species over all molecular orientations. The integration was carried out by using a five-point Gaussian quadrature. The resonances were assumed to have a Lorentzian shape. The widths were assumed to be anisotropic and were calculated according to

$$W(\theta) = (W_{\parallel}^2 \cos^2\theta + W_{\perp}^2 \sin^2\theta)^{1/2}$$

The angle θ is taken as the angle between the magnetic field and the principal symmetry axis of the triplet species. The simulated spectrum in Figure 1 was calculated with $W_{\parallel}$ and $W_{\perp}$ values of 220 and 120 G, respectively. It seems likely in this case that the primary contribution to the line widths is from unresolved hyperfine interactions. Thus, the use of an anisotropic width seems quite justified since the hyperfine interactions in most copper(II) complexes are quite anisotropic. The fields and intensities of the transitions between the spin states of the $S = 1$ manifold were calculated as a function of the angle θ using the spin-Hamiltonian parameters in Table II. The direct eigenfield method described by Belford and co-workers was used in this computation.[24-26]

Registry No. $Cu^{II}(AB)\cdot H_2O$, 61104-51-6; $Cu^{II}(AB)(DMEN)$, 61075-81-8; $Cu^{II}(AB)(DMPN)$, 61075-83-0; $Cu^{II}(AB)(TMEDA)$, 61104-48-1; $Cu^{II}(AB)(EM)$, 61075-85-2; 2,2′-dicarboxyazobenzene, 635-54-1; 2-nitrobenzoic acid, 552-16-9.

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Some Properties of Copper and Zinc Complexes of 2-Formylpyridine Thiosemicarbazone

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Substituted 2-formylpyridine thiosemicarbazones and some of their metal complexes are experimental antineoplastic agents. Formation constants for copper and zinc complexes of 2-formylpyridine thiosemicarbazone have been measured in aqueous solution together with other acid–base properties of these complexes and the half-wave reduction potential of the copper(II) complex. Logarithms of the formation constants of the 1:1 copper and zinc complexes are 16.90 and 9.18, respectively. The copper complex forms adducts with Lewis bases such as ethylenediamine (log K^{CuL}_{CuLen} = 5.53) as observed by electron paramagnetic resonance spectroscopy and in the determination of the formation constant for the copper chelate. Its $E_{1/2}$ is +2 mV. These results are compared with data for other related systems. Implications are then drawn about the possible reactions of these materials in biological systems.

Introduction

Recently the examination of the antitumor properties of α(N)-heterocyclic carboxaldehyde thiosemicarbazones has been extended to the consideration of some of their first-row transition metal complexes. Included have been the Fe(II), Cu(II), and Zn complexes of 1-formylisoquinoline thiosemicarbazone and the Fe(II) and Cu(II) complexes of 5-substituted-2-formylpyridine thiosemicarbazones.[1-5] Previously other bis(thiosemicarbazonato)copper and -zinc chelates had been shown to have substantial inhibitory effects against tumor cells.[6-8] Hence an investigation has begun of the chemical properties of metal complexes of 2-formylpyridine thiosemicarbazone to provide a basis for understanding their behavior in living systems. In this work the thermodynamics of ligand binding to Cu^{2+} and Zn^{2+} are described together with properties of the reduction of (2-formylpyridine thiosemicarbazonato)copper(II) to its copper(I) species.

Experimental Section

Materials and Solutions. 2-Formylpyridine thiosemicarbazone (HL) was generously supplied by Frederick A. French. Its copper complex (CuL^+) has been synthesized previously as the acetate salt.[5] Ethylenediamine (en), bp 118 °C, $n^{20}D$ 1.4565, was purchased from Aldrich Chemical Co. and used without further purification. Dimethyl sulfoxide, Gold Label quality, was also obtained from Aldrich. Other chemicals were reagent grade materials. To obtain suitable solutions of CuL^+ it was first necessary to dissolve the solid complex in Me_2SO and then, adding this liquid to an aqueous solution, to obtain final concentrations of 0.10 M KCl and 1.0% v/v Me_2SO.

