47-0; Cl^-, 16887-00-6; SO_4^{2-}, 14808-79-8; NCS^-, 302-04-5.

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Mixed-Ligand Complexes of Copper(II) with Imidazole and Selected Ligands

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The formation constants have been measured for the mixed-ligand complexes MLA and MLA_2, where M = Cu(II), A = imidazole, and L = bipyridyl, histamine, glycine, aspartic acid, malonic acid, and 5-sulfosalicylic acid. The lower stability of the MLA_2 complexes as compared to that of MLA is attributed to the loss of π bonding resulting from the two cis-coordinated imidazoles being out of plane. Imidazole, unlike bipyridyl, does not enhance the affinity of Cu(II) for the oxygen donor sites of anionic ligands. In the series of mixed complexes studied the order of stability for the ligand L is glycine > aspartic acid > bipyridyl > malonic acid > 5-sulfosalicylic acid > histamine.

Introduction

The imidazole group of histidine is one of the important binding sites for Cu(II) in biological systems. X-ray, spectroscopy, and various other techniques show that the imidazole moiety binds Cu(II) in sperm whale myoglobin,[1a] bovine serum albumin,[1b] human albumin,[1c] hemocyanin,[1d] ceruloplasmin, and ribonuclease as well as in a number of other bimolecules.[1e] The effectiveness of the imidazole group to act as a metal binding site has been attributed to its great flexibility (the metal–N bond can lie up to 30° from the imidazole plane), its availability at physiological pH (pK ca. 7.0), and its capacity to form both σ and π bonds with metal ions.[2]

In recent years considerable research has been carried out on model mixed-ligand complexes in an effort to understand the nature of metal-ion complexation in biological systems. Studies on mixed-ligand complexes containing bipyridyl[3] and

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histamine[4] show that when metal ions are bound to these aromatic nitrogen donors they prefer to coordinate ligands with oxygen donors rather than those with nitrogen donors. The affinity for ligands with nitrogen and oxygen donors like glycine lies between those observed for the pure O and N ligands. On the basis of these results it has been suggested that imidazole would impart similar discriminatory qualities to metal ions.[5] Since bipyridyl and histamine are typically chelating while the histidyl residues in proteins are typically nonchelating,[2] we felt that it would be interesting to study mixed-ligand complexes of imidazole and determine whether bipyridyl, histamine, and imidazole behave analogously in mixed-ligand complexes. We have therefore carried out a detailed study of the formation of mixed-ligand complexes containing Cu(II), imidazole (im), and the ligands bipyridyl (bpy), histamine (hs), glycine (gly), aspartic acid (asp), malonic acid (mal), and sulfosalicylic acid (ssa). Prior to this work very few studies on mixed-ligand complexes containing imidazole have been reported.[6]

Experimental Section

Reagents. The ligands imidazole (grade III), α,α-bipyridyl, glcyine, aspartic acid, and 5-sulfosalicylic acid were obtained from Sigma Chemical Co., while malonic acid, copper(II) nitrate trihydrate, sodium hydroxide, ethylenediaminetetraacetic acid, potassium hydrogen phthalate, and potassium nitrate were Baker's analyzed grade. The purity of the ligands was checked and their molecular weights were determined by potentiometric titration with standard carbonate-free sodium hydroxide. Imidazole was used in the monoprotonated form while aspartic acid and 5-sulfosalicylic acid were used in the triprotonated forms. The other ligands were used in the diprotonated form. A stock solution of Cu(II) was prepared and standardized by titrating with the disodium salt of EDTA,[7] while the carbonate-free sodium hydroxide was prepared and standardized by titrating with potassium hydrogen phthalate. Double-distilled water was used in the preparation of all stock and experimental solutions.

