Stability Constants of Metal(II) Complexes with Amines and Aminocarboxylates with Special Reference to Chelation

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Equations derived on the basis of mechanistic considerations have been utilized to calculate the stability constants of binary and ternary copper(II) complexes of amine(s) or aminocarboxylates. Calculated values of 185 copper(II) amine complexes have been compared with the observed. For 89 complexes including ammonia, ethylenediamine, cyclohexane-1,2-diamine, imidazole, pyridine, and some substituted analogs, the calculated values agree with the observed within 0.3 log unit. These complexes may be regarded as regular. Among the remaining non-regular complexes we find some complexes with lower stability constants due to steric hindrance, and some others with higher constants resulting from aromatic π–π interactions and/or hydrophobic interactions between coordinated ligands. Mechanistic considerations have also been successfully utilized to predict stability constants of polyamine and aminocarboxylate chelates of nickel(II), cobalt(II), and copper(II) according to Adamson's approach.

In our earlier reports[1] too much emphasis has been put on the successful application of mechanistic considerations to the prediction of stability constants of binary and ternary metal complexes from the stability constants of the 1:1 complexes. For amines and/or aminocarboxylates (A or L) the stability constant of metal complexes [MAL] and [ML$_n$] is given by the following equations.[1a]

$$\begin{aligned}\log K(\mathrm{MA}+\mathrm{L}) &= \log K_1(\mathrm{ML}) + \{\log K_{\mathrm{OS}}(\mathrm{MA},\mathrm{L}) - \log K_{\mathrm{OS}}(\mathrm{M},\mathrm{L})\} \\ &\quad + \{\log n_{\mathrm{w}}(\mathrm{MA}) - \log n_{\mathrm{w}}(\mathrm{M})\} \\ &\quad + \sum_{i}^{I}\sum_{<j}^{J} \delta_{ij} X_i(\mathrm{A}) Y_j(L) \end{aligned} \tag{1}$$

$$\begin{aligned}\log K(\mathrm{ML}_n) &= \log K_1(\mathrm{ML}) + \{\log K_{\mathrm{OS}}(\mathrm{ML}_{n-1},\mathrm{L}) - \log K_{\mathrm{OS}}(\mathrm{M},\mathrm{L})\} \\ &\quad + \{\log n_{\mathrm{w}}(\mathrm{ML}_{n-1}) - \log n_{\mathrm{w}}(\mathrm{M})\} \\ &\quad + \sum_{i}^{I}\sum_{<j}^{J} \delta_{ij} X_i(\mathrm{L}_{n-1}) Y_j(\mathrm{L}) - \log n \end{aligned} \tag{2}$$

In the above equations and in the following, we denote K_{OS}: the formation constant of the outer-sphere complex indicated; n_{w}: the number of water molecules coordinated to the species indicated; δ_{ij}: the effect of the donor atom i in the incoming ligand on the donor atom j in the coordinated ligand(s); $\log n$: the statistical correction term for the number of ways that [ML$_n$] can dissociate. Stability constants are defined as follows:[2]

$$\begin{aligned} K_1 &= [\mathrm{ML}][\mathrm{M}]^{-1}[\mathrm{L}]^{-1}, \\ K(\mathrm{MA}+\mathrm{L}) &= [\mathrm{MAL}][\mathrm{MA}]^{-1}[\mathrm{L}]^{-1}, \\ K_n &= [\mathrm{ML}_n][\mathrm{ML}_{n-1}]^{-1}[\mathrm{L}]^{-1} \end{aligned} \tag{3}$$

Because of the distorted octahedral structure of the copper(II) complexes some additional factors should be taken into account in their formation. In the reaction of copper(II) ion with ligands occupying less than four coordination sites terms with n_{w} need not be taken into consideration: the dissociation of the water molecule at the axial position of the distorted octahedron of the hydrated copper(II) complexes is the rate determining step followed by rapid pseudo-rotation leading to the coordination of the incoming ligand on the equatorial position.[1b]

In the coordination of non-charged amine nitrogen the second term involving the formation constant of outer-sphere complexes in eqs 1 and 2[1a] may be dropped, and we have simpler eqs 4 and 5.

$$\log K(\mathrm{CuA}+\mathrm{L}) = \log K_1 + \sum_{i}^{I}\sum_{<j}^{J} \delta_{ij} X_i(\mathrm{A}) Y_j(\mathrm{L}) \tag{4}$$

$$\log K_n = \log K_1 + \sum_{i}^{I}\sum_{<j}^{J} \delta_{ij} X_i(\mathrm{L}_{n-1}) Y_j(\mathrm{L}) - \log n \tag{5}$$

Donor atom–donor atom interaction terms δ_{ij} for copper(II) are given in Table 1. In this work we calculated 185 copper(II) amine complexes using eqs 4 and 5 and compared with the observed values. From the difference between the calculated and observed values we classified the ligand as "regular" complexes and "non-regular" complexes and have discussed the higher or lower stability constants from the reaction mechanism of the metal complex formation, steric hindrance, hydrophobic interaction, aromatic π–π interaction, and chelation. Mechanistic considerations have also been utilized to predict stability constants of polyamine and aminocarboxylate chelates of nickel(II), cobalt(II), and copper(II) according to Adamson's approach using the stability constants of 1:1 complexes of $[\mathrm{M(NH_3)}]^{2+}$ and/or $[\mathrm{M(CH_3COO)}]^{+}$ (M = Ni and Co).