Formation Constants for CuL^+ and CuLen. The pH-independent formation constant, K^{Cu}_{CuL}, of CuL was determined by the method of competing equilibria, using ethylenediamine, a ligand of known

thermodynamic stability with Cu^{2+}, to dissociate CuL^+.[9] By adding an excess of en to a solution of CuL^+, the following equilibrium is established at a fixed pH

$$CuL^+ + 2en \overset{K}{\rightleftharpoons} Cu(en)_2^{2+} + L^- \quad (1)$$

in which the symbols used here represent the sums of all forms of these molecules present at the given pH. For the pH range used total concentrations of these species are respectively

$$C_1 = [CuL^+] + [CuLOH] + [CuLen]^+ \quad (2)$$

$$= [CuL^+]\{1 + K_a(CuL^+)/[H^+] + K^{CuL}_{CuLen}[en]\} \quad (3)$$

$$C_2 = [en] + [Hen^+] + [H_2en^{2+}] \quad (4)$$

$$= [en]\{1 + K^{en}_{12}[H^+] + K^{en}_1 K^{en}_{12}[H^+]^2\} \quad (5)$$

$$C_3 = [Cu(en)_2^{2+}] \quad (6)$$

under conditions of these determinations

$$C_4 = [L^-] + [HL] \quad (7)$$

$$= [L^-]\{1 + K^{HL}_1[H^+]\} \quad (8)$$

The constants for eq 3, 5, and 8 are defined as

$$K_a(CuL^+) = [H^+][CuLOH]/[CuL^+] \quad (9)$$

$$K^{CuL}_{CuLen^+} = [CuLen^+]/[CuL^+][en] \quad (10)$$

$$K^{en}_1 = [Hen^+]/[H^+][en] \quad (11)$$

$$K^{en}_{12} = [H_2en^{2+}]/[H^+][Hen^+] \quad (12)$$

$$K^{HL}_1 = [HL]/[H^+][L^-] \quad (13)$$

Then

$$K = \frac{C_3C_4}{C_1C_2^2} = \frac{\beta_2}{K^{Cu}_{CuL}}\{1 + K^{HL}_1[H^+]\}/\{1 + K_a(CuL^+)/[H^+] + K^{CuL}_{CuLen}C_2/(1 + K^{en}_{12}[H^+] + K^{en}_1K^{en}_{12}[H^+]^2)\}\{1 + K^{en}_{12}[H^+] + K^{en}_1K^{en}_{12}[H^+]^2\}^2 \quad (14)$$

in which

$$\beta_2 = [Cu(en)_2^{2+}]/[Cu^{2+}][en]^2 \quad (15)$$

and

$$K^{Cu}_{CuL} = [CuL^+]/[Cu^{2+}][L^-] \quad (16)$$

As described below

$$C_1 = A_{400nm}/\epsilon_{CuL,400nm} \quad (17)$$

$$C_2 = C_{2,initial} - 2C_3 \quad (18)$$

$$C_3 = C_{1,initial} - C_1 \quad (19)$$

$$C_4 = C_3 \quad (20)$$

in which all C's are equilibrium values unless otherwise indicated.

At 400 nm the molar absorptivities of CuL^+, CuLOH, and $CuLen^+$ are identical. For any of the determinations of K^{Cu}_{CuL} there is no contribution to the absorbance, A_{400nm}, from ligand species or $Cu(en)_2^{2+}$ at the concentrations used. The stock concentration of en was determined by titration with HCl. Hence the measurement of absorbance at 400 nm of solutions of CuL^+ [$\epsilon(CuL^+)$ 7400 M^{-1} cm^{-1}] containing various amounts of en together with the values for the equilibrium constants defined in eq 9 and 11–13 and β_2 define a set of equations in two unknowns, K^{Cu}_{CuL} and K^{CuL}_{CuLen}. The expressions are solved pairwise to obtain these constants.

All of the measurements were carried out in solutions of final concentration 0.10 M KCl with 1.0% Me_2SO v/v at 25 °C, using HCl or KOH to adjust pH. Equilibria were attained rapidly and spectral measurements were taken after the change in absorbance was complete. A Radiometer PHM 26 pH meter standardized with two buffer standards was used. Spectra were recorded on an Acta V spectrophotometer. The presence of 1% Me_2SO in solution was shown not to change pH readings in 0.1 M KCl and not to affect the protonation constant for tris(hydroxymethyl)aminomethane.

Formation Constant for ZnL^+. The titration of HL by Zn^{2+} can be observed spectrophotometrically. The measurement of the end point absorbance leads to a value of $\epsilon(ZnL^+)$ 17 200 at 363 nm. Because the binding is weak in the pH range below 7, the data in the region of the stoichiometric end point of the titration may be treated directly to obtain K^{Zn}_{ZnL}. Measurements were made in 0.10 M KCl at 25 °C with pH adjustment after each addition of Zn^{2+} to ligand.

For the equilibrium of all forms at a given pH

$$Zn^{2+} + HL \overset{K'}{\rightleftharpoons} ZnL^+ + H^+ \quad (21)$$

the function K' can be calculated, given the initial concentration of the ligand, the amount of zinc ion added, and the concentration of ZnL, measured by the absorbance at 363 nm.