Potentiometric Measurements. Proton association constants for imidazole, aspartic acid, and 5-sulfosalicylic acid were determined by potentiometric titration of these ligands with standard NaOH. The stability constants for the binary metal complexes were computed from titration curves in which the metal:ligand ratio was 1:10 for imidazole and 1:2 for aspartic acid and sulfosalicylic acid. The corresponding data for bipyridyl, histamine, glycine, and malonic acid at 25.0 °C and μ = 0.2 M (KNO_3) were taken from our previous work.[8] The equilibrium constants for the ternary systems were computed from titrations in which the total concentrations of Cu(II), the bidentate or tridentate ligand, and imidazole were in a 1:1:1, 1:1:2, and 1:1:3 molar ratio. The concentration of Cu(II) was approximately 2.0×10^{-3} M. Multiple titrations were carried out for each system. Mixed-ligand complexes for copper(II)–pyrocatechol–imidazole and copper(II)–ethylenediamine–imidazole could not be quantitatively studied because of slow equilibration and insolubility.

The potentiometric titrations were carried out at 25.0 ± 0.1 °C with the apparatus and procedure described previously.[9] A constant ionic strength of 0.2 M was maintained by addition of KNO_3. The equilibrium constants reported in this paper are all concentration constants.

Calculations. The proton association constants for the free ligands and the stability constants for binary and ternary equilibria 1–8 were

$$M + L \rightleftharpoons ML \qquad (1)$$

$$M + 2L \rightleftharpoons ML_2 \qquad (2)$$

$$M + A \rightleftharpoons MA \qquad (3)$$

$$M + 2A \rightleftharpoons MA_2 \qquad (4)$$

$$M + 3A \rightleftharpoons MA_3 \qquad (5)$$

$$M + 4A \rightleftharpoons MA_4 \qquad (6)$$

$$M + L + A \rightleftharpoons MLA \qquad (7)$$

$$M + L + 2A \rightleftharpoons MLA_2 \qquad (8)$$

calculated from the titration data by using a corrected version of the computer program SCOGS.[10] (M = Cu(II), A = im, L = ssa and asp in equilibria 1 and 2 and L = bpy, hs, gly, asp, mal, and ssa for equilibria 7–9.) In the case of bpy and hs, constants for the formation for a hydroxo complex according to the equilibrium 9 were also obtained.

$$M + L + A + OH \rightleftharpoons MLA(OH) \qquad (9)$$

In titrations involving a 1:1:1 molar ratio of M, L, and A (where L = hs, gly, asp, mal, and ssa) the association constants for equilibria 7–9 were calculated by taking into consideration the proton association constants and the stability constants for the binary mono and bis complexes for L and A. For titrations involving a 1:1:2 molar ratio, in addition to the above species the MA_3 complex was also taken into consideration in calculating the constants for equilibria 7–9. Analysis of titration curves with a 1:1:3 molar ratio of M, L, and A shows that complexes of the type MLA_3 are not formed appreciably under the experimental conditions employed. The constants for ternary systems involving bipyridyl were calculated by two different methods. In one approach the 1:1 Cu(bpy) complex was considered to be completely formed and the ternary constants were calculated by taking into consideration the proton association constants for imidazole only. The validity of these constants was checked by the second approach wherein no assumptions were made and the ternary constants were calculated by taking into consideration the proton association constants and the stability constants for the binary complexes of bpy and im. As found in the previous study,[8] the constants obtained by the two methods are found to be in very good agreement. The stability constants for any given species were in excellent agreement irrespective of whether they were obtained from titration curves with a 1:1:1, a 1:1:2, or a 1:1:3 molar ratio of M, L, and A.

The stepwise formation constants for equilibria 10–16 could be

$$ML + L \rightleftharpoons ML_2 \qquad (10)$$

$$MA + A \rightleftharpoons MA_2 \qquad (11)$$

$$MA_2 + A \rightleftharpoons MA_3 \qquad (12)$$

$$MA_3 + A \rightleftharpoons MA_4 \qquad (13)$$

$$ML + A \rightleftharpoons MLA \qquad (14)$$

$$MLA + OH \rightleftharpoons MLA(OH) \qquad (15)$$

$$ML + 2A \rightleftharpoons MLA_2 \qquad (16)$$

readily calculated by considering the relevant data for the proton association constants and the cumulative binary and ternary constants.

Results

Binary Systems. The proton association constants and the stability constants for the binary systems involving imidazole, ssa, and asp have been reported earlier.[11] We have redetermined these constants under the experimental conditions [t = 25.0 °C, μ = 0.2 M (KNO_3)] used in this work for determining the ternary constants. We have previously reported the binary constants for gly, asp, ssa, and mal at 25.0 °C and μ = 0.2 M.[8] The proton association constants and the binary metal constants are tabulated in Tables I and II.