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Table 1. Value of δ_{ij} for Copper(II) Complexes and Effect of Donor Atom Xi in the Ligand A (or L) on the Donor Atom Y_j in the Ligand L[a)]

$\delta_{\mathrm{N(AL)N(AL)}}$	−0.33
$\delta_{\mathrm{N(HC)N(HC)}}$	−0.39
$\delta_{\mathrm{N(AL)N(HC)}}$	−0.36
$\delta_{\mathrm{N(HC)N(AN)}}$	−0.28
$\delta_{\mathrm{N(AN)N(AN)}}$	−0.18
$\delta_{\mathrm{N(AN)O(AL)}}$	−0.07
$\delta_{\mathrm{N(AL)O(AL)}}$	−0.10
$\delta_{\mathrm{N(HC)O(PHEN)}}$	+0.10
$\delta_{\mathrm{N(HC)O(AL)}}$	+0.02
$\delta_{\mathrm{N(AL)O(PHEN)}}$	−0.05
$\delta_{\mathrm{O(AL)O(AL)}}$	−0.10
$\delta_{\mathrm{O(PHEN)O(PHEN)}}$	−0.25

a) N(AL): Aliphatic N, N(HC): Heterocyclic N, N(AN): Anilinic N, O(AL): Aliphatic and benzoate O, O(PHEN): Phenolic O.

Results and Discussion

Stability Constant of Copper(II) Complexes with Amines. Needless to say the objective selection of reported stability constants is essential for discussion of extraordinary effects such as steric, aromatic π–π and/or hydrophobic interactions in complex formation. Thus data for 1:2 and higher complexes given in "critical stability constants"[3] have all been used and they have been compared to formation constants calculated according to eq 5 (Tables 1 and 2 in Supporting Information (SI)). Data for amine complexes have been obtained elsewhere.[4]

For 90 of 185 copper(II) amine complexes the calculated values agreed with the observed within 0.3 log unit. These complexes may be regarded as regular. The regular and non-regular complexes are summarized in Table 2.

Ligands Giving Complexes of Stability Lower than the Calculated (by More than 0.3 log Unit). Among the

Table 2. Classification of Ligands According to Stability Constants of Copper(II) Complexes

1. Ligands giving regular complexes

Aliphatic amines and anilines

Ammonia (1:2, 1:3, 1:4)
L-Tyrosine ethyl ester (1:2)
β-Alanineamide (1:2)
2-Methylthioethylamine (1:2)
2-(2-Aminoethylthio)ethanol (1:2)
Ethylenediamine (en) (1:2)
DL-1-Methyl-en (1:2)
DL-1,2-Dimethyl-en (1:2)
meso-1,2-Dimethy-en (1:2)
1,1,2,2-Tetramethyl-en (1:2)
DL(*trans*)-Cyclohexane-1,2-diamine (1:2)
DL-Cycloheptane-1,2-diamine (1:2)
1,2-Diamino-4-methylbenzene (1:2)
1,2-Diamino-4-methoxybenzene (1:2)
1,2-Diamino-4-chlorobenzene (1:2)
Pyrrolidine (1:2, 1:3)
2-(Ethylamino)ethanol (1:2)
N-Methyl-en (1:2)
N-Ethyl-en (1:2)
N-2-Propyl-en (1:2)
N-Butyl-en (1:2)
1-(2-Propylamino)-2-methyl-2-propylamine (1:2)
1-(Cyclohexylamino)-2-methyl-2-propylamine (1:2)
DL-2-(Aminomethyl)piperidine (1:2)
Perhydro-1,4-diazepine (1:2)
2-(Dimethylamino)ethanol (1:2, 1:3, 1:4)
2-(Diethylamino)ethanol (1:2)
N-Methyliminodi-2-ethanol (1:2, 1:3)
N-(2-Aminomethyl)piperazine (1:2)
Tryptophan methyl ester (1:2)
Aminomethylphosphonic acid (1:2)
2-Aminoethyldihydrogenphosphate (1:2)
NO-Coordinate bidentate
DL-1-Aminoethylphosphonic acid (1:2)
DL-1-Amino-propylphosphonic acid (1:2)
DL-1-Amino-2-methylpropylphosphonic acid (1:2)

Heterocyclic amines

Imidazole (1:2, 1:3, 1:4)
1-Methylimidazole (1:2, 1:3, 1:4)
4-Methylimidazole (1:2, 1:3)
2-Hydroxymethylimidazole (1:3)
4-Hydroxymethylimidazole (1:3)
Benzo-1,3-diazole (1:2, 1:4)
Pyridine (1:2, 1:3, 1:4)
2-Methylpyridine (1:2)
3-Methylpyridine (1:2, 1:3, 1:4)
4-Methylpyridine (1:2, 1:3, 1:4)
2,5-Dimethylpyridine (1:2)
3,4-Dimethylpyridine (1:2, 1:3, 1:4)
3,5-Dimethylpyridine (1:2, 1:3, 1:4)
2-(Hydroxymethyl)pyridine (1:2)
3-(Hydroxymethyl)pyridine (1:2)
4-(Hydroxymethyl)pyridine (1:2, 1:3)
Pyridine-2-carbaldehyde (1:2)
Nicotinamide (1:2, 1:3)
2-(2-Pyridyl)-1,3-thiazole (1:2)
4-(2-Pyridyl)-1,3-thiazole (1:3)
3-Aminopyridine (1:2, 1:3, 1:4)
(only the coordination of pyridine N assumed)
2-(Aminomethyl)pyridine (1:2)
DL-2-(1-Aminoethyl)pyridine (1:2)
2-(Methylaminomethyl)-6-methylpyridine (1:2)
8-Aminoquinoline (1:2)
Methylenedi-2-pyridine (1:2)
5-Methyl-1,10-phenanthroline (1:2)
5,6-Dimethyl-1,10-phenanthroline (1:2)
5-Methyl-7-hydroxy-1′,2′,4′-triazolo[1,5-*a*]pyrimidine (1:2)
(coordination of only one heterocyclic amine assumed)