By analogy to the copper complex the pH-independent formation constant, K^{Zn}_{ZnL}, is then

$$K^{Zn}_{ZnL} = K' \frac{1 + [H^+]/K_1^{HL}}{1 + [H^+]/K_a(ZnL^+)} \quad (22)$$

in which

$$K_a(ZnL^+) = [ZnLOH][H^+]/[ZnL^+] \quad (23)$$

Over the range of $[H^+]$ used the amount of $ZnOH^+$ is negligible.[10]

Protonation Constants of CuL^+ Species. CuL^+ was titrated with HCl and KOH and its reactions were observed spectrophotometrically. Plots of absorbance vs. pH were made. To obtain equilibrium constants the data are then fit to the equation $\log\{[HA]/[A]\} = pK - pH$, in which in general $K = [HA]/[H][A^-]$, the protonation constant for a weak acid.

Electron Paramagnetic Resonance Spectra. Spectra were taken on a Varian E-9 spectrometer, using solutions frozen in liquid nitrogen at 77 K.

Half-Wave Potential of CuL^+. The half-wave potential of CuL^+ was determined polarographically using a Princeton Applied Research polarograph and a rotating Pt electrode vs. a saturated calomel electrode. Solutions contained 0.10 M KCl as carrier electrolyte and were adjusted to pH 7.0 and 25 ± 1 °C for measurement.

Results

CuL^+ Species in Solution. The spectrophotometric titration of ligand with Cu^{2+} in aqueous solution produces binding curves which show no evidence of dissociation CuL^+ for pH values as low as 1.4. That the metal–ligand structure is intact is also supported by the comparison of the EPR spectra of the complex at pH 8.2 and 1.85 (Figure 1). Although there are some changes in the spectrum presumably attributable to protonation of the complex, there is no evidence of formation of free Cu^{2+}. We have no explanation for the apparent shoulder on the lowest field hyperfine line. Although it is possible to formulate the complex as a dimer in solution by linkage through the vacant in-plane coordination site, the positive charge on the complex would mitigate against this association. Furthermore, there is no evidence of spin exchange in the EPR spectra of the complex. Finally, the magnetic moment of the solid of a very similar complex (8-formylquinoline thiosemicarbazonato)copper(II) is 1.75, normal for a spin $^1/_2$ system.[10]

When the complex is titrated with acid and base, log (dissociation constants) of −2.40 and −8.30 are detected according to changes seen in the spectrum of CuL^+. Spectra associated with the three species of CuL^+ are shown in Figure 2. The larger constant is presumed to characterize the protonation of CuL^+ at the N^4 nitrogen of the thiosemicarbazone moiety, since the pyridine ring nitrogen is bound to copper. The smaller constant is attributed to the protonation of CuLOH (eq 9).

Formation Constants for CuL^+ and $CuLen^+$. Because of the presence of undissociated $CuLH^{2+}$ at very low pH, indicating an inability of H^+ to compete well with Cu^{2+} for the ligand, the formation constant was examined by the method of competitive equilibria, using ethylenediamine as the competing