Ternary Systems. The titration curves a, b, and c in Figure 1 were obtained for ternary systems involving Cu(II), bipyridyl, and imidazole in a 1:1:1, a 1:1:2, and a 1:1:3 molar ratio. Curve d was obtained for a 1:1:2 ternary system involving histamine. With both these ligands an additional proton is titrated in excess of that expected for diprotonated bpy and

Table I. Association Constants[a] for the Free Ligands at 25.0 °C and $\mu = 0.2$ M (KNO_3)

ligand L	$\log K^{H}_{HL}$	$\log K^{HL}_{H_2L}$	$\log K^{H_2L}_{H_3L}$
bpy	4.45	CD[b]	
hs	9.88	6.16	
gly	9.60	2.33	
asp	9.65	3.68	2.00
mal	5.22	2.64	
5-ssa	11.86	2.43	CD[b]

[a] All constants are accurate to ±0.02. Values for bpy, hs, gly, and mal are from ref 8. $\log K^{H}_{HA}$ for imidazole is 7.00 at 25.0 °C, $\mu = 0.2$ M. [b] CD = completely dissociated.

Table II. Association Constants[a] for the Binary Metal–Ligand Complexes at 25.0 °C and $\mu = 0.2$ M (KNO_3)

ligand L	$\log K^{M}_{ML}$	$\log K^{ML}_{ML_2}$
bpy[b]	8.10	5.50
hs	9.25	6.52
gly	8.16	6.82
asp	8.84	6.98
mal	4.81	2.66
5-ssa	9.57	7.05

[a] All constants are accurate to ±0.02. For imidazole the values of $\log K^{M}_{MA}$, $\log K^{MA}_{MA_2}$, $\log K^{MA_2}_{MA_3}$, and $\log K^{MA_3}_{MA_4}$ at 25.0 °C and $\mu = 0.2$ M are 4.28, 3.46, 2.83, and 2.05, respectively. [b] Values at 25.0 °C and $\mu = 0.1$ M.[15] Values for hs, gly, and mal are from ref 8.

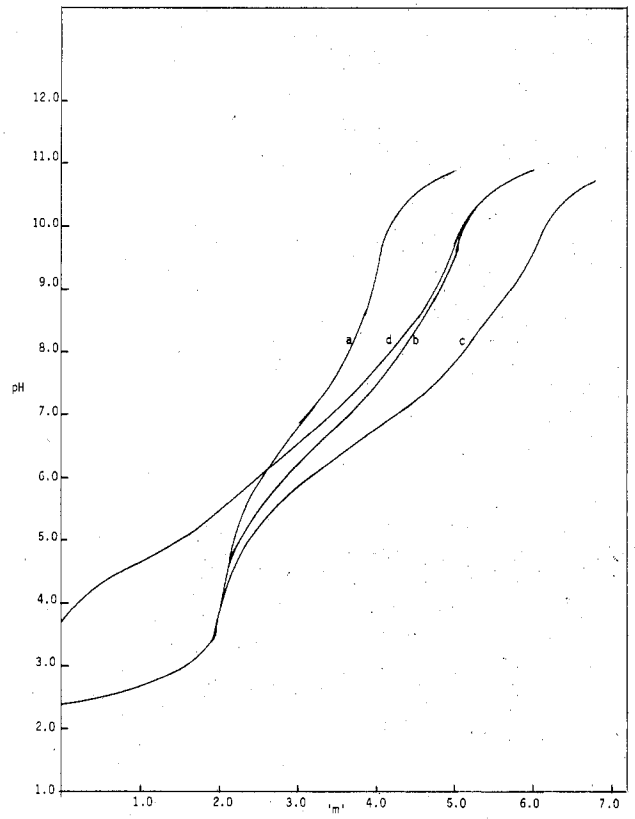


Figure 1. Titration curves for ternary systems (m = moles of base added per mole of metal ion): (a) Cu(II) + bipyridyl + imidazole (1:1:1); (b) Cu(II) + bipyridyl + imidazole (1:1:2); (c) Cu(II) + bipyridyl + imidazole (1:1:3); (d) Cu(II) + histamine + imidazole (1:1:2).

monoprotonated imidazole. Analysis of these curves in terms of the species discussed earlier indicates that in both these systems the ternary complexes MLA, MLA_2, and MLA(OH) are formed. The formation constants for these complexes are listed in Table III.

