Formation and Stability of Ternary Complexes of Copper(II) with Ethylenediamine-*N*-acetic Acid and Amino Acids in Aqueous Solution

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The stability constants have been determined potentiometrically for the ternary copper(II)–edma–amino acid systems, where edma refers to ethylenediamine-*N*-acetate, and amino acid to glycine (Gly), L-alanine (Ala), L-norvaline (Nor), L-phenylalanine (Phe), or L-tryptophan (Trp). The tendency of mixed complex formation ($\Delta \log K$) decreased in the order Trp $>$ Phe $>$ Nor $\simeq$ Ala $\simeq$ Gly. The stability enhancement in the complex formation equilibria was found to be additive and proportional to the aromatic ring size. This trend can be explained on the basis of the proximity of an aromatic ring to the central copper(II) ion increasing the electronegativity of the metal by both copper(II)–aromatic ring interactions and decreased hydration. The co-ordination types of these complexes are discussed.

Transition metal ions in biological systems most probably exist in the form of different ternary complexes. Thus, the enzyme–metal–substrate complex, formed as an intermediate product in enzymatic reactions in the presence of a metal ion, is a kind of mixed-ligand complex, and the reaction itself is regarded as a ligand–ligand contact supported by the co-operative action of the central metal ion. The solution equilibria of bivalent metal-ion complexes with ethylenediamine-*N*-acetic acid (Hedma) and related ligands, described in the present paper, have been investigated[1–6] for many years. In particular, the Cu^{II}–edma system[7] has been extensively studied, both in terms of stability constants and the species existing in aqueous solution. Absorption and circular dichroism (c.d.) spectral properties in water and in 50% aqueous ethanol have been carried out on copper(II)–edma–amino acid systems[8] in order to obtain structural information. In recent years, the study of the mixed-ligand complexes of transition metal ions has become of great interest as their existence provides evidence of different structures due to various types of ligand stacking. In view of the biological importance of the aromatic moiety in the copper co-ordination sphere, I carried out a potentiometric study of the ternary complexes consisting of a tridentate ligand (edma) and an amino acid in order to shed light on the intramolecular electrostatic ligand–ligand interactions and on the electronic effects of aromatic rings by accurate examination of the formation constants. Among the intramolecular ligand–ligand interactions occurring in ternary complexes, the stacking interactions between suitable aromatic moieties of the co-ordinated ligands are of particular interest. For example, the aromatic ring of phenylalanine and the indole moiety of tryptophan contribute to the stability of Cu^{II} ternary complexes through π-back donation and aromatic ring stacking.

Experimental

Reagents.—Ethylenediamine-*N*-acetic acid bis(hydrogen chloride) dihydrate (Hedma·2HCl·2H_2O) was prepared and purified using doubly distilled water by the method described by Fujii *et al.*[1] Its purity was checked by analysis (Found: C, 20.60; H, 7.20; N, 12.45. Calc. for $C_4H_{16}Cl_2N_2O_4$: C, 21.15; H, 7.10; N, 12.35%) and the concentrations of edma or hydrogen chloride solutions were estimated from potentiometric titrations by using the interpolation of Fortuin.[9] Glycine (Gly), L-alanine (Ala), L-norvaline (Nor), L-phenylalanine (Phe), and L-tryptophan (Trp) were Merck or C. Erba RPE products and were used without further purification (purity > 99.5%). Concentrations of stock solutions of amino acids and bivalent metal chlorides (AnalaR Products) were determined by conventional analytical methods. All other chemical reagents employed were of the highest grade available and were used as previously described.[10–12]