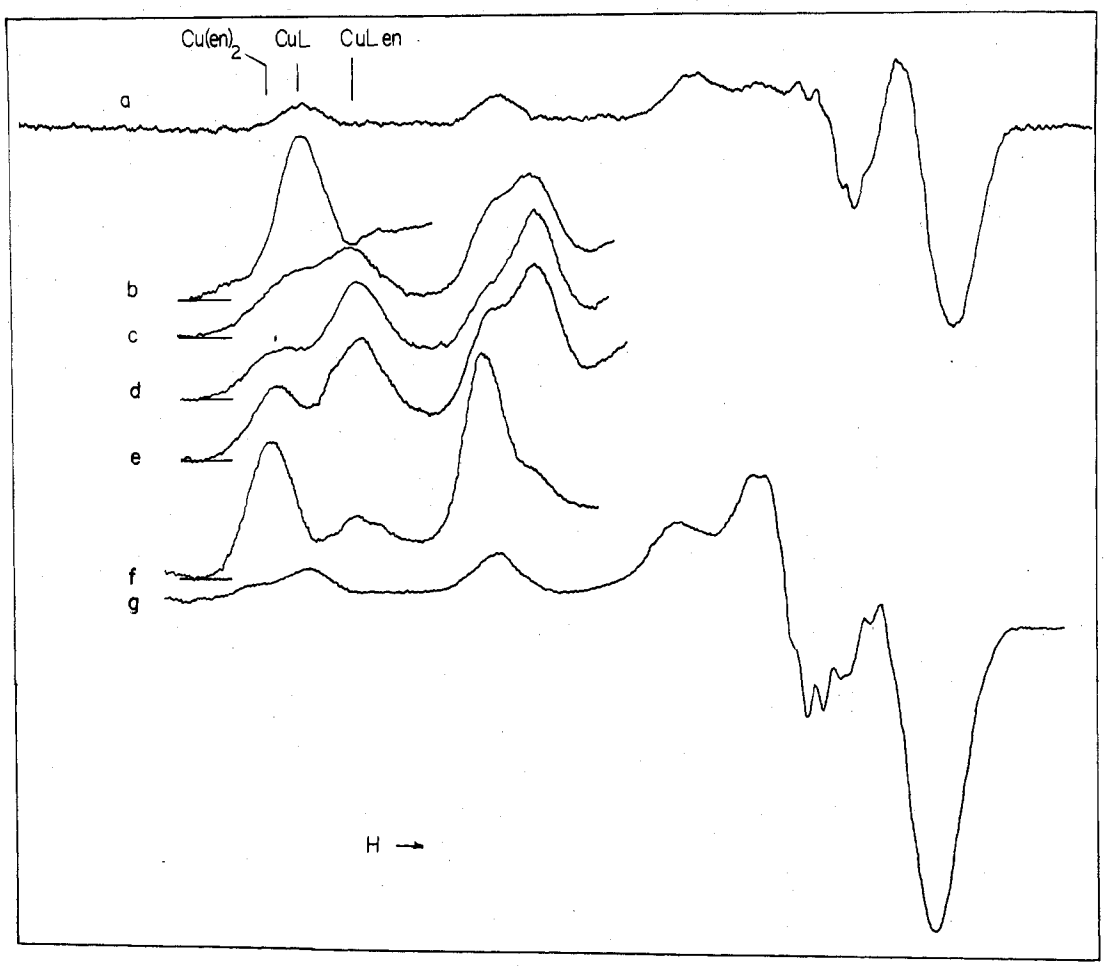

Figure 1. EPR spectra of CuL^+ at 77 K: titration of 6.13×10^{-4} M CuL^+ at (a–f) pH 8.2 ± 0.1 and (g) pH 1.85 in 0.10 M KCl and 30% Me_2SO. Microwave power 2 mW; microwave frequency 9.147 GHz; modulation amplitude 5 G; b–f, ×10 gain: (b) CuL^+; (c) CuL^+ + 1 en; (d) CuL^+ + 2 en; (e) CuL^+ + 10 en; (f) CuL^+ + 100 en.

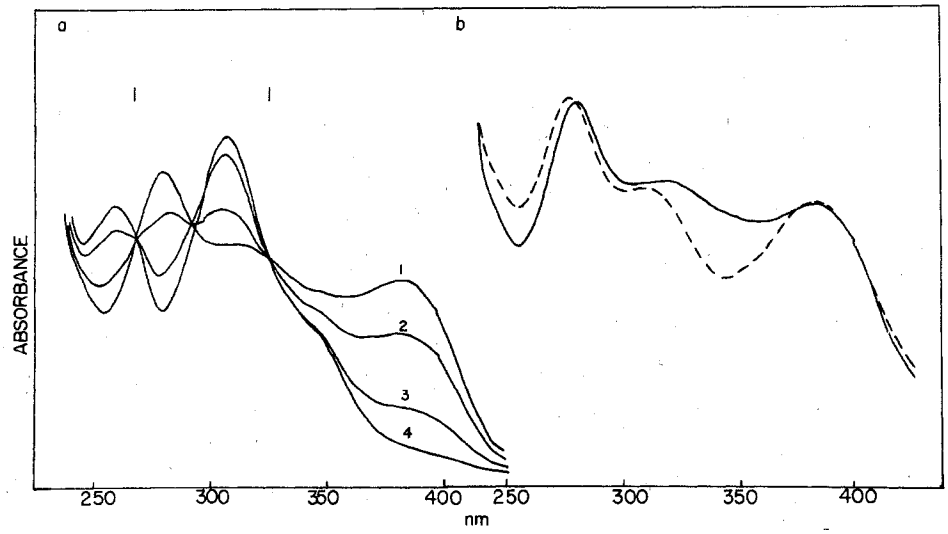

Figure 2. Spectral forms of CuL^+ as a function of pH: (a) titration of CuL^+ with HCl, isosbestic points at 324 and 268 nm; (1) pH 3.67, (4) pH 1.31; (b) CuL^+ at pH 6.13 (—) and CuLOH at pH 9.90 (– –).

