−f]

$$\eta \approx (I - A)/2 \tag{6}$$

where I is the ionization energy and A is the electron affinity of the ligand. I and A taken with a negative sign approximate the energy of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), which means that a very hard base corresponds to a compound where

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(17) (a) Sceger, D. M.; Kozziniewsky, C.; Kowalchyk, W. *J. Phys. Chem.* **1991**, *95*, 68. (b) The above authors[17a] find that low level calculations generally overestimate the frequency values and suggest that the values should be multiplied by a factor ~0.8. However the comparisons are based largely on the more abundant high frequencies. Very low frequencies make the major contributions to entropies $S°$ evaluated at 298 K or below. It is not clear whether the same factor holds also for the very low frequencies, therefore, we have used the HF/3-21G* evaluated frequencies without change.

(18) The bonds of AgL_2^+ are weaker than those for CuL_2^+. On that basis the difference observed for ΔH_2° between $Ag(MeOH)_2^+$ and $Ag(H_2O)_2^+$ should be smaller than that for the analogous Cu compounds. However MeOH is a softer base than HOH, and Ag^+ is a softer acid than Cu^+. On that basis the bonding difference between MeOH and H_2O should be larger than that for Cu^+. The two opposing trends thus indicate that the ΔH_2° differences for MeOH and H_2O may be quite similar for the Ag and Cu complexes.

(19) (a) Bassolo, F.; Pearson, R. G. *Mechanism of Inorganic Reactions*, 2nd ed.; Wiley: New York, 1967; p 33ff. (b) Huheey, J. E. *Inorganic Chemistry*, 3rd ed.; Harper & Row: New York, 1983; p 312ff. (c) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512. (d) Pearson, R. G. *Inorg. Chem.* **1988**, *27*, 734. (e) Pearson, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 7684. (f) Pearson, R. G. *J. Org. Chem.* **1989**, *54*, 1423. (f) Pearson, R. G. *Inorg. Chim. Acta* **1995**, *240*, 93.

Table 4. Calculated[a] Classical Electrostatic Bond Energy 2E, Due to Ion-Permanent Dipole Interactions in CuL_2^+

L	μ^b (Debye)	r^c (Å)	$-E$ (kcal/mol)	$2E^i$ (kcal/mol)
H_2O	1.8	2.38^d	22.0	44
NH_3	1.5	2.24^e	20.6	41.2
Me_2S	1.5	2.72^f	14.0	28.0
Me_2SO	3.9	3.07^g	28.6	57.2
MeCN	3.9	2.76^h	35.3	70.6

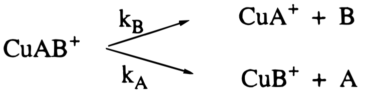
[a] Obtained with equation $E = e\mu/(4p\epsilon_o r^2)$. Values obtained are only rough estimates since distance r is estimated. [b] Dipole moment in Debye units: McClellan, A. L. *Table of Experimental Dipole Moments*; W. H. Freeman and Co.: 1963. [c] The distance r between the dipole and Ag^+ was evaluated from the bond lengths obtained from the HF/3-21G* calculations of CuL_2^+ and estimates of the position of the dipole on L. [d] $Cu^+-O = 1.78$ Å; dipole halfway on projection of O−H bonds on $Cu^+\cdots O$ axis. [e] $Cu^+-N = 2.0$ Å; dipole halfway on projection of N−H bonds on $Cu^+\cdots N$ axis. [f] $Cu^+-S = 2.25$ Å, dipole halfway on projection of S−C bonds on Cu^+-Saxis. [g] $Cu^+-O = 1.75$ Å, dipole at 0.8 of O═S bond length. [h] $Cu^+-N = 1.8$ Å, dipole at 0.8 of N≡C bond length. [i] Dipole−dipole repulsions not considered.

the difference between the LUMO and HOMO is big, while a small difference leads to a soft base. The values η for the ligands L, when available,[19d] are given in Table 3. On the basis of the HSAB concept one expects that the soft Lewis acid Cu^+ should lead to stronger bonds in CuL_2^+ as the ligands become softer, i.e., ΔH_2 in Table 3 should increase as the η of L decreases. Although such a trend is definitely present in the data, the correlation is not strong. Very obvious exceptions are NH_3, $\eta = 8.2$, and MeCN, $\eta = 7.5$, which have relatively high η values but bond relatively strongly. The correlation within a given series of bases such as the oxygen bases or the nitrogen bases appears to be better. Unfortunately the available data are very limited and do not allow good comparisons to be made.