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2. Ligands giving complexes of stability lower than the calculated (by more than 0.3 log unit)

Aliphatic amines and anilines

2-Aminoethanol (1:2, 1:3, 1:4)
DL-2-Amino-1-phenylethanol (1:2)
L-Tyrosine ethyl ester (1:3, 1:4)
Glycineamide (1:2)
Glycine-*N*,*N*-dimethylamide (1:2)
1,2-Diaminobenzene (1:2)
Trimethylenediamine (1:2)
1,3-Diaminobutane (1:2)
2,2-Dimethyl-1,3-diaminopropane (1:2)
Oxobis(2-ethylamine) (1:2)
Thiobis(2-ethylamine) (1:2)
1,2,3-Triaminopropane (1:2)
Tetrakis(aminomethyl)methane (1:2)
2-(Methylamino)ethanol (1:2, 1:3, 1:4)
2-(Ethylamino)ethanol (1:3, 1:4)
Iminodi-2-ethanol (1:2, 1:3, 1:4)
DL-2-(Aminoethyl)piperidine (1:2)
N,*N*′-Dimethyl-en (1:2)
N,*N*′-Diethyl-en (1:2)
N,*N*′-Dipropyl-en (1:2)
N,*N*′-Dibutyl-en (1:2)
N-(Hydroxyethyl)-en (1:2)
DL-1-(2-Aminoethylamino)-2-propanol (1:2)
Ethylenediiminodi-2-ethanol (1:2)
DL-Ethylenediiminodi-2-propanol (1:2)
2-(Dimethylamino)ethanol (1:3)
2-(Diethylamino)ethanol (1:3, 1:4)
N-Methyliminodi-2-ethanol (1:4)
Nitrilotri-2-ethanol (1:2)
N,*N*-Dimethyl-en (1:2)
N,*N*-Diethyl-en (1:2)
N-(2-Aminoethyl)pyrrolidine (1:2)
N-(2-Aminoethyl)piperidine (1:2)
N,*N*-Diethyl-*N*′-methyl-en (1:2)
N,*N*,*N*′,*N*′-Tetramethyl-en (1:2)
N-(2-Aminoethyl)morpholine (1:2)

Heterocyclic amines

4-Methylimidazole (1:4)
2-Hydroxymethylimidazole (1:4)
4-Hydroxymethylimidazole (1:4)
2-(2-Aminoethyl)imidazole (1:2)
4-(2-Aminoethyl)imidazole (histamine) (1:2)
DL-4-(2-Amino-3-hydroxypropyl)imidazole (1:2)
L-Histidine methyl ester (1:2)
2-(2-Pyridyl)imidazole (1:2)
4-(2-Pyridyl)imidazole (1:2)
4-Aminomethyl-3-hydroxy-5-hydroxymethyl-2-methylpyridine (1:2)
2-(Hydroxymethyl)pyridine (1:3, 1:4)
3-(Hydroxymethyl)pyridine (1:3)
Pyridine-4-carboxamide (isonicotinamide) (1:2)
4-(2-Pyridyl)-1,3-thiazole (1:2)
2-Aminopyridine (1:2)
2-Aminopyridine 1-oxide (1:2)
2-(2-Aminoethyl)pyridine (1:2)
2-(Methylaminomethyl)pyridine (1:2)
8-Hydroxyquinoline (1:2)
8-Hydroxyquinoline-5-sulfonic acid
7-Nitro-8-hydroxyquinoline (1:2)
Ethylenedi-2-pyridine (1:2)
5-Nitro-1,10-phenanthroline (1:2)
DL-2-(2-Chlorophenylhydroxymethyl)-1,4,5,6-tetrahydropyrimidine (1:2)
DL-2-(2,6-Dichlorophenylhydroxymethyl)-1,4,5,6-tetrahydropyrimidine (1:2)
DL-(1-Phenyl-1-hydroxymethyl)-1,4,5,6-tetrahydropyrimidine (1:2)

For these three ligands, coordination of heterocyclic N and O is assumed.

3. Ligands giving complexes of stability higher than the calculated (by more than 0.3 log unit)

Aliphatic amines and anilines

2-Amino-2-(hydroxymethyl)-1,3-propanediol (1:2, 1:3, 1:4)
β-Alanine-*N*,*N*-dimethylamide (1:2)
DL-1-Ethyl-en (1:2)
DL-1-Phenyl-en (1:2)
Bicyclohexyl-1,1′-diamine (1:2)
meso(*cis*)-Cyclohexane-1,2-diamine (1:2)
1,2-Diaminobenzene (1:2)
DL-2,3-Diaminopropanoic acid methyl ester (1:2)
Pyrrolidine (1:4)
N-Propyl-en (1:2)
2-Aminomethyldihydrogenphosphate (1:2)