ligand.[9] Although there is virtually no change in the electronic spectrum of the complex upon addition of up to fivefold en under the conditions described in Figure 3, the EPR spectra at 77 K of solutions of CuL^+ with increasing amounts of en are consistent with formation of CuLen. In fact, by following the changes in peak height of hyperfine lines in the $g_\parallel$ region of the spectrum as a function of en concentration, the formation of CuLen followed by its decay and the production of $Cu(en)_2^{2+}$ can be observed (Figure 1a–f). Table I provides the parameters for these EPR spectra. $A_\parallel$ was estimated from

Table I. EPR Parameters of Copper Complexes

	$g_\parallel$	$A_\parallel$, G
CuL^+	2.204	186
$CuLen^+$	2.188	169
$Cu(en)_2^{2+}$	2.213	190

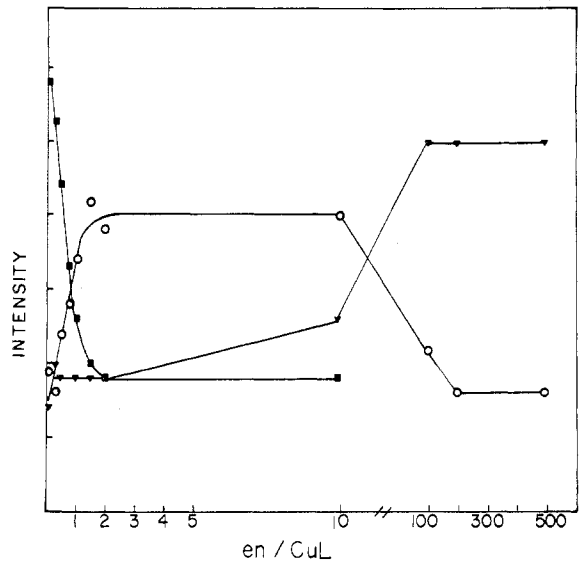

Figure 3. EPR titration of CuL^+ with en; intensity measured in $g_\parallel$ hyperfine region as shown in Figure 1: ■, CuL^+; ○, CuLen; ▼, $Cu(en)_2^{2+}$.

Table II. Formation Constant of CuL^+

pH	log K^a		log K_{CuL}	log K_{CuLen}	
11.28	−0.550				
			16.99	5.44	
10.88	−0.304				
			17.00	5.43	
10.41	−0.028				
			16.62	5.83	
10.00	0.161				
			17.09	5.35	
9.52	0.303				
			17.16	5.27	
8.51	0.346				
		Av[b]	16.90 ± 0.04	5.54 ± 0.05	(15)[c]
			16.84 ± 0.04	5.57 ± 0.05	(12)
			16.92 ± 0.05	5.50 ± 0.06	(13)
			16.98 ± 0.04	5.46 ± 0.05	(13)
			16.87 ± 0.09	5.57 ± 0.10	(9)
		Av	16.90	5.53	

[a] $C_3(CuL^+) = 58.3\ \mu M$; $C_2(en) = 6.088$ mM; $T = 25$ °C, 0.10 M KCl, 1.0% v/v Me_2SO; $\beta_2(Cu(en)_2) = 19.72$;[11] $K_1^{en} = 7.49$; $K_{12}^{en} = 10.05$;[11] $K_1^{HL} = 10.97$.[20] Concentration changes corrected for volume additions of HCl. [b] Average values and standard error for five separate experiments. [c] Number of pairs of simultaneous equations included in average value.

the spread of the two low-field lines (Figure 1 and Table I) while $g_\parallel$ was estimated as the center of the second and third parallel components. The remainder of the spectrum is complicated presumably due to the rhombic in-plane character of the complex which contains two nonequivalent nitrogen ligands.

That similar events are occurring at 25 °C is inferred from the results of the reaction of CuL^+ with en. In this determination of K_{CuL}^{Cu} (eq 16) from the data on the equilibria between CuL^+, $Cu(en)_2^{2+}$ and their ligands (eq 1), a constant is obtained when a term for $CuLen^+$ is included in the calculation. Hence the system may be considered as

$$CuL^+ + en \overset{K_{CuLen}^{Cu}}{\rightleftharpoons} CuL(en)^+$$

$$CuL(en)^+ + en \rightleftharpoons Cu(en)_2^{2+} + L^- \qquad (24)$$

At the large concentrations of en necessary to dissociate the copper complex, CuL^+ is partially in the adduct form. Over the pH range used EPR spectroscopy shows the presence of only one adduct species. The consistency of the calculated

