Inorganica Chimica Acta, 20 (1976) 19–25

Thermodynamic and Structural Study of the Parent and Some Mixed Ligand Complexes of Histamine and 1,3-Diaminopropane with Copper(II) and Nickel(II) Ions

A. GERGELY and I. SÓVÁGÓ

Institute of Inorganic and Analytical Chemistry, Lajos Kossuth University, H-4010 Debrecen, Hungary

Received February 9, 1976

pH-metric equilibrium studies were used to determine the stability constants of the copper(II) and nickel(II) complexes of histamine and 1,3-diaminopropane. In the copper(II)–histamine system it was found that, in addition to the parent complexes CuA^{2+} *and* CuA_2^{2+}*, a protonated complex* CuA_2H^{3+} *and mixed hydroxo complexes* $Cu_2A_2(OH)_2^{2+}$ *and* $CuAOH_n^+$ *are also formed. The protonated complex* CuA_2H^{3+} *is formed in the case of a higher ligand excess at around pH = 5–6, and it is probable that one of the imidazole N atoms does not take part in the coordinate bonding. Electron excitation and ESR spectral data revealed that a certain distortion of the bonds must be reckoned with in the copper(II)–histamine complex of composition* CuA_2^{2+}*, because of steric reasons, and this phenomenon increases the stability of the mixed ligand complexes.*

Introduction

During the past twenty years, numerous authors have dealt with the investigation of the complex-forming properties of histamine, which is of importance, among others, from a biological aspect [1]. As regards its transition metal complexes, studies on its complexes with copper(II) and nickel(II) ions have included the determination of equilibrium and thermodynamic data [2–7]. However, very considerable differences were sometimes observed in the earlier-determined data. This can probably be explained by the fact that the authors referred to assumed the formation only of the parent complexes MA^{2+} and MA_2^{2+} in the copper(II)–histamine and nickel(II)–histamine systems.

Attention was first drawn to the possibility of formation of hydroxo complexes in the copper(II)–histamine system by Perrin and Sharma [8]. In the systems with a metal:ligand ratio of 1:1, Eilbeck *et al.* [9] later similarly suggested the formation of mixed hydroxo complexes in the pH range > 6. More recently, in solutions of similar composition, Aiba *et al.* [10] used magnetic measurements to prove the formation of the diamagnetic binuclear mixed hydroxo complex of composition $Cu_2A_2(OH)_2^{2+}$. In the higher pH range, these authors also strongly suggested deprotonation of the –NH– group of the imidazole ring. However, if the metal:ligand ratio is larger than 1:2, then the authors referred to considered that below pH ~ 7 no other species need be taken into account apart from the complexes CuA^{2+} and CuA_2^{2+}.

In contrast with the above, in one of our earlier publications [11] relating to the copper(II)–histamine system it was assumed that other equilibrium processes besides the formation of CuA^{2+} and CuA_2^{2+} must be taken into consideration even at pH ~5–6. These contradictions made it necessary for further examinations to be carried out in the interest of a better understanding of the complex-forming properties of histamine. Similarly to 1,3-diaminopropane, histamine forms a six-membered chelate ring. However, because of the large size of the molecule and the participation of the hetero N atom in complex formation, the complex-forming properties of histamine may differ considerably from those of the aliphatic diamine. Consequently, in order to draw appropriate conclusions it is logical to compare the behaviours of the two ligands; the investigations were thus extended to the complexes of 1,3-diaminopropane too.

In accordance with the above, the aim of this work was the study of the equilibrium and structural conditions of the parent complexes of copper(II) and nickel(II) ions with histamine and with 1,3-diaminopropane, and also of their mixed ligand complexes containing glycine.

Experimental

Chemicals

The chemicals used were Reanal products of p.a. quality. The glycine and histamine·2HCl were purified by recrystallization from ethanol–water mixtures, and the 1,3-diaminopropane by vacuum distillation. The concentrations of stock solution of 1,3-diaminopropane containing excess acid were determined potentiometrically, with the use of the Gran function [12]. Concentrations of copper(II)

chloride and nickel(II) chloride solutions were checked gravimetrically *via* the oxinates.

pH-Metric Measurements

pH-Metric examinations for the determination of stability constants were carried out at 25 °C, with an ionic strength of 0.2 mol/dm^3 KCl, in the manner reported previously [11]. The measurement of pH was performed with a Radiometer pHM-72 instrument, using G-202-B glass and K-101 calomel electrodes. In the study of the copper(II)–histamine system, titrations were made at 8 different metal: ligand ratios, while in the other cases they were generally made at 3 different ratios. In every case the concentration of the ligand was 0.01 mol/dm^3. The concentration of the metal ion was varied in the interval 0.002–0.01 mol/dm^3.