Potentiometric Measurements.—The potentiometric measurements were made by using a Metrohm Titroprocessor E 636, equipped with an H 268 glass electrode (Schott-Jena glass) and a B 343 Talamid reference electrode (Schott-Jena glass). The alkalimetric titrations were carried out at 25 ± 0.1 °C and I = 0.5 mol dm^{-3} KCl as previously reported[7,12] for solutions of binary and ternary systems containing copper(II), edma, and/or amino acid at different molar ratios. In the potentiometric measurements the standard potential of the chain, E°, the coefficients of the correction terms for both effects of liquid junction potential in acid (A_j) and basic (B_j) solution, the concentration of the potassium hydroxide solution, and K_w were determined before and after each experiment using the computer program NBAR[13] following the calculation procedures described previously.[7,12,14] The results reported in Table 1 show excellent agreement between the parameters (E°, N, A_j, and B_j) calculated in acid and in alkaline solution. Moreover, the liquid junction potentials in acid and basic solution, which are relatively small and not very significant in the refinement of the equilibrium constants, have not been included. All the calculations were performed on the CDC CYBER computer 70/76 of the Consorzio per la Gestione del Centro di Calcolo Elettronico Interuniversitario dell'Italia Nord Orientale, Casalecchio, Bologna, with financial support from the University of Parma. The compositions of the starting solutions for each potentiometric titration are quoted in Table 2.

Calculations.—The stability constants, β_{pqrs}, which are defined by equation (1) (charges are omitted for simplicity),

$$p\mathrm{Cu} + q\mathrm{L} + r\mathrm{A} + s\mathrm{H} \rightleftharpoons \mathrm{Cu}_p\mathrm{L}_q\mathrm{A}_r\mathrm{H}_s \qquad (1)$$

$$\beta_{pqrs} = [\mathrm{Cu}_p\mathrm{L}_q\mathrm{A}_r\mathrm{H}_s]/[\mathrm{Cu}]^p[\mathrm{L}]^q[\mathrm{A}]^r[\mathrm{H}]^s$$

were refined by the method of rigorous least squares using the computer program BETAREF;[15] p, q, r, and s are the number of Cu^{II}, edma (L), amino acid (A), and proton, respectively, in the complex $Cu_pL_qA_rH_s$. The program BETAREF calculates the values of the cumulative protonation or formation constants which minimize the sum of the squared

Table 1. Evaluation of $E^{\ominus}$ (standard potential),* A_j and B_j (junction potentials/mV mol^{-1}), N (normality of KOH), and K_w (ionic product) from potentiometric titrations of HCl with KOH both in acidic and alkaline media, using the NBAR program

Run no.	$E^{\ominus}$/mV Acid	$E^{\ominus}$/mV Basic	A_j Acid	B_j Basic	N/mol dm^{-3} Acid	N/mol dm^{-3} Basic	10^{14} K_w
1	1 162.9(2)	1 162.8(1)	−42.8	−98.2	0.407 845	0.409 342	2.1997
2	1 161.2(1)	1 161.3(1)	17.2	−47.9	0.408 286	0.409 996	2.1897
3	1 160.2(1)	1 160.5(1)	20.7	−140.7	0.408 183	0.409 587	2.3397
4	1 162.8(1)	1 162.6(1)	12.9	−110.9	0.271 369	0.271 611	2.2317
5	1 160.8(1)	1 161.2(2)	−6.7	−162.4	0.272 375	0.273 450	2.2237
6	1 162.4(1)	1 162.5(1)	−3.0	−112.7	0.271 490	0.271 758	2.1694
7	1 159.7(1)	1 160.2(1)	−9.8	−154.2	0.271 686	0.272 890	2.1842
8	1 159.7(1)	1 160.1(2)	−10.4	−154.2	0.272 544	0.272 890	2.1722
9	1 161.1(1)	1 160.7(1)	−36.5	−98.5	0.272 041	0.272 962	2.1838
10	1 159.5(1)	1 160.1(1)	22.8	−131.2	0.272 526	0.272 614	2.2144
11	1 160.9(1)	1 160.3(1)	−24.0	−68.5	0.272 019	0.272 775	2.1833

* Standard deviations in $E^{\ominus}$ are given in parentheses.