Actually, close correlations between the bonding (ΔH_2) and η cannot be expected because η accounts largely for one component of the bonding, i.e., the covalent component associated with electron transfer. Pure electrostatic components to bonding, such as the attraction between the positive charge of Cu^+ and the permanent dipole of the ligand, is not accounted by HSAB, yet this interaction makes a very significant contribution to the bonding as illustrated in Table 4 for L = H_2O, NH_3, MeCN, Me_2S, and Me_2SO. The results obtained with the classical ion−dipole calculation are only estimates because the distance between the ion and the dipole cannot be established accurately. The data show that the dipole contribution is close to half of the total ΔH_2° for the ligands with large dipoles, *i.e.*, MeCN and Me_2SO. On the other hand, the ligands with the smaller dipoles, H_2O, NH_3, Me_2S, have ion−dipole interaction energies which are some 15−20 kcal/mol smaller. Considering the large ion−dipole contributions to the bonding, it is obvious that one cannot expect a good correlation between the hardness values η and the bond energies, ΔH_2°. Because of such "interference" of other bonding factors, the effect of the HSAB component is seen better through correlations such as the LiL^+ versus CuL_2° plot (Figure 2), which "filter out" the common electrostatic components. Pearson[19f] has discussed some other causes for the absence of a close correlation between HSAB predictions and the actual bond energies.

In solvents with high dielectric constants such as water, the effect of electrostatic forces on the bonding will be greatly reduced and a closer correlation of the bond energies with the HSAB predictions can be expected. In proteins a dual behavior should occur. Cu sites located largely inside the protein will be subject to electrostatic forces and show bonding closer to that observed in the gas phase while Cu sites near the surface which are exposed to the solvent will exhibit bonding which is intermediate between that observed in the gas phase and in solution.

(b) Bond Energies in CuL_2^+ and Relationships with Peptide Residues Bonding to Cu^+ in Peptides and Enzymes. Several of the ligands for which bond energy information, ΔG_2° and ΔH_2°, was obtained, Table 3, have the same or very similar functional groups as peptide residues which are very frequently involved in complexing Cu to form the active site of an enzyme. This is the case for MeSH ($-CH_2SH$) cysteine (cys), MeSMe ($-(CH_2)_2SCH_3$) methionine (met), *n*-Pr−NH_2 ($-(CH_2)_4-NH_2$) lysine (lys), and imidazole in histidine (his). Cerda and Wesdemiotis[5] have obtained relative bond energies in the gas phase between Cu^+ and each of the 20 common amino acids using the kinetic method.[20] The relative rates of decomposition of $CuAB^+$ complexes



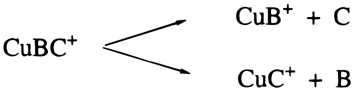
(7)

were determined where A = glycine was kept constant, while B was one of the other amino acids. From the relative rates, dissociation energies of the amino acids relative to that for glycine, which was taken as zero, were deduced.[5] Shown in Figure 3 are results by these authors for amino acids which have residues with functional groups equal or very similar to the ligands L used in the present experiments (Table 3). The amino acid energies are plotted versus $\Delta H_2^\circ/2$ because the amino acid dissociation corresponds to the cleavage of one Cu^+-L bond. The procedure is justified by the previous findings that the CuL^+-L and Cu^+-L bond energies are close to equal, see Bauschlicher[1] and references therein.

Examination of Figure 3 shows that a fairly good linear relationship is observed for six out of seven of the amino acids used. The slope of this line is 1.3, i.e., the amino acid energies[5] increase somewhat more slowly than the Cu^+-L energies obtained from Table 3. The factor of 1.3 rather than 1.0 may be associated with an underestimation of the effective temperature, T_{eff}, chosen in the kinetic method work[5] (see eq 7 in ref 5).