Calorimetric Measurements

These measurements were performed with an LKB 8700-2 titration calorimeter. In the course of the measurement the sample (metal ion + ligand) in the 100 cm^3 reaction vessel was titrated continuously with KOH solution of known concentration. The titration was carried out with a Radiometer ABU-13 automatic burette. The titration at a strictly constant rate permitted transformation of the measured resistance *vs.* time curve to resistance *vs.* volume curves. Evaluation was effected according to the Regnault–Pfaundler method proposed by Wadsö [13]. The correction arising from heat transfer and from the temperature difference between the titrated and the titrant solutions was taken into account separately for each measurement point. Dilution heat-free conditions were ensured [11] by making the concentrations of the titrant solutions the same as the ionic strength of the samples examined (0.2 mol/dm^3).

The continuous titration is substantially faster than the widely-used customary methods. Its accuracy is proved by the fact that, just as in our earlier ampoule measurement [11], a value of −13.56 kcal/mol was also obtained here for the formation heat of water in 0.2 mol/dm^3 KCl.

Spectral Examinations

In the spectrophotometric examinations in the visible range, the absorbance of aqueous solutions of parent comprexes of the type CuA^2 was measured as a function of the wavelength. In the study of the mixed ligand complexes, the measured spectrum was a combination of the absorbances due to the two parent complexes and the mixed complex. In the knowledge of the total concentrations taken, the stability constants, the pH and the spectral data on the parent complexes, however, the measured curves were reduced to absorbance curves characteristic of the mixed ligand complexes.

In the case of the copper(II) complexes, the measurements were made on a Beckmann DB-GT double-beam recording photometer. Because of the recording of the absorption band in the near infrared, the nickel(II) parent complexes were examined on a Beckmann DU single-beam spectrophotometer.

ESR spectral studies were made both on aqueous solutions at room temperature and on water–methanol solutions frozen to the temperature of liquid nitrogen. A JEOL JES-ME-IX ESR spectrometer was used for these measurements. The g values were determined by comparison with the signal of Mn^{2+} in MgO.

Calculations

The complexes formed in the systems examined can be characterized by the following general equilibrium process:

$$pM + qH + rA + sB \rightleftharpoons M_pH_qA_rB_s + \Delta H_{pqrs} \qquad (1)$$

The stability constant of the species is given by the equation:

$$\beta_{pqrs} = \frac{[M_pH_qA_rB_s]}{[M]^p[H]^q[A]^r[B]^s} \qquad (2)$$

The enthalpy changes defined by eqn. (1) and the corresponding stability constants were calculated from the relevant calorimetric and pH-metric titration curves as reported earlier [14, 15].

Results and Discussion

From the calculations of the titration curves recorded at various metal:ligand ratios for the copper (II)–histamine system it could be established that the equilibrium conditions cannot be described merely by the assumption of the species CuA^{2+}, CuA_2^{2+} and $Cu_2A_2(OH)_2^{2+}$. The measured and calculated titration curves exhibited a good agreement at every ratio only if the complexes $CuAOH^+$ and CuA_2H^{3+} were also assumed in the equilibrium. The average difference characteristic of the goodness of the fit was then less than 0.01 cm^3.

In the nickel(II)–histamine system, good agreement was generally obtained by consideration of the complexes NiA^{2+}, NiA_2^{2+} and NiA_3^{2+}. A slight difference between the measured and calculated titration curves appeared only in the more acidic solutions. This difference could be eliminated by the assumption of the protonated complex $NiAH^{3+}$ (its maximum concentration was *ca.* 5%). The stability constants calculated on the above basis for the histamine complexes of copper(II) and nickel(II) are listed in Table I, together with the protonation constants of the ligands. The Table also contains values determined in the present work for the complexes of 1,3-diaminopropane.

TABLE I. Stability Constants of Copper(II) and Nickel(II) Complexes of Histamine and 1,3-Diaminopropane; t = 25 °C, I = 0.2 mol/dm³ KCl.