Table 2. Complex formation constant determinations. Initial concentrations (T_{Cu}, T_L, T_A, T_H/mmol) of the reagents* for alkalimetric titrations of the copper(II)–edma–amino acid systems at 25 °C and I = 0.5 mol dm^{-3} KCl

Run no.	System	T_{Cu}	T_L	T_A	T_H
1	Cu^{II}–edma–Gly	0.042 95	0.338 49	0.358 33	1.401 86
2		0.053 69	0.451 32	0.519 12	1.910 48
3		0.111 10	0.457 21	0.520 26	1.940 08
4		0.161 06	0.338 49	0.414 55	1.458 07
5		0.214 74	0.564 15	1.013 05	2.752 26
6		0.107 37	0.451 32	0.731 32	2.122 68
7		0.064 42	0.406 19	0.415 08	1.667 31
8	Cu^{II}–edma–Ala	0.026 84	0.473 89	0.362 86	1.823 80
9		0.107 37	0.473 89	0.395 07	1.856 01
10		0.161 06	0.473 89	0.413 93	1.874 86
11		0.053 69	0.676 98	0.464 55	2.551 60
12		0.080 53	0.676 98	0.599 01	2.686 06
13		0.107 37	0.225 66	0.481 50	1.177 18
14		0.107 37	0.112 83	0.702 49	1.050 33
15	Cu^{II}–edma–Nor	0.068 72	0.451 32	0.177 04	1.568 40
16		0.128 84	0.451 32	0.264 28	1.655 64
17		0.171 79	0.496 45	0.384 12	1.914 62
18		0.096 63	0.338 49	0.417 50	1.461 02
19		0.064 42	0.564 15	0.541 53	2.280 73
20		0.150 32	0.315 92	0.509 18	1.483 13
21		0.064 42	0.338 49	0.384 81	1.428 33
22	Cu^{II}–edma–Phe	0.064 42	0.406 22	0.504 88	1.757 20
23		0.128 84	0.451 36	0.673 17	2.064 63
24		0.171 79	0.338 52	0.841 46	1.885 06
25		0.257 69	0.451 36	0.420 73	1.812 20
26		0.107 05	0.564 20	0.639 51	2.378 84
27	Cu^{II}–edma–Trp	0.214 10	0.451 36	0.301 99	1.693 46
28		0.107 05	0.338 52	0.301 99	1.345 99
29		0.107 05	0.451 36	0.483 19	1.874 65
30		0.214 10	0.564 20	0.362 39	2.101 72

* T_L = mmol of edma, T_A = mmol of amino acid in the titration vessel.

$$U = \sum_{i=1}^{Z} w_i(E_i^{\text{obs.}} - E_i^{\text{calc.}})^2 \qquad (2)$$

residual between observed and calculated e.m.f. values, equation (2); Z is the total number of potentiometric data and w_i is the weighting factor assigned to the i-th observation. The parameter w_i is defined by equation (3) (v = volume of KOH added)

$$w_i = 1/\sigma_i^2 = 1/[\sigma_E^2 + (\partial E_i/\partial v_i)^2\sigma_v^2] \qquad (3)$$

using the cubic spline interpolation method, with the modification from Stanton and Hoskins.[16] At first the protonation constants for some of the ligands (edma, Nor, and Trp) were determined separately through the refinement of several sets of potentiometric data; the values obtained were introduced as constants into the refinement process of the complex formation constants for binary systems. At this point all the known β_{pqrs} values were kept constant and the computer program BETAREF was employed for a second stage of refinement in which solutions containing various ratios of copper(II)–edma–amino acid were processed in order to explore the ternary systems. In the final section of calculations to determine the formation constants of the ternary complexes, the initial amounts (mmol) of reagent (T_L, T_H) were minimized for each titration also. The standard deviations in the refined quantities were very small and in the light of the statistical analysis of data, the results were good. Many protonation and stability constants, for binary complexes under the same experimental conditions, used in the refinement were taken from the literature (see refs. in Table 3).

Results and Discussion

The calculated formation constants, log β_{pqrs}, of the binary and ternary complexes are given in Table 3. Using the stability constants in Table 3 and the protonation constants of the ligands under the same experimental conditions, the percentage of each complex involving Cu^{2+}–edma–amino acid has been calculated with the aid of the HALTAFALL computer program.[17] The results were reported by a PLOTTER Calcomp 936 on-line to give profiles of the distribution of each complex species *versus* pH applicable to various concentrations of ligands and metal ion. A typical species-distribution graph for the copper(II)–edma–alanine mixture is shown in Figure 1. The titration curve (Figure 2) of the protonated ligand (H_3L^{2+}) in the presence of amino acid and Cu^{2+} is clearly different from those of the protonated ligand alone or in the presence of Cu^{2+}. These curves did not reveal an appreciable complexing capacity in the strongly acidic media, but showed, after neutralization of the COOH groups, two distinct buffer zones, at pH intervals of *ca.* 2.5—3.9 and 5.2—6.8, respectively. The tendency of mixed complex formation can be demonstrated in various ways. As is usual, to compare the stability of ternary complexes with that of the parent binary ones, the constant log $K'^{CuL}_{Cu(L)A}$ according to equilibrium (4) was calculated from equation (5). Of course,