Table III. Association Constants[a] for Mixed-Ligand Complexes of Imidazole at 25.0 °C and $\mu = 0.2$ M (KNO_3)

ligand L	$\log K^{ML}_{MLA}$[b]	$\Delta \log K_1$[c]	$\log K^{ML}_{MLA_2}$	$\Delta \log K_2$[c]
bpy	3.92	−0.36	6.76	−0.98
hs	3.44	−0.84	5.12	−2.62
gly	4.00	−0.28	6.98	−0.76
asp	3.93	−0.35	6.88	−0.86
mal	3.77	−0.51	6.34	−1.40
5-ssa	3.69	−0.59	6.26	−1.48

[a] All constants are accurate to ±0.05. [b] A = imidazole. [c] $\Delta \log K_1$ is defined by eq 17 and $\Delta \log K_2$ by eq 18.

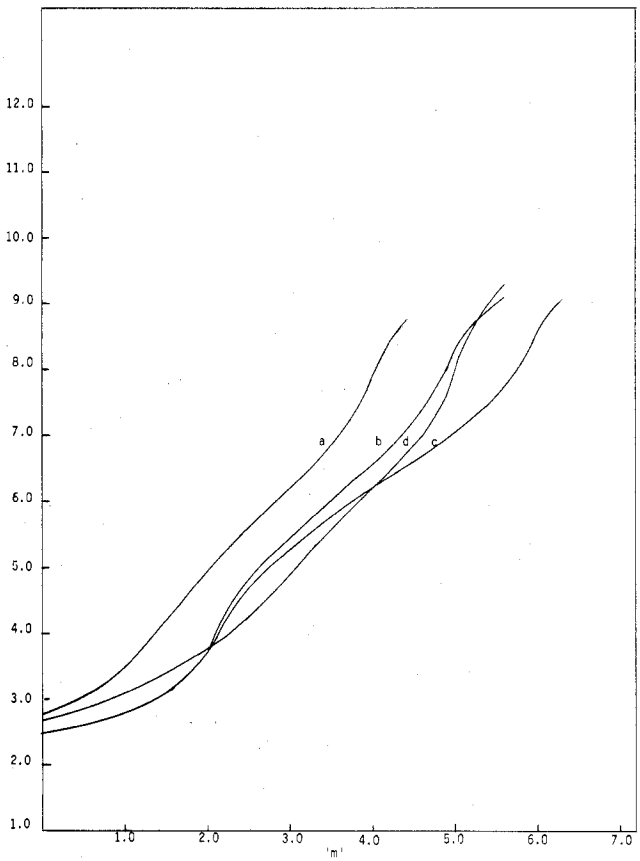


Figure 2. Titration curves for ternary systems (m = moles of base added per mole of metal ion): (a) Cu(II) + glycine + imidazole (1:1:2) (a similar curve was obtained for malonic acid); (b) Cu(II) + sulfosalicylic acid + imidazole (1:1:2); (c) Cu(II) + sulfosalicylic acid + imidazole (1:1:3); (d) Cu(II) + aspartic acid + imidazole (1:1:2).

Representative titration curves for ternary systems involving gly, asp, ssa, and mal are given in Figure 2. Unlike the ternary systems involving bpy and hs, these systems do not indicate the titration of any excess protons. Analysis of these curves shows that the ternary complexes MLA and MLA_2 are formed in all cases. The formation constants for these complexes are listed in Table III.