Heterocyclic amines

2-Hydroxymethylimidazole (1:2)
4-Hydroxymethylimidazole (1:2)
4-Aminoethylimidazole (1:2)
3-Hydroxy-5-hydroxymethylpyridine-4-carboxaldehyde (pyridoxal) (1:2)
2-(Aminomethyl-6-methyl)pyridine (1:2)
Ethylenedi-2-pyridine (1:2)
2-Chloro-phen (1:2)
2-Methyl-phen (1:2)
2,9-Dimethyl-phen (1:2)
4,7-Dimethyl-phen (1:2)
5-Propyl-7-hydroxy-1′,2′,4′-triazolo[1,5-*a*]pyrimidine (1:2)
5-Methyl-6-ethyl-7-hydroxy-1′,2′,4′-triazolo[1,5-*a*]pyrimidine (1:2)

remaining non-regular complexes, we find some complexes of lower observed stability constant resulting from steric effects, and others of higher constant due to aromatic π–π interaction and/or hydrophobic interactions.[5,6]

By comparing the difference of $\log K_2$(calc) and $\log K_2$(obs) (see Dif in Table 1 in SI) it is evident that steric effects increase in the following order, where en denotes 1,2-diaminoethane (ethylenediamine): 1. *N*,*N*′-dimethyl-en $\cong$ *N*,*N*′-diethyl-en $<$

N,*N*′-dipropyl-en < *N*,*N*′-dibutyl-en; 2. *N*,*N*-dimethyl-en < *N*,*N*′-dimethyl-en and *N*,*N*-diethyl-en < *N*,*N*′-diethyl-en; 3. *N*,*N*-dimethyl-en < *N*,*N*,*N*′,*N*′-tetramethyl-en < *N*,*N*-diethyl-en < *N*,*N*-diethyl-*N*′-methyl-en; 4. *N*-(2-hydroxyethyl)-en < DL-1-(2-aminoethylamino)-2-propanol < ethylenediiminodi-2-ethanol < DL-ethylenediiminodi-2-propanol; 5. *N*-(2-aminoethyl)piperidine < *N*-(2-aminoethyl)morpholine ≅ *N*-(2-aminoethyl)pyrrolidine.

There are some complexes included in the group of non-regular complexes because of doubtful observed stability. For 2-aminoethanol $\log K_i$ calculated from $\log K_1(\text{obs}) = 5.7$ is definitely higher than the observed:

$$\log K_2(\text{calc}) = 5.1 \text{ for } \log K_2(\text{obs}) = 4.1 \tag{6}$$

$$\log K_3(\text{calc}) = 4.56 \text{ for } \log K_3(\text{obs}) = 3.2 \tag{7}$$

$$\log K_4(\text{calc}) = 3.11 \text{ for } \log K_4(\text{obs}) = 2.2 \tag{8}$$

Specifically $\log K_1(\text{obs}) = 5.7$ is too high compared to $\log K_1(\text{obs})$ for the NH_3 complex even though the higher basicity of the ligand is taken into account. A literature survey revealed that 5.7 for $\log K_1$ is the highest among the values reported so far.[7] Now data given by Hancock[8] compare favorably with the calculated from $\log K_1(\text{obs}) = 4.50$:

$$\log K_2(\text{calc}) = 3.87 \text{ for } \log K_2(\text{obs}) = 4.05 \tag{9}$$

$$\log K_3(\text{calc}) = 3.36 \text{ for } \log K_3(\text{obs}) = 3.33 \tag{10}$$

Thus the copper(II) complexes with 2-aminoethanol should be included in the group of regular complexes with neither deprotonation of the coordinated ligand nor chelate formation of the deprotonated ligand.[8]

Ligands Giving Complexes of Stability Higher than the Calculated (by More than 0.3 log Unit). Ligands giving higher stability constants are summarized in Table 2. The higher stability constants are ascribed to hydrophobic and aromatic π–π interactions.[1d,1e] Since the hydrophobicity scale of amines is not reported, logarithmic values of partition constants of amines into octanol were utilized as a measure of hydrophobicity[9] and then higher stability constants were correlated to hydrophobicity of amines as well as amino acids bound to copper(II). In this connection a few words are given on copper(II) complexes with phenyl-substituted ethylenediamine and ethanolamine: relevant data are summarized in Table 3. From Table 3 it is evident that substitution with electron-withdrawing phenyl makes ethylenediamine less basic, whereas ethanolamine becomes more basic with the phenyl substitution. As expected more basic ligands form more stable copper(II) complexes. For DL-1-phenylethylenediamine $K_2 > K_1$. This is unusual and should be a result of the π–π aromatic interaction[1e] between coordinated phenyl-en.

Table 3. Stability Constants of Copper(II) Complexes with Ethylenediamine, Ethanolamine, and Their Phenyl Derivative

Ligand (L)	pK_a(HL)	$\log K_1$(CuL)	$\log K_2(CuL_2)$
Ethylenediamine (en)	9.89	10.54	9.06
DL-1-Phenyl-en	8.85	8.36	8.91
Ethanolamine	9.52	5.7	4.1
DL-2-Amino-1-phenylethanol	11.9	9.50	6.0

Table 4. Stability Constants of Copper(II) Complexes with 2,2′-Bipyridyl (bpy), and Substituted 1,10-Phenanthrolines (phen)

Ligand	$\log K_1$(obs)	$\log K_2$(obs)	$\log K_2$(calc)	Dif	Ref.
bpy	8.15	5.50	6.29	−0.79	10e
	8.0	5.60	6.14	−0.54	10b
	8.10	5.34	6.24	−0.90	10c
phen	9.25	6.75	7.39	−0.64	10b
	9.00	6.70	7.14	−0.44	10c
	9.16	6.96	7.30	−0.34	10d
2-Chloro-phen	5.07	5.00	3.22	+1.79	10j
5-Nitro-phen	8.00	5.47	6.14	−0.67	10i
2-Methyl-phen	7.40	6.45	5.54	+0.91	10f
5-Methyl-phen	8.35	6.45	6.49	−0.04	10g
2,9-Dimethyl-phen	5.2	5.8	3.34	+2.46	10f
4,7-Dimethyl-phen	8.76	7.26	6.90	+0.34	10h
5,6-Dimethyl-phen	8.71	7.0	6.85	+0.15	10h