The only large deviation in the plot given in Figure 3 involves histidine, where the Cu^+-L value based on L = 1-Me imidazole is some 8 kcal/mol higher than the correlation with the other amino acids would indicate. The best choice for a representative of the residue on histidine would have been 4-Me imidazole; however, this compound was not available from commercial suppliers. The bonding of the 1-Me imidazole to Cu^+ may be expected to be somewhat stronger than that with 4-Me imidazole but only by a few kcal/mol. It is almost certain that the large discrepancy in Figure 3 cannot be explained on the basis of having used the 1-methyl rather than the 4-methyl isomer.

With the $CuAB^+$ kinetic method studies, where A = glycine and B = lysine or B = histidine, see eq 7, it could only be established[5] that the bond energies are approximately equal, as shown in Figure 3. On the basis of additional measurements of the decomposition



(8)

where B = lysine and C = histidine, Wesdemiotis and

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(20) McLuckey, S. A.; Cameron, D.; Cooks, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 1313.

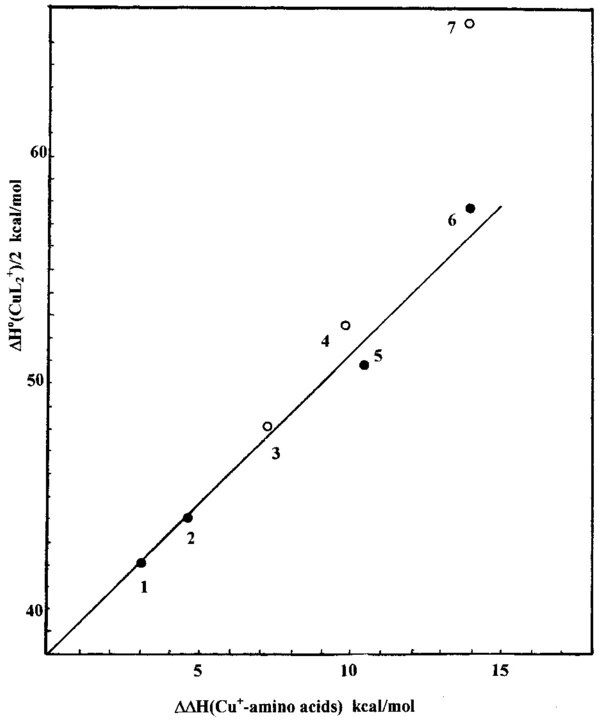
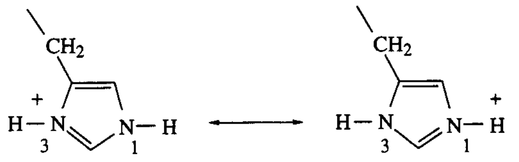


Figure 3. Plot of bond dissociation enthalpies for reaction $CuL_2^+ = Cu^+ + 2L$, divided by two versus relative amino acid affinities to Cu^+ obtained by Cerda and Wesdemiotis[5] with the kinetic method. The relative amino acid affinities are expressed[5] relative to glycine being equal to zero. A given ligand L whose $\Delta H°$ (CuL_2^+) was determined (Table 3) is paired with a given amino acid which has a residue identical or similar to L. The points shown correspond to the following (L/amino acid residue): ($HOCH_3/HOCH_2$-ser) 1; (HOC_2H_5/CH_3CHOH-thr) 2; ($CH_3OCOCH_3/HOCO(CH_2)_2$-glu) 3; ($CH_3SCH_3/CH_3S(CH_2)_2$-met) 4; ($CH_3NHCOCH_3/H_2NCO(CH_2)_2$-glu) 5; ($H_2N(CH_2)_2CH_3/H_2N(CH_2)_4$-lys) 6; (1-$CH_3$ imidazole/5-CH_2 imidazole/his) 7. Points for which the match between L and residue is very close are shown as full black circles. Note that a fair linear correlation is observed for all pairs except pair 7, i.e., imidazole/his.