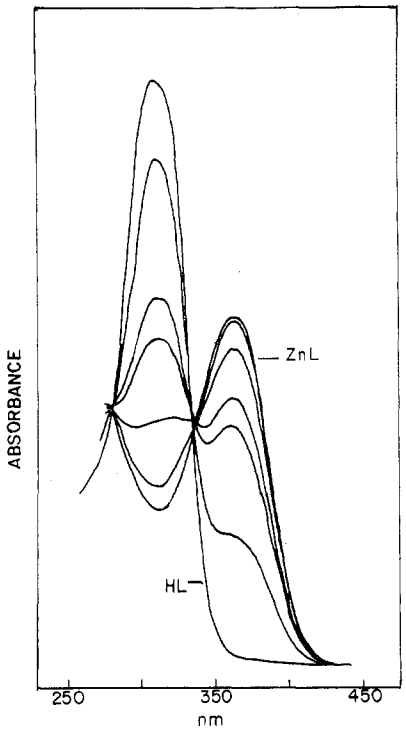

Figure 4. Titration of HL with Zn^{2+}; $[HL_{initial}] = 8.9 \times 10^{-5}$ M, pH 6.30 ± 0.03, $T = 25$ °C. Only several points along the titration are shown.

Table III. Formation Constant of ZnL^+

pH	log K'	log K_{ZnL}^a	pH	log K'	log K_{ZnL}^a
5.72	4.06	9.15	6.63	5.40	9.20
5.92	4.37	9.21	6.93	5.87	9.16
6.31	4.84	9.16			Av 9.18 ± 0.01

[a] $K_a(ZnL) = -7.35$.

constants as discussed below supports the presence of a single adduct species $CuLen^+$.

Some of the results obtained are given in Table II. Where these results are used in every pair combination,[15] the average value and standard error for log K_{CuL}^{Cu} and log K_{CuLen}^{CuL} are 16.90 ± 0.04 and 5.54 ± 0.05, respectively. The experiment was repeated four times, giving average values for these constants of 16.90 and 5.53. Other determinations in which $C_{2,en}$ is varied from 0.45 to 9.21 mM give similar results. Of importance for comparisons of stability in aqueous solution are the corresponding conditional values. For a fixed pH of 7.4 considering all forms of the molecules in solution

$$K'_{CuL} = [CuL^+]/[Cu^{2+}][HL] = 1.7 \times 10^{13} \qquad (25)$$

and

$$K'_{CuLen} = [CuLen]/[CuL^+][en] = 3.7 \times 10^2 \qquad (26)$$

Reduction of CuL^+. The half-wave potential for the reduction of $Cu^{II}L^+$ to $Cu^{I}L$ has been measured in aqueous solution. A value of 2 ± 10 mV vs. the hydrogen electrode is obtained in 0.1 M KCl at pH 7 and 25 °C. The reduction follows Nernst-like behavior as shown by a plot of E vs. log {[Ox]/[Red]} in which the slope is 57 mV in comparison with the theoretical value of 59 mV for a one-electron process.

Formation Constant of ZnL^+. The titration of HL with $ZnCl_2$ has been carried out at pH 6.3 using spectrophotometry to follow the association of metal and ligand (Figure 4). As complexation occurs, the ligand absorbance band at 310 nm is replaced by new bands at 363 and 327 nm. An isosbestic point at 337 nm is also observed. A 1:1 complex forms. The

Table IV. Comparative Formation Constants of Copper and Zinc Complexes

Metal		log (formn const)	Ref	log (app formn const)[a]	log K_1, log K_2 (of ligand)
Cu^{2+}	Histidine	18.53 (CuL_2)	18	15.2	9.08, 5.98
	Histidine, cystine	19.0[b] ($CuLL'^-$)	13	14.4	9.08, 5.98; 9.2, 8.45[b]
	2-Formylpyridine thiosemicarbazone	16.90 (CuL^+)		13.3	
	3-Ethoxy-2-oxobutyraldehyde bis(thiosemicarbazone)	(CuL)	14	18.4	
Zn^{2+}	Cysteine	17.54 (ZnL_2^{2+})	15	10.6	10.11, 8.13
	Histidine, cysteine	15.73 ($ZnLL'^-$)	13	10.5	
	Histidine	11.42 (ZnL_2^+)	16	7.6	
	2-Formylpyridine thiosemicarbazone	9.18		5.6	

[a] $K' = [\text{metal complex}]_{\text{all forms}}/[M^{2+}][\text{ligand}]_{\text{all forms}}$ as in eq 1, calculated at pH 7.4. [b] From ref 13 together with the equations log $K(25\ ^\circ C) = \log K(37\ ^\circ C) + 0.5$ and for cystine $pK_a(25\ ^\circ C) = pK_a(37\ ^\circ C) + 0.5$, for which 0.5 is an approximate conversion factor based upon data in ref 11 for several amino acid complexes.

average values for K' are given in Table III. Also shown here are values over a range of pH. It is found that a term for [ZnLOH] is necessary to obtain K^{Zn}_{ZnL} as calculated from eq 23. Solving pairs of eq 22 substituted with K' at various $[H^+]$ gives $K_a(ZnL^+) = 2.25 \times 10^{-8}$. Then this value is substituted into eq 22 to obtain $K^{Zn}_{ZnL} = 1.5 \times 10^9$. In these titrations at different pH's no difference in ϵ or spectral detail is observed. Hence the spectrum of ZnLOH is identical with that of ZnL^+.