Ligand	pK_1	pK_2	Metal Ion	$\log \beta_{pqrs}$							$\log K_1/K_2$
				MA	MA_2	MA_3	MAH	MA_2H	$M_2A_2(OH)_2$	MAOH	
Histamine	6.17	9.89	Cu(II)	9.58	16.06	–	–	21.79	7.0	1.2	3.10
			Ni(II)	6.85	11.93	15.13	11.56	–	–	–	1.77
1,3-Diaminopropane	8.84	10.53	Cu(II)	9.65	16.82	–	–	–	–	–	2.48
			Ni(II)	6.31	10.62	13.40	–	–	–	–	2.00

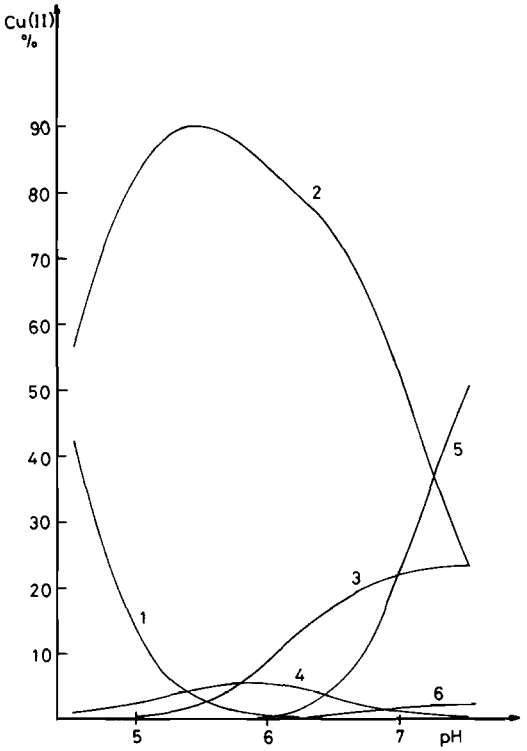

Fig. 1. pH-Dependent percentage concentration distribution of species formed in the copper(II)–histamine system. C_A = 0.01 mol/dm³, C_M = 0.008 mol/dm³, I = 0.2 mol/dm³ KCl, t = 25 °C. Notations: 1. Cu(II); 2. CuA^{2+}; 3. CuA_2^{2+}; 4. CuA_2H^{3+}; 5. $Cu_2A_2(OH)_2^{2+}$; 6. $CuA(OH)^+$.

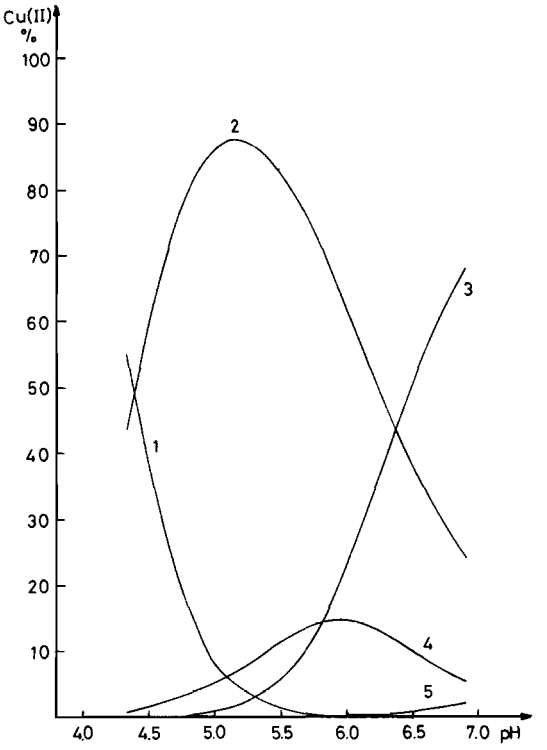

Fig. 2. pH-Dependent percentage concentration distribution of species formed in the copper(II)–histamine system. C_A = 0.01 mol/dm³, C_M = 0.005 mol/dm³, I = 0.2 mol/dm³ KCl, t = 25 °C. Notations: 1. Cu(II); 2. CuA^{2+}; 3. CuA_2^{2+}; 4. CuA_2H^{3+}; 5. $Cu_2A_2(OH)_2^{2+}$.

Figures 1 and 2 show the pH-dependent percentage concentration distributions of the species at two different metal:ligand ratios in the copper(II)–histamine system.