Unusual Stability Constants of Cu–bpy and Cu–phen. Phen and bpy normally stabilize copper(II) ternary complexes with aromatic ligands through π–π and hydrophobic interactions. We, however, have noticed $\log K_1$ values for $[Cu(phen)]^{2+}$ (7.4)[10a] and $[Cu(bpy)]^{2+}$ (6.33)[10a] given in Ref. 3 seem doubtful because they are both lower than the corresponding values for nickel(II) complexes (8.8 for $[Ni(phen)]^{2+}$ and 7.13 for $[Ni(bpy)]^{2+}$.[10b] This would lead to lower stability constants calculated for $[Cu(phen)_2]^{2+}$ and $[Cu(bpy)_2]^{2+}$. Stability constants of copper(II) complexes with bpy, phen, and substituted phen are summarized in Table 4, and have been discussed in relation to the structural change from [CuL] to $[CuL_2]$ and the hydrophobic interactions between coordinated ligands[11d] (Table 2-d in SI). The calculated $\log K_2$ values for $[Cu(bpy)_2]^{2+}$ and $[Cu(phen)_2]^{2+}$ complexes are definitely higher than the observed because the structure of the 1:1 complex is different from that of the 1:2 complex:[11] the 1:1 complex has axially elongated octahedral structure with 4 additional coordinated water molecules. The free energy for the structural change from the distorted octahedron to the trigonal bypyramid was estimated to be $-4.5\,\text{kJ}\,\text{mol}^{-1}$ for the bpy complex and $-2.7\,\text{kJ}\,\text{mol}^{-1}$ for the phen complex.[11d] In this respect the ring-closure should also be noted as the rate-limiting step (chelation-controlled substitution).[12]

It is well known that steric hindrance occurs in the complexes with phen derivatives substituted at the 2- and 2,9-positions.[13] This is why values of $\log K_1$ of these complexes are definitely low as compared to the corresponding constants for complexes with phen substituted neither at 2- nor at 9-posotion. It should be noted that $\log K_2$(obs) for complexes with 2- or 2,9-substituted phen is obviously higher than the calculated value. Particularly it is extraordinary to find $\log K_2$ value for the 2,9-dimethyl-phen complex (5.8, obs) higher than $\log K_1 = 5.2$ (obs) due to both steric hindrance in 1:1 complex and change in structure of 1:2 complex as described above.

Stability Constant of Copper(II) Complexes with Amino Acids. The mechanism of formation of aminocarboxylate complexes has been the subject of extensive study with discussions on the location of the rate-determining step.[12,14,15] Two possible pathways may be assumed for the formation of metal complexes with a mono-anionic ligand like glycinate:

one involving the preferential coordination of the uncharged nitrogen followed by ring-closure at the carboxylate O and the other with the preferential coordination of mono-anionic carboxylate oxygen followed by subsequent ring-closure at the amino N terminus.

In Tables 5 and 6 formation rate constants (k_f) are tabulated for the formation of some aminocarboxylate chelates and related complexes. From Table 5 we realize that for Ni^{2+} and Cu^{2+} $k_f(NH_3) < k_f(\text{chelate})$.[16] We know further that the formation rate constant of nickel(II) amine complexes decreases significantly as a function of increasing bulkiness of and number of alkyl groups on the amine nitrogen.[16d] Then we may conclude the preferential coordination of amino N terminus at the first step, followed by chelation for the formation of aminocarboxylate complexes.

On the other hand, we notice that $k_f(OAc) > k_f(\text{chelate})$ for Ni^{2+} and for Cu^{2+} $k_f(OAc) \cong k_f(\text{chelate})$: the formation of aminocarboxylate chelates may proceed via preferential coordination of carboxylate. Thus previous supposition[1b] of the preferential coordination of the amino N is not justifiable. It should be noted that for Ni^{2+} the ring closure is clearly rate-limiting, whereas for Cu^{2+} the mechanism is close to an I_d (dissociative interchange) mechanism: $k_f(\text{chelate})$ values for copper(II) are slightly higher than $k_f(OAc)$ for glycine,[15a] leucine,[14f] serine,[14j] sarcosine,[15f] and proline.[14g] This may be due to a small internal conjugate base (ICB) effect.[17] The chelation controlled substitution is relevant to copper(II) β-alaninate formation, judging from the ratio $k_f(\text{chelate})/k_f(OAc) = 0.13$. The effect of the rate-limiting ring closure, if any, is included in the donor atom interaction terms δ's.

Table 5. Comparison of Formation Rate Constants of Aminocarboxylate Chelates and Related Complexes, $k_f/M^{-1}\,s^{-1}$, 25 °C, $I = 0.1\,M$[a)]

M^{2+}	Ligand	$\log k_f(L)$	$k_f(\text{chelate})/k_f(NH_3)$	$k_f(\text{chelate})/k_f(OAc)$	Ref.
Ni^{2+}	NH_3	3.65			16d
	CH_3NH_2	3.1			16d
	OAc	5.18			14d
	Gly	4.61	9.1	0.27	14b
	α-Ala	4.48	6.8	0.20	14c
	β-Ala	3.70	1.1	0.03	14c
Cu^{2+}	NH_3	8.3			16c
	OAc	9.18			16d
	Gly	9.53	20	2.24	15a
	α-Ala	9.1	6.5	0.83	15b
	β-Ala	8.3	1	0.13	15b

a) Charges of carboxylate and amino acids are omitted.