Comparative formation constants of Cu and Zn complexes are given in Table IV.

Discussion

Studies of the thermodynamic behavior of CuL^+ have been carried out in order to form a basis for the understanding of the interactions of this and related complexes with biological systems. Such systems contain a multitude of metal complexes (ML_{org}) and metal-binding ligands (L_{org}). Hence, in general when external ligands or metal complexes (L_{ex}, ML_{ex}) enter an organism, a variety of substitution reactions may occur as summarized in eq 27 and 28 which do not involve the enzymatic conversion of these molecules to new products.

$$L_{ex} + ML_{org} \rightleftharpoons ML_{ex} + L_{org} \quad (27)$$

$$ML_{ex} + L'_{org} \rightleftharpoons L_{ex} + ML'_{org} \quad (28)$$

It is clear that CuL^+ may well be stable in the presence of a variety of typical cellular ligands such as amino acids which can strongly chelate Cu^{2+}. That is, Perrin and Agrawal have described a model for the metal–ligand interactions in blood plasma.[17] By their calculations greater than 80% of the copper in plasma is bound at pH 7.4 and 37 °C to histidine and as histidine–cystine mixed complexes. Others have argued the importance of the mixed copper complex of histidine and threonine.[18] At the plasma concentrations of histidine and histidine–cystine complexes of copper at pH 7.4 very little CuL^+ is expected to be dissociated in plasma[13] In fact when the actual experiment is done to measure the stability of CuL^+ in human plasma, no dissociation is observed.[19]

This picture must be expanded because CuL^+ can also form strong adducts. An earlier report by Ablov et al. had also shown that the bipyridyl adduct of a related complex (8-formylquinoline thiosemicarbazonato)copper(II) can be made and isolated in the solid state.[10] It may be expected, therefore, that adducts do form in biological systems. Evidence is available for adduct formation in human plasma and Ehrlich ascites tumor cells.[19,20]

Recently Patterson and Holm have compiled an extensive list of half-wave potentials of copper chelates.[21] A number of these determined in aqueous solution are collected in Table V. It is evident that CuL^+ has an unusually high reduction potential. In the qualitative analysis of the factors influencing $E_{1/2}$ in copper complexes James and Williams have pointed to the electron donor–acceptor characteristics of the ligand and the ligand constraint on the geometry of the Cu(I)

Table V. Half-Wave Potentials for Copper Complexes in Aqueous Solution

Ligand	Ligand:metal	$E_{1/2}$, mV
o-Phenanthroline	2:1	+174[a]
Bipyridyl	2:1	+120[a]
2-Formylpyridine thiosemicarbazone	1:1	+2
Terpyridine	1:1	−80[a]
3-Ethoxy-2-oxobutyraldehyde bis(thiosemicarbazone)	1:1	−120[b]
Glycine	2:1	−160[a]
Ethylenediamine	2:1	−360[a]

[a] Reference 22. [b] Reference 26.

species.[22] For instance, the σ-bonding ligands glycine and en have more negative potentials than *o*-phen and bipyridyl, which can also π bond and accept electron density from filled orbitals on the metal thereby facilitating the addition of an electron to the complex. The operation of the second factor is seen in the comparison of bipyridyl and terpyridine. Both have the possibility of metal to ligand π back-donation. In fact, copper terpyridine has one less σ-donating nitrogen than the bis(bipyridyl) complex yet has a substantially lower potential. The difference in $E_{1/2}$ may then be considered a result largely of the greater flexibility of the bis(bipyridyl)copper(I) complex which permits distortion of the molecule to a more energetically favorable nonplanar geometry relative to the more rigid terpyridine structure. In terms of this explanation, the much higher $E_{1/2}$ of CuL^+ than of the corresponding terdentate copper–terpyridine chelate would suggest that L^- is a much more effective π-bonding ligand than terpyridine.