Table 3. Stability constants (log β_{pqrs}) of binary (Cu_pL_q or Cu_pA_r) and ternary complexes ($Cu_pL_qA_rH_s$) with related parameters[a] (Δ log *K*, log *K*′, log *X*) at 25 °C and I = 0.5 mol dm^{-3} KCl; estimated standard deviations (σ) are given in parentheses

	log β_{pqrs}		
pqrs	edma^{b}	dben^{c}	en^{d}
1100	12.854(11)	7.963(2)	10.523
1200	20.373(19)	12.754(9)	19.505
0101	9.888(2)	8.938(1)	9.976
0102	16.860(3)	14.941(2)	17.148
0103	18.350(4)		

	log β_{pqrs}					
pqrs	Gly^{e}	Ala^{e}	Val^{d}	Nor	Phe^{e}	Trp
1010	8.14(2)	8.14(7)	8.049	8.155(3)	7.86	8.145(6)
1020	14.97(10)	14.90(10)	14.913	15.034(4)	14.77	15.678(7)
0011	9.54(1)	9.66(2)	9.573	9.186(2)	9.11(2)	9.381(5)
0012	11.90(4)	11.95(2)		11.453(3)	11.29(3)	11.751(6)

		log β_{pqrs}						log *K*′					
HA	*pqrs*	edma	dben^{c}	en^{c}	edta^{f}	bipy^{g}	phen^{g}	edma	dben^{c}	en^{c}	edta^{f}	bipy^{g}	phen^{g}
Gly	1110	18.244(5)			21.25(8)			5.39 10.10			2.95 13.25		
Ala	1110	18.284(13)	15.853(2)	17.949(3)				5.43 10.14	7.89 7.52	7.43 9.62			
Val	1110		15.695(1)	17.726(2)					7.73 7.65	7.20 9.68			
Nor	1110	18.348(9)						5.49 10.19					
Phe	1110	18.225(7)	15.487(4)	17.746(1)	20.97(7)			5.37 10.37	7.52 7.56	7.22 9.82	2.67 13.38		
Trp	1110	18.837(9)	16.113(2)	18.078(3)	21.42(5)			5.98 10.69	8.15 8.09	7.56 10.06	3.12 13.38		
dhb	1110					22.39	23.56(3)					14.39 8.43	14.31 9.60
dhbds	1110					22.39(2)	23.44(1)					14.39 8.11	14.19 9.16
dhmb	1110					21.39(1)	22.56(1)					13.39 8.39	13.31 9.56
dhns	1110					22.52(6)	23.90(7)					14.52 8.69	14.65 10.07

		Δ log *K*						log *X*					
HA	*pqrs*	edma	dben^{c}	en^{c}	edta^{f}	bipy^{g}	phen^{g}	edma	dben^{c}	en^{c}	edta^{f}	bipy^{g}	phen^{g}
Gly	1110	−2.75			−5.05			1.15					
Ala	1110	−2.71	−0.44	−0.90				1.30	3.68	1.12			
Val	1110		−0.32	−0.85					3.72	1.03			
Nor	1110	−2.66						1.29					
Phe	1110	−2.49	−0.41	−0.71	−4.92			1.31	3.39	1.15			
Trp	1110	−2.16	+0.13	−0.47	−4.92			1.62	3.91	1.09			
dhb	1110					0.43	0.35					6.15	6.09
dhbds	1110					0.11	−0.09					5.76	5.46
dhmb	1110					0.39	0.31					6.12	6.06
dhns	1110					0.69	0.82					6.60	6.96