It is clear from Fig. 1 that if the metal:ligand ratio is less than 1:2 in the copper(II)–histamine system, then it is necessary to reckon with the formation of both protonated and hydroxo complexes. It can be stated further that, similarly as in the results of Aiba *et al.* [10], of the hydroxo complexes the binuclear species $Cu_2A_2(OH)_2^{2+}$ predominates, $CuA(OH)^+$ being formed only in very small amounts in the pH range under investigation. On the other hand, Fig. 2 shows that at a metal:ligand ratio of 1:2 hydrolysis of the species CuA^{2+} is repressed, and at pH < 7–7.5 only the complexes CuA^{2+}, CuA_2^{2+} and CuA_2H^{3+} are present in appreciable amounts in the equilibrium system.

It can be seen from the data of Table I that for copper(II) $\log K_1/K_2$ is larger for histamine than for 1,3-diaminopropane. In the copper(II)–histamine system, therefore, formation of species of the type CuA_2^{2+} is only slightly favoured. The cause of this phenomenon is clearly the steric hindrance resulting

from the comparatively large size of the molecule, which at the same time also permits formation of the protonated complex CuA_2H^{3+}. Because of the octahedral arrangement in the nickel(II) complexes, the role of steric factors is not very important. This is manifested by the fact that the histamine complexes are more stable than those of 1,3-diaminopropane when the central ion is nickel(II). Accordingly, as regards the two ligands, the change in the log K_1/K_2 values is just the opposite of that observed for the copper(II) complexes. Thus, log K_1/K_2 is larger in the nickel(II)–1,3-diaminopropane system than in the nickel(II)–histamine system.

The above conclusions are supported by the spectral examinations relating to the parent complexes. The relevant spectra are to be seen in Fig. 3, while the corresponding data are listed in Table II.

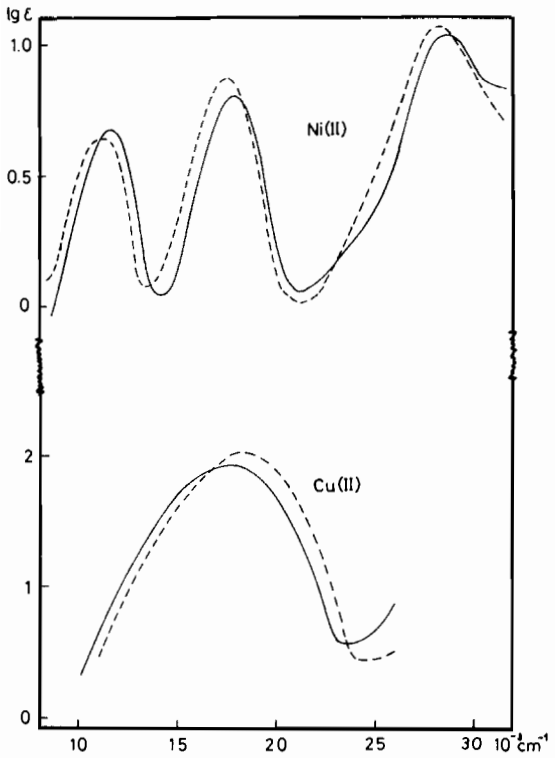

Fig. 3. Spectra of MA_2 type complexes of copper(II) and nickel(II) with histamine (———) and 1,3-diaminopropane (– – – –) in aqueous solution.

It can be established from Fig. 3 that in the case of the copper(II) complexes the absorption maximum of the 1,3-diaminopropane complex of type CuA_2^{2+} appears at a higher energy value. At the same time, the magnitude of the ligand field splitting is larger in the case of the nickel(II)–histamine system.

The ESR spectra obtained for the species of type CuA_2^{2+} in the copper(II)–histamine system at room temperature and in the frozen state, are depicted in Fig. 4.

TABLE II. Main Data of the Electron-excitation Spectra of Copper(II) and Nickel(II) Complexes of Histamine and 1,3-Diaminopropane of the Type MA_2^{2+}.