The K_{OS} terms are now taken into account and the donor atom–donor atom interaction terms $\delta_{N(AL)O(AL)}$ and $\delta_{O(AL)O(AL)}$ have been revised as given in Table 1 in order to make possible reasonable prediction of stability constants of binary and ternary complexes of copper(II) with aminocarboxylates L and A $[CuL_2]$ and $[CuAL]$. $\log K_2(CuL_2)$ and $\log K(CuA + L)$ are given by eqs 11 and 12:

$$\log K_2(CuL_2) = \log K_1(CuL) - 1.33 \tag{11}$$

$$\log K(CuA + L) = \log K_1(CuL) - 1.03 \tag{12}$$

Stability of binary and ternary copper(II) complexes with aminocarboxylates has been shown to be enhanced by non-covalent interaction between side chains of amino acids. Enhanced stability given by eqs 13 and 14 has been discussed[1d] on the basis of the hydrophobicity of the side chain of amino acids.[18]

$$\Delta K(CuA + L) = \log K(CuA + L)(\text{obs}) - \log K(CuA + L)(\text{calc}) \tag{13}$$

$$\Delta K_2(CuL_2) = \log K_2(CuL_2)(\text{obs}) - \log K_2(CuL_2)(\text{calc}) \tag{14}$$

(1) No extra stabilization occurs in complexes containing the following combination of amino acids: Gly–Gly, Gly–Ala, Gly–Ser, Gly–Thr, Ala–Ala, Ala–Ser, Ala–Thr, Val–Val, Leu–Leu, Ser–Ser, Ser–Thr, and Thr–Thr. These complexes may be regarded as regular. (2) Small but definite stabilization is observed for complexes with the following combination of ligands: Gly–Tyr, Gly–Phe, Ala–Tyr, Ala–Phe, Ser–Tyr, and Met–Met. (3) Stability constants are enhanced appreciably for complexes with the following: Val–Tyr, Ser–Phe, Tyr–Tyr, Tyr–Phe, Tyr–Trp, Phe–Phe, and Trp–Trp.

The extra stabilization given by eqs 13 and 14 is roughly

Table 6. Rate Constants for Complexation of Nickel(II) and Copper(II) with Amino Acids(HL): $k_n/M^{-1}\,s^{-1}$ at 25 °C and $I = 0.1\,M$[a)]

Ligand (L^-)	$M = Ni^{2+}$			$M = Cu^{2+}$		
	$\log k_1$	$\log k_2$	Ref.	$\log k_1$	$\log k_2$	Ref.
Gly	4.61	4.75	11b	9.53	8.60	15a
α-Ala	4.48	4.48	11c	9.10	8.30	15b
β-Ala	3.70	3.78	11c	8.30	6.90	15b
Leu	4.23	4.61	12f	9.20	8.90	14f
Ser	4.46	4.53	12j	9.45 (37 °C)	8.70 (37 °C)	14j
Sar	4.11	4.08	13f	9.45	8.0	15f
α-Abu	4.0 (20 °C)	4.18 (20 °C)				14e
β-Abu	3.60 (20 °C)	3.90 (20 °C)				14e
Proline	4.53	3.94	12g	9.40	8.43	14g
Hydroxyproline	4.08	4.26	12g	8.87	8.45	14g
L-Tyrosine	4.15	4.38	13g	9.04	8.49	15g
L-Phenylalanine				9.08	8.48	15i

a) $[ML_{n-1}]^{(3-n)+} + L^- \rightarrow [ML_n]^{(2-n)+}$

proportional to the hydrophobicity of the side-chain of amino acids $\sum G_t$.[1d,1e,18] The enhanced stability of metal complexes will be related to the enhanced rate of their formation due to the hydrophobic and/or π–π aromatic interactions.[1e,19]

For the stability constants of binary and ternary nickel(II) complexes with amino acids, we have eqs 15 and 16 from eqs 1 and 2, respectively. In deriving these equations, we used $\Sigma\delta'\text{s} = -0.10$, the sum of the δ's involved in chelation-controlled substitution, instead of the normal value of $\sum\delta'\text{s} = -0.19$ obtained from δ_{ij} values in Table 8.

$$\log K_2(\mathrm{NiL_2}) = \log K_1(\mathrm{NiL}) - 0.98 \tag{15}$$

$$\log K(\mathrm{NiA + L}) = \log K_1(\mathrm{NiL}) - 0.68 \tag{16}$$

The extra stabilization due to hydrophobic and/or aromatic π–π interactions is also observed in nickel(II) complexes with the following amino acids: phenylalanine, tyrosine, and tryptophan.

On the other hand, the following amino acids give regular complexes with nickel(II) (the logarithmic stability constants agree with the observed values within 0.2): glycine, α-alanine, DL-2-aminobutanoic acid, norvaline, norleucine, cycloleucine, homoserine, threonine, *N*-methylglycine, *N*-ethylglycine, *N*-propylglycine, *N*-butylglycine, proline, and hydroxyproline.