[a] All the parameters were calculated starting from the equilibrium constants reported in the original papers; log *K*′ values were obtained by equations (5) and (6). Abbreviations: bipy = 2,2′-bipyridyl, phen = 1,10-phenanthroline, dhb = 1,2-dihydroxybenzene, dhbds = 1,2-dihydroxybenzene-3,5-disulphonate, dhmb = 1,2-dihydroxy-3-methoxybenzene, dhns = 6,7-dihydroxynaphthalene-2-sulphonate, en = ethylenediamine, dben = N,N′-dibenzylethylenediamine. [b] Data taken from ref. 7. [c] Data taken from ref. 28. [d] Data taken from G. Brookes and L. D. Pettit, *J. Chem. Soc., Dalton Trans.*, 1977, 1918. [e] Data taken from A. E. Martell and R. M. Smith, 'Critical Stability Constants,' Plenum Press, New York and London, 1974, vol. 1. [f] Data taken from ref. 30. [g] Data taken from H. Sigel, P. R. Huber, R. Griesser, and B. Prijs, *Inorg. Chem.*, 1973, **12**, 1198.

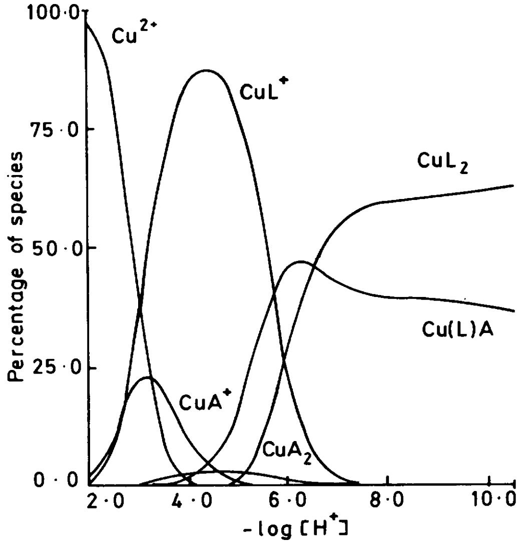

Figure 1. Typical distribution diagram for the Cu^{II}–edma–L-alanine system. The percentage of each species has been calculated from the data of a hypothetical solution of copper ions (0.006 442 mol dm^{-3}), edma (0.010 955 mol dm^{-3}), and L-alanine (0.022 557 mol dm^{-3}) by the HALTAFALL program, equipped with a PLOTTER Calcomp 936. The concentrations of the species not containing metal have been calculated, but are not reported, for simplicity

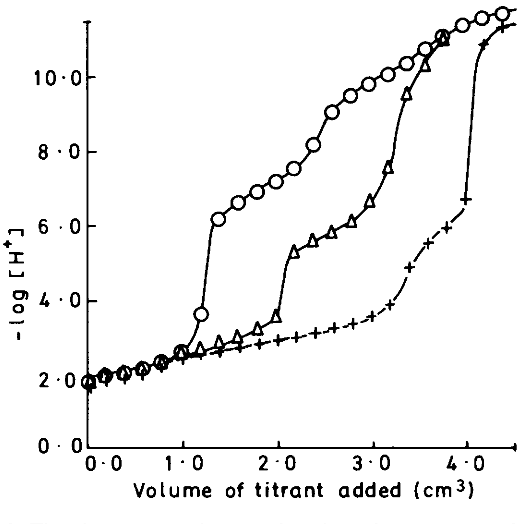

Figure 2. Titration curves of pH as function of the volume of KOH added, calculated by HALTAFALL program (N. Ingri, W. Kakalowicz, L. G. Sillén, and B. Warnqvist, *Talanta*, 1967, **14**, 1261), equipped with a PLOTTER Calcomp 936; edma (○), edma–Cu^{2+} (△), and edma–Ala–Cu^{2+} (+). Initial concentrations of solutions: (○) $c_H = 5.687 \times 10^{-2}$, $c_L = 1.896 \times 10^{-2}$, $c_{KOH} = 0.3873$ mol dm^{-3}, $V_0 = 25$ cm^3; (△) $c_H = 5.687 \times 10^{-2}$, $c_L = 1.896 \times 10^{-2}$, $c_{Cu} = 0.644 \times 10^{-2}$, $c_{KOH} = 0.3873$ mol dm^{-3}, $V_0 = 25$ cm^3; (+) $c_H = 6.331 \times 10^{-2}$, $c_L = 1.896 \times 10^{-2}$, $c_A = 0.644 \times 10^{-2}$, $c_{Cu} = 1.656 \times 10^{-2}$, $c_{KOH} = 0.3873$ mol dm^{-3}, $V_0 = 25$ cm^3