Metal Ion	Ligand	$\bar{\nu}_{max.}$ kK	$\bar{\nu}_1$ (10Dq) kK	$\bar{\nu}_2$ kK	$\bar{\nu}_3$ kK
Cu(II)	Histamine	16.61	–	–	–
	1,3-Diaminopropane	17.42	–	–	–
Ni(II)	Histamine	–	10.9	17.5	27.7
	1,3-Diaminopropane	–	10.6	17.0	27.0

Figure 4 shows that the g_o and A_o values corresponding to the isotropic hyperfine splitting can be determined from the ESR spectra of the aqueous solutions at room temperature. From the measurements in frozen state the $A_\parallel$ and $g_\parallel$ parameters were obtained. The values of $g_\perp$ and $A_\perp$ were determined *via* the following relation [16]:

$$g_o = \frac{1}{3}(2g_\perp + g_\parallel) \qquad (3)$$

The ESR parameters thus found for the copper (II) parent complexes are given in Table III. For purposes of easier comparability, the Table also contains the data determined for the copper(II)–glycine complex of the type CuA_2.

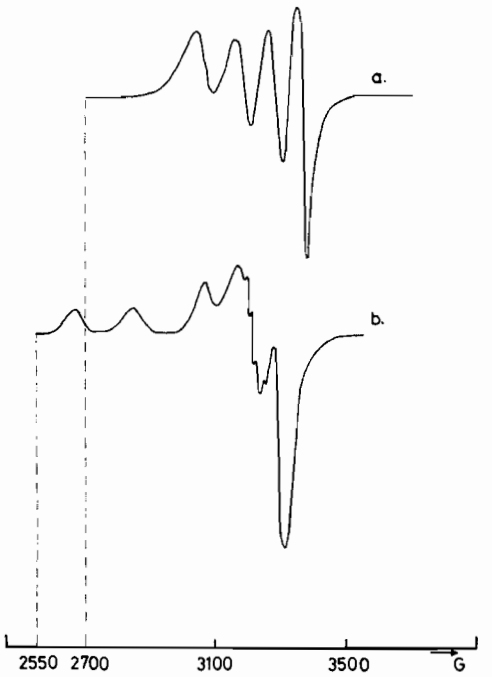

Fig. 4. ESR spectra of the copper(II)–histamine complex of composition CuA_2^{2+}: (a) in aqueous solution at room temperature, and (b) in a 1:1 methanol:water solvent mixture frozen to 77 K.

TABLE III. Main Data of ESR Spectra of Complexes of the Type CuA_2 in the Cases of Glycine, Histamine and 1,3-Diaminopropane.

System	g_o	A_o 10^{-4} cm^{-1}	$g_\perp$	$g_\parallel$	$A_\perp$ 10^{-4} cm^{-1}	$A_\parallel$ 10^{-4} cm^{-1}	$A_\parallel(^{14}N)$ 10^{-4} cm^{-1}
Cu(II)–glycine	2.125	66.9	2.053	2.269	17.8	174.8	–
Cu(II)–histamine	2.109	76.6	2.049	2.229	19.6	199.5	13.4
Cu(II)–1,3-diaminopropane	2.092	80.5	2.037	2.203	26.2	187.5	–

TABLE IV. Thermodynamic Data on Copper(II) and Nickel(II) Complexes of Histamine and 1,3-Diaminopropane; t = 25 °C, I = 0.2 mol/dm^3 KCl.

Ligand	Equilibrium Process	$-\Delta H$ kJ mol^{-1}	ΔS J mol^{-1} K^{-1}
Histamine	$H^+ + A \rightleftharpoons HA^+$	53.2	13
	$2H^+ + A \rightleftharpoons H_2A^{2+}$	85.5	22
	$Cu^{2+} + A \rightleftharpoons CuA^{2+}$	54.3	1
	$Cu^{2+} + 2A \rightleftharpoons CuA_2^{2+}$	95.4	−13
	$Cu^{2+} + H^+ + 2A \rightleftharpoons CuA_2H^{3+}$	129.0	−16
	$2Cu^{2+} + 2H_2O + 2A \rightleftharpoons Cu_2A_2(OH)_2^{2+} + 2H^+$	45.6	−19
	$Ni^{2+} + A \rightleftharpoons NiA^{2+}$	42.7	−12
	$Ni^{2+} + 2A \rightleftharpoons NiA_2^{2+}$	79.5	−39
1,3-Diaminopropane	$H^+ + A \rightleftharpoons HA^+$	53.4	23
	$2H^+ + A \rightleftharpoons H_2A^{2+}$	104.1	24
	$Cu^{2+} + A \rightleftharpoons CuA^{2+}$	49.5	19
	$Cu^{2+} + 2A \rightleftharpoons CuA_2^{2+}$	95.5	2
	$Ni^{2+} + A \rightleftharpoons NiA^{2+}$	36.0	−9
	$Ni^{2+} + 2A \rightleftharpoons NiA_2^{2+}$	67.4	−31