A comparison of log $K_a(CuL^+)$ (eq 9) for CuL^+ with the values for other bi- and tridentate copper complexes composed of σ-donating ligands shows only a modest difference in the in-plane electronic effects. For a variety of 1:1 bidentate ligands differing in overall charge, including aspartic acid and ethylenediamine, log K_a values ranged from −7.1 to −7.5.[23] For tridentate ligands such as dien and iminodiacetic acid values of 8.9 and 8.4, respectively, have been determined.[24,25] This increase presumably reflects the greater electron density on the metal center due to the addition of another strong ligating group to the coordination plane. Bidentate π-bonding ligands do not markedly change these values. For instance, log K_a values for 1:1 complexes of copper(II) with *o*-phenanthroline or bipyridyl are 6.9 and 6.6, respectively.[23] CuL^+ seems to fall naturally in the category of tridentate ligands, having a log $K_a(CuL^+)$ of −8.30. In this case, as well, the possibility for π back-donation from copper to ligand does not seem to influence strongly in-plane electron distribution.

Finally, in Table III the formation constant for ZnL^+ is compared with those for typical complexes involving amino acids which comprise about 50% of the zinc chelates in plasma as determined by Hallman et al.[13] Although K^{Zn}_{ZnL} is sizable

for a zinc complex, the competition of proton for the ligand at pH 7.4 substantially reduces the effective stability of the complex.

Although quantitative studies have not been done, ligand substitution involving either CuL^+ or ZnL^+ occurs rapidly. Hence the comparison of the thermodynamics of ligand substitution is a useful means of predicting the behavior of these complexes in biological systems. Studies to be reported elsewhere which do examine the reactions of metal complexes of HL with biomolecules appear to support the utility of such work.[19] A strong case has already been made for the usefulness of model studies with bis(thiosemicarbazonato)copper and -zinc complexes, which have antitumor effects, for it has now been shown that the biochemical and cellular reactivity of these chelates can be understood in some detail on the basis of their physicochemical properties.[8,14,20,26-30]

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Registry No. CuL^+, 60804-19-5; $CuLen^+$, 60804-20-8; $Cu(en)_2^{2+}$, 45650-15-5; ZnL^+, 60804-21-9.

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Reversible Electron Transfer in Ruthenium Nitrosyl Complexes

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Electrochemical studies in acetonitrile show that the nitrosyl complexes $[(bpy)_2Ru(NO)X]^{n+}$ (bpy is 2,2′-bipyridine; X = N_3^-, Cl^-, NO_2^- (n = 2); X = NH_3, pyridine, CH_3CN (n = 3)) undergo reversible, one-electron reductions in the potential range 0.1–0.6 V vs. the SSCE at room temperature and a further, irreversible reduction at more cathodic potentials. The one-electron reduction product $[(bpy)_2Ru(NO)Cl]I$ has been isolated. A nearly linear correlation is observed between ν(NO) and $E_{1/2}$ for the reversible reduction wave. The results of IR, EPR, ESCA, Mössbauer, spectral, and chemical studies are consistent with a picture in which there is extensive $d\pi$(Ru) to π^*(NO) back-bonding, and yet the site of reduction remains largely π^*(NO) in character. The results of electron-transfer studies indicate that activation barriers for electron-transfer processes to and from the nitrosyl ligands are relatively low.

Introduction

The chemistry of metal nitrosyl complexes remains a source of chemical interest, in part because the area illustrates certain problems and ambiguities which are largely unresolved in many chemical systems. The problems include the question of the oxidation-state formalism in cases where metal and ligand levels may be closely matched energetically, a quantitative understanding of the relative roles of σ and π bonding in determining the electronic structure and stereochemistry of metal complexes, the role of the metal in determining the reactivity of coordinated ligands and of the ligands in determining the reactivity of a metal center.

Recently, the electronic structures of metal nitrosyl complexes have been treated by using molecular orbital theory and by applying the qualitative molecular orbital ideas developed by Walsh.[1-6] The picture of electronic structure which is evolving is highly developed, at least qualitatively, and introduces some interesting and experimentally testable ideas concerning electronic structure and reactivity.

Nitrosyl complexes are known to undergo a variety of reactions.[2,5,7,8] Among the most chemically useful complexes are the strong-field d^6 complexes of iron(II) and ruthenium(II). Certain of these complexes undergo chemical reactions which are consistent with the presence of a nitrosyl group having nitrosonium ion (NO^+) like reactivity. Reactions observed include typical acid–base behavior at the electrophilic nitrosyl group and, in addition, both diazotization and nitrosation of activated aromatic amines.[7,9-13]

Perhaps the simplest chemical reaction to consider in such complexes is electron transfer. The nitrosonium ion is known to be a relatively strong oxidant,[14] and reversible electron transfer has been reported for the nitroprusside ion.[15,16] An understanding of the origin of the electron-transfer properties in these complexes is of importance in terms of both electronic structure and chemical reactivity. The work described here has appeared, in part, in a preliminary communication.[17]

Experimental Section

Measurements. Ultraviolet–visible and near-infrared spectra were