The relative stability of the ternary complexes as compared to that of the corresponding binary complexes can be quantitatively expressed in different ways. A recent review of these methods[12] has shown that for a variety of reasons the most suitable comparison is in terms of $\Delta \log K$. We have therefore tabulated in Table III the difference in stabilities of the binary and ternary complexes in terms of $\Delta \log K$ as defined by eq 17 and 18. $\Delta \log K_1$ represents the difference in stability for

$$\Delta \log K_1 = \log K^{ML}_{MLA} - \log K^{M}_{MA} \quad (17)$$

$$\Delta \log K_2 = \log K^{ML}_{MLA_2} - \log K^{M}_{MA_2} \quad (18)$$

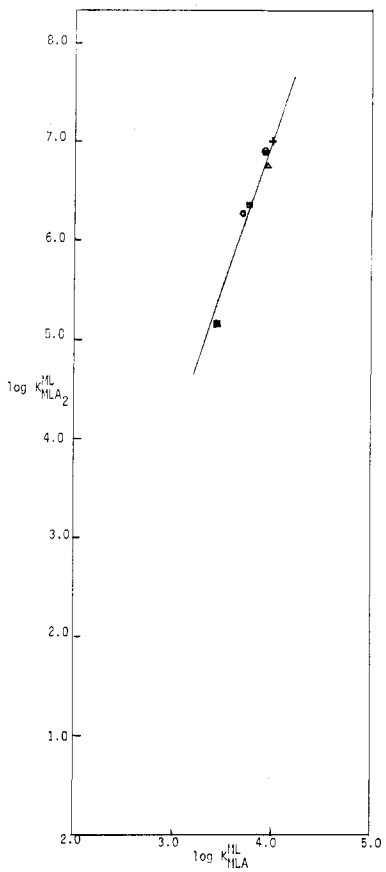


Figure 3. Plot of log K^{ML}_{MLA} vs. log $K^{ML}_{MLA_2}$; M = Cu(II), A = imidazole. L: (□) histamine, (○) sulfosalicylic acid, (□) malonic acid, (△) bipyridyl, (○) aspartic acid, (+) glycine.

the addition of an imidazole to the 1:1 Cu(II)–L complex and to Cu(II). $\Delta \log K_2$ represents the difference in stability for the addition of two imidazoles to the 1:1 Cu(II)–L complex and to Cu(II). It should be kept firmly in mind that the magnitudes of $\Delta \log K_1$ and $\Delta \log K_2$ are strongly influenced by statistical differences in the formation of each complex as well as differences in bonding. If the structures of the complexes were known and if the magnitude of the thermodynamic trans effect were also known for ML where L is unsymmetrical, then statistical corrections could be applied. Since these data are unavailable, we have chosen to report uncorrected values of $\Delta \log K$. However, under the assumption that these Cu(II) complexes are square planar and that the thermodynamic trans effect is negligible, there is a statistical correction of log 2 for both $\Delta \log K_1$ and $\Delta \log K_2$. If the statistical correction is the same for each, then it does not affect comparison between the two.

Discussion

Imidazole coordination of Cu(II) in binary and mixed-ligand complexes has been studied in considerable detail by X-ray crystallography.[13] It is found that, where possible, the imidazole ring prefers to be coplanar with the four major binding sites of Cu(II).[13a] If these four sites are considered to be in the *xy* plane, then the imidazole ring is held in the *xy* plane by π bonds between the d_{xz} or d_{yz} metal orbital and a vacant π^* orbital at the imidazole nitrogen. This in-plane π bonding is sufficiently weak so that steric effects can readily twist the imidazole ring away from the *xy* plane. In particular, when two imidazole molecules occupy cis positions on Cu(II), neither is in plane. In these cases the imidazole rings range from 30 to 60° out of the *xy* plane. This indicates that the Cu(II) d_{xy} orbital is of sufficiently high energy so that it does not π bond