$$\mathrm{CuL} + \mathrm{A} \rightleftharpoons \mathrm{Cu(L)A};\ K'^{\mathrm{CuL}}_{\mathrm{Cu(L)A}} = \frac{[\mathrm{Cu(L)A}]}{[\mathrm{CuL}][\mathrm{A}]} \qquad (4)$$

$$\log K'^{\mathrm{CuL}}_{\mathrm{Cu(L)A}} = \log \beta_{1110} - \log \beta_{1100} \qquad (5)$$

one may also consider the reaction between CuA and L (A = monodeprotonated amino acid, L = $edma^-$); the corresponding equilibrium constant log $K'^{\mathrm{CuA}}_{\mathrm{Cu(L)A}}$ was calculated according to equation (6).

$$\log K'^{\mathrm{CuA}}_{\mathrm{Cu(L)A}} = \log \beta_{1110} - \log \beta_{1010} \qquad (6)$$

There are two convenient ways to characterize the stability of mixed-ligand complexes. One is according to equation (7), *i.e.*, by comparing the difference in stability, Δ log *K*,[18]* *e.g.* for the reaction between CuL and CuA [equation (7)]. This parameter

$$\mathrm{CuL} + \mathrm{CuA} \rightleftharpoons \mathrm{Cu(L)A} + \mathrm{Cu}$$

$$\Delta \log K = \log \beta_{1110} - \log \beta_{1100} - \log \beta_{1010} \qquad (7)$$

may be the most convenient because there is no change in the net charge of the mixed complexes investigated. The other is based on the disproportionation constant, log *X*, as defined by equilibrium (8) [calculated with equation (9)].

$$\mathrm{CuL_2} + \mathrm{CuA_2} \rightleftharpoons 2\mathrm{Cu(L)A};\ X = \frac{[\mathrm{Cu(L)A}]^2}{[\mathrm{CuL_2}][\mathrm{CuA_2}]} \qquad (8)$$

$$\log X = 2 \log \beta_{1110} - \log \beta_{1200} - \log \beta_{1020} \qquad (9)$$

Generally, one would expect to observe negative values for Δ log *K* [equation (7)], since usually it holds that $\beta_{1010} > K^{\mathrm{CuA}}_{\mathrm{CuA_2}}$ or $\beta_{1100} > K^{\mathrm{CuL}}_{\mathrm{CuL_2}}$ (*cf.* Table 3). The method using equilibrium (8) for characterization of mixed complexes is somewhat more objective, as the value expected for *X* can be obtained from statistical arguments: $X = 4$, *i.e.* $\log X = 0.6$.[20,21] Table 3 gives the stability constants for different mixed-ligand complexes and derived constants relating to the substitution and addition process. The experimental data referring to the mixed-ligand complexes of edma with amino acids show that it forms more stable mixed complexes than those of ethylenediaminetetra-acetate (edta), while various substituted amines exhibit a relatively higher stability in mixed ternary complexes with amino acids. The Δ log *K* values increase in the order edta < edma < amines. A straight-line relationship of positive slope was observed by plotting complex stability (Δ log *K*) against ligand basicity (ΣpK_a or log β_{010x} of nitrogen atoms; *x* indicates the number of protons bound to the ligand). These conclusions have been confirmed in subsequent studies of mixed-ligand complexes.[22] An additional factor favouring complexation of edta or edma systems is the presence of the carboxylate groups, which appear to interact with copper(II). Values of log *K′* in all the systems examined indicate that the ternary complexes are more stable than the corresponding binary ones of ML or MA type, but this doesn't always take place for binary complexes of ML_2 or MA_2 type. It can be stated from Table 3 that log β_{1110} of the copper(II)–edma–Gly (or Ala, Nor) system increases slightly, because of the electron-donating effect of the alkyl moiety. The side-chain shows a distinct influence[23] on the equilibrium constants of the complexes. In fact the only effects which the substituents can have will be through their inductive effect on the α-amino group and increasing the alkyl side-chain leads to higher stability of the complex which is also shown by the commencement of complex formation at lower pH values. The crucial point of Figure 3 is, however, that all the ternary complexes containing a phenyl moiety are significantly more stable than expected on the basis of the glycine-like chelate with N,O donor atoms. The Δ log *K* values increased in the order Nor < Phe < Trp, where the second involves a benzene ring and the last an indole ring. The result suggests that the stabilization of ternary complexes depends upon the aromatic ring size. The stability enhancements may be explained by solvation effects alone. Further, in support of this, the log K_2 enhancement observed for $Cu(Tyr)_2$