The data in Table III reveal that the g values increase in the sequence 1,3-diaminopropane < histamine < glycine. This is presumably indicative of the strengthening of tetragonal distortion in the direction glycine → 1,3-diaminopropane, and may confirm the increase of the bond strength in the former sequence. This conclusion is supported by the stability and visible spectral data. However, it is striking that the lines of the super-hyperfine splitting originating from the ^{14}N (see Fig. 4b) can be observed only in the copper(II)–histamine parent complex, and thus these probably arise from participation of the imidazole N atom in the coordination. It should be noted that although the observation of super-hyperfine splitting provides only limited possibilities for detailed conclusions to be drawn [17], nevertheless it is very probable that, in comparison with 1,3-diaminopropane, histamine forms more stable complexes and stronger bonds with copper(II) ions. The enthalpy and entropy values determined in the calorimetric examinations similarly support the above conclusions. The relevant data are given in Table IV.

On the basis of the parallel measurements, the error in the enthalpy values in Table IV is ±0.5 kjoule/mol for the proton dissociation heats, and ±1 kjoule/mol for the complexes. The enthalpy changes reported show that the formations of the histamine and 1,3-diaminopropane complexes of the type CuA_2^{2+} are accompanied by nearly the same heat effect. On the other hand, the formation of the complex of type CuA^{2+} is accompanied by a larger enthalpy change in the case of histamine, in agreement with the development of a more stable bond between the copper(II) ion and the aromatic N atom of the imidazole. As a consequence of the smaller role of the steric factors in the complexes of the nickel(II) ion, the formation of the histamine complexes is accompanied by larger enthalpy changes in both steps.

If the equilibrium data also are taken into account, the enthalpy change relating to the protonated complex CuA_2H^{3+} provides a possibility for the determination of the site of protonation. From the stability data the protonation constant of the complex CuA_2^{2+} is 5.73, which is only a little less than the value of

pK_1 = 6.17 for the tertiary N atom of the free ligand. By comparison of the data relating to the complexes CuA_2^{2+} and CuA_2H^{3+} in Table IV, the protonation heat of the parent complex is −33.6 kjoule/mol, which similarly does not differ considerably from the relevant value for the free ligand (ΔH = −32.3 kjoule/mol). On this basis, it may be presumed that in the species CuA_2H^{3+} the copper(II) ion is coordinated to the two primary amino groups and one tertiary N atom, while the other imidazole nitrogen remains protonated.

In the copper(II)–histamine system the role of the steric factors is also shown by the results relating to the mixed ligand complexes. Detailed investigations connected with the mixed complexes of copper(II) with various ligands are discussed in the following publication [18]. Here, therefore, we shall give an account only of those few systems which are connected with the above conclusions. The stability constants determined for the mixed ligand complexes, and the spectral data on the copper(II) mixed ligand complexes are contained in Table V.

TABLE V. Equilibrium and Spectral Data on Mixed Ligand Complexes.

System	$\log \beta_{111}$	$\Delta\log \beta_{111}$	$\bar{\nu}_{av.}$ kK	$\bar{\nu}_{max.}$ kK
Copper(II)–Histamine–Glycine	17.00	1.25	16.22	16.53
Copper(II)–1,3-Diaminopropane–Glycine	16.91	0.78	16.62	16.81
Copper(II)–Ethylenediamine–Glycine	17.69	0.13	17.09	17.04
Nickel(II)–Histamine–Glycine	11.77	0.30	–	–
Nickel(II)–1,3-Diaminopropane–Glycine	11.60	0.79	–	–

The stabilization constant $\Delta\log \beta_{111}$ in Table V results from the difference of the stability constant measured for the mixed complex, and that calculated from statistical considerations. The stability data on the glycine parent complexes were reported in earlier publications [11, 19]. The stability constants of the copper(II)–ethylenediamine complex were found [18] to be $\log \beta_1$ = 10.57, and $\log \beta_2$ = 19.68. As regards the spectral data in Table V, $\bar{\nu}_{av.}$ is the average value calculated from the absorption maxima of the parent complexes, while $\bar{\nu}_{max.}$ is the absorption maximum measured for the mixed ligand complex (data relating to the parent complexes of type CuA_2 and not appearing in Table II: for glycine, $\bar{\nu}_{max.}$ = 15.82 kK, and for ethylenediamine, $\bar{\nu}_{max.}$ = 18.35 kK).