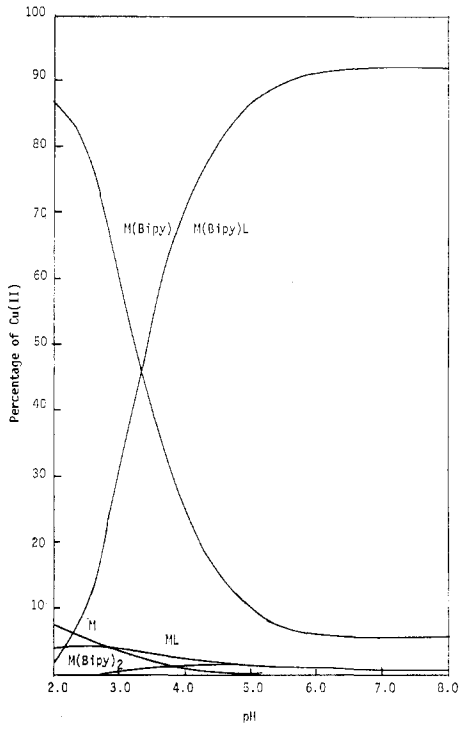
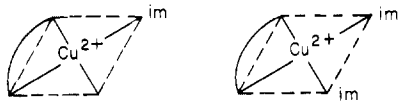


Figure 4. Relative concentrations of binary and ternary complex species in the copper(II)–bipyridyl–malonic acid system (0.001 M each). t = 25.0 °C, μ = 0.1 M. Calculated with constants in ref 3b. M = Cu(II); bpy = bipyridyl; L = malonic acid.

productively with imidazole in the *cis*-bis(imidazole) complexes.

Equilibria 14 and 16 measure the tendency of imidazole to form mixed-ligand complexes. The constant K^{ML}_{MLA} measures the addition of a single imidazole to the binary ML complex to form the ternary MLA complex with structure I. The



I II

constant $K^{ML}_{MLA_2}$ measures the addition of two imidazoles to the binary ML complex to form the ternary MLA_2 complex with structure II. The $\Delta \log K_1$ and $\Delta \log K_2$ values listed in Table III are negative in all cases indicating that imidazole binds better to Cu(II) than to the binary ML complexes. The negative value for $\Delta \log K_1$ can be attributed to the fact that there are fewer coordination positions available on the binary ML complex than on Cu(II). The much more negative values for $\Delta \log K_2$ can be due to a combination of the statistical effect resulting from the reduction in available binding sites plus the loss of π bonding in going from an in-plane coordinated imidazole to two out-of-plane cis-coordinated imidazoles. π-Bonding effects have been previously invoked to explain the decrease in stability with an increase in the number of coordinated imidazole molecules in binary Cu(II) complexes.[14] In the ternary complexes, the addition of the two imidazoles occurs without a substantial steric interaction between the imidazole rings and the ligands L. Our basis for this assertion is the linear correlation between K^{ML}_{MLA} and $K^{ML}_{MLA_2}$ shown in Figure 3. Specific steric interactions between the imidazole and the ligand L should cause the ratio of K^{ML}_{MLA} and $K^{ML}_{MLA_2}$ to differ from complex to complex.

A convenient way to compare the influence of imidazole and bpy on the interaction of Cu(II) with oxygen and nitrogen

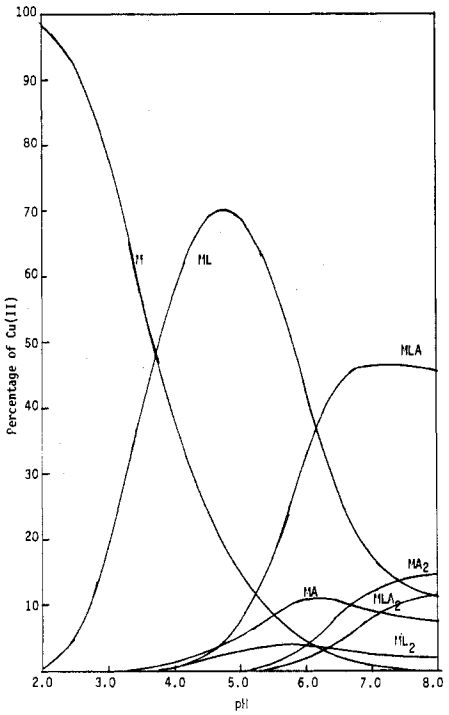


Figure 5. Relative concentrations of binary and ternary complex species in the copper(II)–imidazole–malonic acid system (Cu(II) = malonic acid = 0.001 M; imidazole = 0.002 M). t = 25.0 °C, μ = 0.2 M. Calculated with constants reported in Tables II and III. M = Cu(II); A = imidazole; L = malonic acid.