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* For a general discussion of the factors governing the stability of mixed-ligand complexes, see ref. 19.

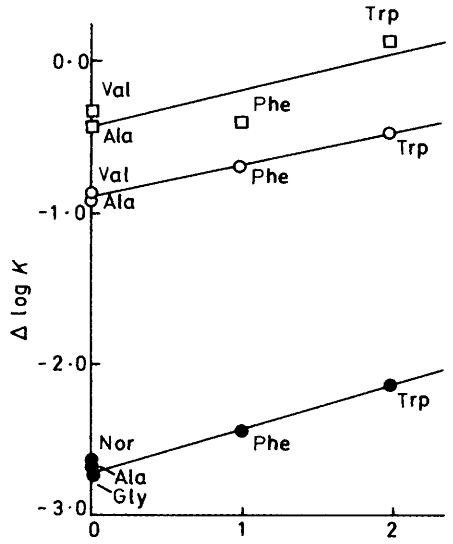

Figure 3. Relationship between Δ log *K* and aromatic ring size in Cu^{II}–edma–amino acid (●), Cu^{II}–en–amino acid (○), and Cu^{II}–dben–amino acid systems (□)

(Tyr = tyrosine) and Cu(Trp)$_2$ complexes in water disappears in dioxane–water (1:1 v/v) mixture[24] which mimics the decreased hydration of copper(II) complexes as a whole by side-chain aromatic rings. The influence of the solvent–side-chain interactions on total stability constants has been shown in various systems, *e.g.* copper(II)–dipeptide systems.[25] The importance of solvation was also proposed in determining the preferential orientation of the aromatic side-chain.[26] The Δ log *K* values for Cu^{II}–amine–aromatic amino acid systems are enhanced relative to those for Cu^{II}–edma–aromatic amino acid systems, but the differences in Δ log *K* between Cu^{II}–amine–amino acid and Cu^{II}–edma–amino acid systems are approximately the same with regard to the amino acid involved (*cf.* straight lines of Figure 3). This suggests that the formation of ternary complexes involving an aromatic ring is apparently proportional to the ring size. Moreover, the presence of an aromatic ring above the Cu^{II} co-ordination plane[27] is probably essential for the preference in the formation of ternary complexes. However, when an aromatic ring is located above the copper(II) plane it generates an increase in the electronegativity of copper(II) and thus its affinity for the second ligand through electron flow *via* copper(II) ⟶ aromatic ring and a decrease in hydration of the central ion including removal of the apically co-ordinated water molecule.[28–31]

By using the results of Table 3, the values for Δ log *K* [equation (7)] and log *X* [equation (9)] were calculated. These data are listed in Table 3 together with some results taken from the literature. A comparison of the data for a mixed-ligand system containing 2,2′-bipyridylcopper(II) or 1,10-phenanthrolinecopper(II) and a ligand with O-donor atoms demonstrates unequivocally that the electron density in the ligand with O-donor atoms has a significant influence on the stability of the ternary Cu^{2+} complexes. The log *X* values, reported in Table 3, give good evidence for such behaviour: the ternary complexes formed with ligands containing mixed N- and O-donor atoms are remarkably less stable than those formed with ligands having only O-donor atoms. In the ternary complex, bidentate and tridentate modes bonding would be expected, as in the binary mono- and bis-complexes. This may be easily accounted for by considering the tridentate bonding of edma *via* the N-amine and O-carboxylate groups and the bidentate bonding of the amino acid in a glycine-like manner.

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