From the stability data listed in Table V it may be stated that the greater the difference between the $\log K_1/K_2$ values for the parent complexes, the more favoured is the formation of mixed ligand complexes. Thus, as regards the copper(II) complexes involving glycine, the most extensive stability increase is observed for histamine. The situation is the reverse with regard to histamine and 1,3-diaminopropane in the nickel(II) complexes. The spectral data relating to the copper(II) mixed ligand complexes reveal that the measured and calculated absorption maxima differ to the greatest extent in the copper(II)–histamine–glycine system. The average environment rule [20, 21] can thus be regarded as holding strictly only in the copper(II)–ethylenediamine–glycine mixed complex. Significant differences are observed in the case of 1,3-diaminopropane, and particularly histamine. In this case too the cause of the phenomenon is the steric hindrance accompanying formation of the histamine complex of type CuA_2^{2+}, which no longer appears in the mixed ligand complexes, however, with the smaller glycine.

Acknowledgments

The authors are indebted to Dr. Antal Rockenbauer of the Central Chemical Research Institute of the Hungarian Academy of Sciences, for valuable advice and assistance in the recording and evaluation of ESR spectra.

References

1 R. W. Schayer, "Histamine and its Role in Biological Systems; in Biogenic Amines and Physiological Membranes in Drug Therapy"; ed. by J. H. Biel and L. G. Abood, Dekker, New York (1971).
2 B. L. Mickel and A. C. Andrews, *J. Am. Chem. Soc.*, *77*, 323 (1955).
3 W. C. Nicholas and W. C. Fernelius, *J. Phys. Chem.*, *65*, 1047 (1961).
4 A. Chakravorty and F. A. Cotton, *J. Phys. Chem.*, *67*, 2788 (1963).
5 F. Holmes and D. R. Williams, *J. Chem. Soc. A*, 1702 (1967).
6 J. L. Meyer and J. E. Bauman, Jr., *J. Am. Chem. Soc.*, *92*, 4210 (1970).
7 B. Rao and H. B. Mathur, *J. Inorg. Nucl. Chem.*, *33*, 809 (1971).
8 D. D. Perrin and V. S. Sharma, *J. Inorg. Nucl. Chem.*, *28*, 1271 (1966).
9 W. J. Eilbeck, F. Holmes and T. W. Thomas, *J. Chem. Soc. A*, 2062 (1970).
10 H. Aiba, A. Yokoyama and H. Tanaka, *Bull. Chem. Soc. Japan*, *47*, 1003 (1974).
11 A. Gergely and I. Sovago, *J. Inorg. Nucl. Chem.*, *35*, 4355 (1973).
12 F. J. C. Rossotti and H. Rossotti, *J. Chem. Educ.*, *42*, 375 (1965).

13 I. Wadsö, *Science Tools LKB Instr. J., 13,* 33 (1966).
14 I. Nagypál, *Acta Chim. Acad. Sci. Hung., 82,* 29 (1974).
15 A. Gergely, I. Nagypál and E. Farkas, *Acta Chim. Acad. Sci. Hung., 82,* 43 (1974).
16 B. A. Goodman and J. B. Raynor, "ESR of Transition Metal Complexes"; in *Advances in Inorganic Chemistry and Radiochemistry, Vol. 13,* Academic Press, New York and London (1970).
17 Y. Nonanaka, T. Tokii and S. Kida, *Bull. Chem. Soc. Japan, 47,* 312 (1974).
18 I. Sóvágó and A. Gergely, *Inorg. Chim. Acta, 20,* 27 (1976).
19 I. Sóvágó, A. Gergely and J. Posta, *Acta Chim. Acad. Sci. Hung., 85,* 153 (1975).
20 C. K. Jörgensen, "Absorption Spectra and Chemical Bonding in Complexes", Pergamon Press, Oxford (1962).
21 E. J. Billo, *Inorg. Nucl. Chem. Letters, 10,* 613 (1974).