donors is to consider the addition of the ligand L to the binary Cu(im) and Cu(bpy) complexes in terms of the $\Delta \log K$ values for eq 19–21. The $\Delta \log K$ values for eq 19 and 20 will be

$$\Delta \log K = \log K^{M(im)}_{M(im)L} - \log K^{M}_{ML} \quad (19)$$

$$\Delta \log K = \log K^{M(im)_2}_{M(im)_2L} - \log K^{M}_{ML} \quad (20)$$

$$\Delta \log K = \log K^{M(bpy)}_{M(bpy)L} - \log K^{M}_{ML} \quad (21)$$

the same as for eq 17 and 18 since in a ternary complex both ligands are stabilized or destabilized to the same extent.[5] In Table IV the $\Delta \log K$ values for the ternary complexes of imidazole and bpy are collected. The available values for the ternary complexes of histamine are also included. For bpy the $\Delta \log K$ values clearly show that interaction is favored with anionic donors as compared to neutral donors. The positive $\Delta \log K$ values for systems 5–7 in Table IV indicate that the Cu(bpy) complex interacts better with the anionic oxygen donors than Cu(II) itself. For histamine the $\Delta \log K$ values are negative for both oxygen and nitrogen donors. Nonetheless, the more positive value for system 7 as compared to the values for systems 1, 2, and 4 has been used to argue that histamine also promotes binding to anionic oxygen donors, although on a more modest scale than bpy. For imidazole the $\Delta \log K$ values are negative for all systems. A significant astatistical mixed-ligand formation is not observed in any of the systems. The contrasting behavior of bpy and imidazole is demonstrated by the species distribution plots for the bpy–Cu(II)–mal (Figure 4) and the im–Cu(II)–mal systems (Figure 5). In the former system the concentration of the ternary complex reaches a maximum of ca. 92% while in the latter system the ternary complexes are at a concentration of less than 50% over the pH range 2–8. Much has been made of the astatistical mixed-ligand complex formation between Cu(bpy) and anions.[5] It has been suggested that similar phenomena should occur between substrate ligands and Cu(II) held at an enzyme active site by imidazole moieties.[5] However, the present work does not indicate any significant astatisticality in the formation of any mixed-ligand imidazole complexes, although it is interesting to note that the most stable mixed-ligand complexes are formed with the biologically important amino acids.

Table IV. Comparison of $\Delta \log K$ Values for the Mixed-Ligand Complexes of Bipyridyl, Histamine, and Imidazole (t = 25.0 °C and μ = 0.2 M Unless Stated Otherwise)

		ligand B		ligand A	
no.	ligand L	bpy[a]	hs[a]	im[b]	$(im)_2$[c]
1	bpy		−2.44[d]	−0.36	−0.98
2	en	−1.19[d] (−1.29)[e]	−1.43[f]		
3	hs	−2.44[d]		−0.84	−2.62
4	gly	−0.42[d] (−0.35)[e]	−0.64[g]	−0.28	−0.76
5	mal	+0.31[d] (+0.27)[e]		−0.51	−1.40
6	5-ssa	+0.5[h]		−0.59	−1.48
7	pyrocatechol	+0.31[d] (+0.36)[h]	−0.48[i]		

[a] $\Delta \log K$ calculated from $\Delta \log K = \log K^{MB}_{MLB} - \log K^{M}_{ML}$. [b] $\Delta \log K$ calculated from the equation $\Delta \log K^{MB}_{MLA} - \log K^{M}_{ML}$. [c] $\Delta \log K$ values calculated from the equation $\Delta \log K = \log K^{MA_2}_{MLA_2} - \log K^{M}_{ML}$. [d] Reference 8. [e] Reference 3b. t = 25.0 °C, μ = 0.1 M. [f] Reference 4a. t = 37.0 °C, μ = 0.15 M. [g] Reference 4c. [h] Reference 3a. t = 25.0 °C, μ = 0.1 M. [i] Reference 4b. t = 25.0 °C, μ = 0.1 M.

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Registry No. Cu, 7440-50-8; im, 288-32-4; bpy, 366-18-7; hs, 51-45-6; gly, 56-40-6; asp, 56-84-8; mal, 141-82-2; 5-ssa, 97-05-2.

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