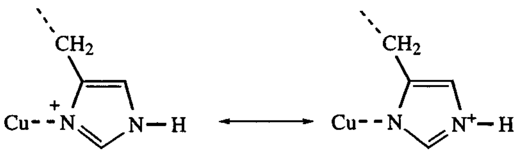
Scheme 1



co-workers[5] found that lysine bonds somewhat more strongly than histidine. The essential agreement[5] between the experiments, eqs 7 and 8, shows that the kinetic method consistently predicts a much weaker bonding for histidine than expected from the present results (Table 3, Figure 3).

One can argue that the stronger bonding of Cu^+ to the imidazole group in histidine indicated by the present work is more likely. The proton affinities (values in kcal/mol from Lias and Hunter[21]) of some model compounds are imidazole 225, Me_2NH 222, *n*-$PrNH_2$ 220, pyridine 222, and pyrrole 209. The high value for imidazole relative to the other compounds should be due to the stabilization by the two resonance structures of imidazole protonated on the N atom in position 3 as shown in Scheme 1. The CH_2 group in position 4 of the structures shown indicates the complete histidine residue. A somewhat similar stabilization can be expected also for the Cu^+ complex. The principle cause for the stabilization in both cases should be due to the achieved charge delocalization.

Scheme 2



The value for histidine obtained by the kinetic method[5] may be too low because the determination depends on the decomposition of the *two* amino acid complexes: $CuGlyHis^+$, eq 7, or $CuLysHis^+$, eq 8. Each of the amino acids forms bidentate bonds to Cu^+. Thus, the bidentate bond with Gly will involve the terminal amino group and the more weakly bonded carbonyl oxygen of the carboxy group. For the approximate relative strength of these bonds a value between L = NH_3 or $PrNH_2$ can be chosen for the amino group and the value L = $MeCO_2$-Me for the carbonyl group (see Table 3). For histidine the two strongest interacting groups will be the terminal amino group and the imidazole group. In the tetracoordinated complex $CuGlyHis^+$ there can be steric constraints, and a bulky group like imidazole may not achieve its full bonding potential. If that is the case, the kinetic method will lead to a lower bonding value for histidine.

We will assume that the present high value provides a more accurate measure of the bonding of the histidine residue to Cu^+. The histidine residue is thus expected to be the strongest bonding of all amino acid residues except the arginine residue for which we have no data so far. Furthermore, the arginine and lysine residues are not expected to compete with histidine in bonding to Cu^+ because under biological pH both of these groups are protonated while histidine is not.[5] The low aqueous solution basicity of the histidine residue may seem surprising, since the gas-phase basicity and proton affinity as represented by imidazole (see above) are very high. The low solution basicity is undoubtedly a consequence of the relatively lower hydration exothermicity due to charge delocalization in the protonated imidazole (see Scheme 1). Many examples of the decrease of solvation exothermicity with charge delocalization are available in the literature.[22] Histidine is thus the strongest binding residue to Cu^+ available under physiological conditions, and the prevalent use by biological systems of this residue as Cu ligand in many Cu enzymes[4] may be at least in part a consequence of the strong bond that can be obtained.

Methionine $-CH_2CH_2SCH_3$ and cysteine $-CH_2SH$ are two other ligands frequently occurring in copper enzymes. In the present work these two ligands were found to be less strongly bonding to Cu^+ than histidine; however, these ligands still showed specific strong bonding due to being soft bases. Thus these bases as residues would be especially selective of soft Lewis acids such as Cu^+.

Acknowledgment. This work was supported by the Canadian Natural Science and Engineering Research Council (NSERC).

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[21] Hunter, E. P.; Lias, S. G. Evaluated Gas-Phase Basicities and Proton Affinities of Molecules: An Update. *J. Phys. Chem. Ref. Data* (to be published) **1997**.

[22] (a) Taagepera, M.; DeFrees, D.; Hehre, W. J.; Taft, R. W. *J. Am. Chem. Soc.* **1980**, *102*, 424. (b) Chowdhurry, S.; Grimsrud, E. P.; Kebarle, P. *J. Phys. Chem.* **1987**, *91*, 2551.