Stability Constant of Copper(II) Chelates with Polyamines and Aminocarboxylates. For the stability of the chelates of an *n*-dentate ligand, Adamson proposed the following equation:[20]

$$\log K_1(n\text{-dentate}) = \log \beta_n(\text{unidentate}) + (n-1)\log 55.5 \tag{17}$$

He postulates that the chelate effect is largely due to the asymmetry of the standard state. For the overall stability constant of alkylamine $\mathrm{RNH_2}$ complex Hancock and Marsicano[21] proposed eq 18:

$$\log \beta_n[n(\mathrm{RNH_2})] = 1.152\left[n \log K_1(\mathrm{NH_3}) - \left(\sum_{i=1}^{n-1} i\right)\lambda\right] \tag{18}$$

and for a complex with *n*: the number of alkylamine group and *m*: the number of carboxylate group, they proposed

$$\begin{aligned}\log \beta_{n,m}&[n(\mathrm{RNH_2}), m(\mathrm{MeCO_2}^-)]\\ &= 1.152 \log \beta_n(\mathrm{NH_3}) + m \log K_1(\mathrm{MeCO_2}^-) - \left(\sum_{i=1}^{m} i\right)\lambda\end{aligned} \tag{19}$$

The term with λ is a parameter adjusting the decrease in $\log K_n(\mathrm{NH_3})$ or $\log K_m(\mathrm{MeCO_2}^-)$ with increasing *n* or *m*, and 1.152 is for taking into account the increased basicity of alkylamine ($\mathrm{RNH_2}$) compared to ammonia.[21] Equations 18 and 19 have been utilized to predict stability constants of chelate complexes containing amines and/or carboxylates as segments.

Equations 1–4 based on the mechanistic considerations[1] can be utilized to calculate the overall stability constant for a complex involving *n* ($\mathrm{RNH_2}$) (and polydentate amines like en) and *m* ($\mathrm{MeCO_2}^-$) (and also bidentate amino acids like glycine). Then together with eq 17 it is possible to calculate the stability constants of chelates with polyamines and aminocarboxylates. Calculated stability constants of polyamine complexes of nickel(II), cobalt(II), and copper(II) are compared with the observed in Table 7.

Table 7. Stability Constants of Polyamine Complexes of Nickel(II), Cobalt(II), and Copper(II)[a)]

Ligand L[b)]	$\log K_1(\mathrm{ML})$	$\mathrm{Co^{2+}}$	$\mathrm{Ni^{2+}}$	$\mathrm{Cu^{2+}}$
en	calc from $\log K_1(\mathrm{MNH_3})$[c)]	5.84	7.40	10.46
	calc from $\log \beta_2(\mathrm{M(NH_3)_2})$[c)]	5.84	7.35	10.38
	obs[c)]	5.87	7.51	10.54
dien	calc from $\log K_1(\mathrm{MNH_3})$[d)]	8.91	11.26	16.04
	calc from $\log \beta_3(\mathrm{M(NH_3)_3})$[d)]	8.68	11.15	15.55
	obs[d)]	8.4	10.7	16.0
trien	calc from $\log K_1(\mathrm{MNH_3})$[d)]	11.71	14.54	21.01
	calc from $\log \beta_4(\mathrm{M(NH_3)_4})$[d)]	11.34	14.22	19.72
	obs[d)]	11.0	14.0	20.4
tren	calc from $\log K_1(\mathrm{MNH_3})$[d)]	11.71	14.54	21.01
	calc from $\log \beta_4(\mathrm{M(NH_3)_4})$[d)]	11.34	14.22	19.67
	obs[d)]	12.8	14.8	19.22
tetren	calc from $\log K_1(\mathrm{MNH_3})$[c)]	13.78	17.06	—
	calc from $\log \beta_5(\mathrm{M(NH_3)_5})$[c)]	13.04	16.54	—
	obs[c)]	13.20	17.1	22.9
penten	calc from $\log K_1(\mathrm{MNH_3})$[d)]	15.64	19.41	—
	calc from $\log \beta_6(\mathrm{M(NH_3)_6})$[d)]	14.14	18.43	—
	obs[d)]	15.55	19.30	22.44

a) $\delta_{\mathrm{N(AL)N(AL)}}$: Co −0.17, Ni −0.25, Cu −0.33. b) en: 1,2-diaminoethane; dien: iminobis(2-ethylamine); trien: 1,4,7,10-tetraazadecane; tren: nitrilotris(2-ethylamine); tetren: 1,4,7,10,13-pentaazatridecane; penten: ethylenedinitrilotetrakis(2-ethylamine). c) Observed value[4] at 25 °C and ionic strength of 0.1 mol dm^{-3}: $\log K_1(\mathrm{MNH_3})$: 2.02 for cobalt(II), 2.73 for nickel(II), 4.06 for copper(II); $\log \beta_2(\mathrm{M(NH_3)_2})$: 3.56 for cobalt(II), 4.87 for nickel(II), 7.50 for copper(II); $\log \beta_5(\mathrm{M(NH_3)_5})$: 5.28 for cobalt(II), 8.32 for nickel(II). d) Observed value[4] at 20 °C and ionic strength of 0.1 mol dm^{-3}: $\log K_1(\mathrm{MNH_3})$: 2.05 for cobalt(II), 2.77 for nickel(II), 4.13 for copper(II); $\log \beta_3(\mathrm{M(NH_3)_3})$: 4.52 for cobalt(II), 6.66 for nickel(II), 10.48 for copper(II); $\log \beta_4(\mathrm{M(NH_3)_4})$: 5.31 for cobalt(II), 7.81 for nickel(II), 12.59 for copper(II); $\log \beta_6(\mathrm{M(NH_3)_6})$: 4.72 for cobalt(II), 8.45 for nickel(II).

Stability constants of the copper(II) polyamine chelates have been calculated by the combined use of eqs 5 and 17. It should be noted that eq 5 is derived for quadridentate distorted octahedral copper(II) complexes. Therefore it is meaningless to calculate values for chelates with tetren (pentadentate) and penten (hexadentate). On the other hand, only three of the four N donors of tren can occupy the equatorial coordination site of the copper(II) ion. This is why the calculated stability constant for the tren chelate is appreciably higher than the observed value. Meanwhile calculated values for the en, dien, and trien chelates compare favorably with the observed.

For nickel(II) and cobalt(II) the combination of eqs 2 and 17 enables us to predict fairly well the stability constants of polyamine chelates.

Now it is evident that the combined use of eqs 1 and 14 allows us to predict the stability constants of aminocarboxylate chelates. In Table 8 the calculated stability constants are compared with the observed for some nickel(II) and copper(II) chelates of aminocarboxylates. In this table we see that the calculated stability constants of copper(II) chelates of glycine, iminodiacetate, ethylenediaminemonoacetate, and ethylenedi-

Table 8. Stability Constants of Aminocarboxylate Chelates of Nickel(II) and Copper(II)[3] a)

Ligand b)		Ni^{2+}	Cu^{2+}	Constants utilized c)
gly	calc	5.75	8.07	K_1(MOAc) and K_1(MNH_3)
	obs	5.78	8.15	
ida	calc	7.76	11.04	K_1(MOAc) and K_1(Mgly)
	obs	8.13	10.57	
nta	calc	9.43	12.96	K_1(MOAc) and K_1(Mida)
	obs	11.50	12.94	
edma	calc	10.45	14.14	K_1(MNH_3) and K_1(Mgly)
	calc	10.16	13.79	K_1(Men) and K_1(MOAc)
	obs	10.51	13.47[6e]	20 °C for nickel(II)
edda(*N*,*N*)	calc	12.80	16.46	K_1(MNH_3) and K_1(Mida)
	obs	13.73	16.2	20 °C for nickel(II)
edda(*N*,*N*′)	calc	12.12	16.71	(Mgly)
	calc	12.22	16.77	β_2(Mgly)
	obs	13.65	16.2	
edta	calc	17.44	20.21	K_1(Mida)
	calc	15.84	18.28	β_2(Mida)
	obs	18.52	18.70	

a) 25 °C and Ionic strength of 0.1 M unless otherwise noted. $\delta_{N(AL)N(AL)}$: Ni −0.25, Cu −0.33; $\delta_{N(AL)O(AL)}$: Ni +0.11, Cu −0.10; $\delta_{O(AL)O(AL)}$: Ni −0.16, Cu −0.10. b) gly: glycine; ida: iminodiacetate; nta: nitrilotriacetate; edma: ethylenediamine-monoacetate; edda(*N*,*N*): ethylenediamine-*N*,*N*-diacetate; edda(*N*,*N*′): ethylenediamine-*N*,*N*′-diacetate; edta: ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetate. c) $\log K_1(\text{NiOAc}) = 0.87$,[22] $\log K_1(\text{CuOAc}) = 1.75$,[22] $\log K_1(\text{NiNH}_3) = 2.73$,[4] $\log K_1(\text{CuNH}_3) = 4.06$,[4] $\log \beta_2(\text{Nigly}) = 10.58$,[3] $\log \beta_2(\text{Cugly}) = 15.03$,[3] $\log \beta_2(\text{Ni(ida)}) = 14.1$,[3] and $\log \beta_2(\text{Cu(ida)}) = 16.54$[3] at 25 °C and ionic strength of 0.1 M.

aminediacetate compare favorably with the observed values.

For copper(II) it is meaningless to discuss calculated values of chelates with nta, edda(*N*,*N*) and edta, because at least one carboxylate cannot occupy equatorial position of the distorted octahedral structure. In this connection it is noted that the stability constant of copper(II) edta chelate calculated from K_1(Cu(ida)) is significantly higher than the observed, while the corresponding value calculated from $\beta_2(\text{Cu(ida)}_2)$ compares favorably with the observed. This is because in $[\text{Cu(ida)}_2]^{2-}$ two acetate groups coordinate weakly to the axial site of the distorted octahedron as in $[\text{Cu(edta)}]^{2-}$.

For nickel(II) the prediction of stability constants of aminocarboxylate chelates is successful only in the case of glycine, iminodiaetate and ethylenediamine monoacetate.

Conclusion

Stability constants of 185 copper(II) amine complexes were calculated based on the equations derived from mechanistic considerations of copper(II) complex formation and the values were compared with the observed. By means of the difference of the observed and calculated values we classified ligands as "regular" and "non-regular" complexes. Most stability constants are regular (difference < 0.3 in log), whereas some observed stability constants deviate from the calculated. The lower stability constants were due to steric hindrance for bulky ligands and for phen and bpy complexes. Unusual reaction mechanism like chelation-controlled substitution yields lower stability. Logarithmic values of partition constants of amines into octanol were utilized as a measure of hydrophobicity and then higher stability constants were correlated to hydrophobicity of amines as well as amino acids bound to copper(II). Mechanistic considerations have also successfully been utilized in prediction of stabilities of metal chelates with polyamines and aminocarboxylates of nickel(II), cobalt(II), and copper(II) from their stability constants of 1:1 complexes with NH_3 and CH_3COO^- according to the Adamson' approach.

Supporting Information

Calculated and observed stability constants of copper(II) complexes (Tables 1-a, 1-b, 1-c, and 1-d: Aliphatic Amines and Anilines; Tables 2-a, 2-b, 2-c, and 2-d: Heterocyclic Amines). Ordering information is given on any current masthead page. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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