Thermodynamic Considerations in Co-ordination. Part XXI.[1] Structures of Copper(II)–Asparaginate, –Histidinate, and –Threoninate Ternary Complexes in Aqueous Solution

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Thermodynamic-based structures are suggested for [Cu(AsnO)(HisO)], [Cu(AsnO)(HHisO)]$^+$, [Cu(AsnO)(ThrO)], [Cu(HisO)(ThrO)], and [Cu(HHisO)(ThrO)]$^+$ in aqueous solution at 25 °C and I = 3.00M (Na[ClO_4]). Histidinate (HisO) appears to be tridentate to Cu^{II}, threoninate (ThrO) bidentate, and asparaginate (AsnO) ambivalent. The site of proton attachment in the protonated complexes is the primary amine nitrogen of histidinate (HHisO). Values of $\Delta G^{\ominus}$, $\Delta H^{\ominus}$, and $\Delta S^{\ominus}$ for formation of all these complexes are reported.

DEVOTEES of metal-ion–amino-acid complexes were excited to learn that the exchangeable portion of copper(II) in blood plasma occurs mainly as the mixed-ligand complexes asparaginato(histidinato)-, asparaginato(threoninato)-, and histidinato(threoninato)-copper(II).[2-7] However, the determination of the exact structures of these complexes in aqueous solution is a formidable challenge since the occurrence of Jahn–Teller-distorted octahedral copper(II) complex bond configurations doubles the number of bond types involved (both axial and planar) when potentially tridentate amino-acid anion ligands chelate onto the metal ion. For example, the copper(II)–histidinate system exhibits six complexes in aqueous solution at room temperature and other tautomers for other physical conditions.[8]

It is inadvisable to base structures of complexes present at physiological conditions solely on formation-constant comparisons [9] or on non-aqueous, non-ambient, temperature methods (*e.g.* *X*-ray crystallography) and so this paper is concerned with $\Delta H^{\ominus}$ and $\Delta S^{\ominus}$ based structures determined by aqueous-titration calorimetry at 25 °C {I = 3.00M (Na[ClO_4])}.* These high-ionic-strength solutions are also somewhat limited as models for the structures occurring *in vivo* but, nevertheless, they are considered preferable to solid-state studies.

* 1M = 1 mol dm^{-3}.

EXPERIMENTAL

Apart from L-threonine (B.D.H., biochemical grade), m.p. 255 °C (lit., 255—257 °C) (Found: C, 40.1; H, 7.7; N, 11.9. Calc. for $C_4H_9NO_3$: C, 40.3; H, 7.6; N, 11.8%), all reagents were as used in refs. 8 and 10.

Potentiometric data were collected as in refs. 10 and 11 and the formation constants were derived by both the SCOGS [12] and MINIQUAD [13] least-squares approaches, the β values obtained being listed in Table 1.

TABLE 1

Log β for the species $A_pA'_{p'}B_qH_r$ at 25 °C, and I = 3.00M (Na[ClO_4]). A And A′ = amino-acid anions, B = Cu^{II}, H = proton, s = logarithm of the standard deviation of β, and n = number of titration readings for each series

$A_pA'_{p'}B_qH_r$							
AsnO	HisO	ThrO	Cu^{II}	H^+	log β	s	n
1	1	0	1	0	18.597	0.012	266
1	1	0	1	1	23.326	0.031	
1	0	1	1	0	16.471	0.026	198
0	1	1	1	0	18.613	0.016	208
0	1	1	1	1	23.426	0.028	
0	0	1	1	0	8.597	0.006	141
0	0	2	1	0	16.031	0.013	

Calorimetric measurements were as described in refs. 10, 14, and 15. The method used for computing corrections for heats of hydrolysis, protonation, and formation of water

[1] Part XX, A. M. Corrie, G. K. R. Makar, M. L. D. Touche, and D. R. Williams, *J.C.S. Dalton*, 1975, 105.
[2] B. Sarkar and T. P. A. Kruck, *Canad. J. Biochem.*, 1967, **45**, 2046.
[3] B. Sarkar and Y. Wigfield, *Canad. J. Biochem.*, 1968, **46**, 601.
[4] S. Lau and B. Sarkar, *J. Biol. Chem.*, 1971, **246**, 5938.
[5] P. Z. Neuman and A. Sass-Kortsak, *J. Clin. Invest.*, 1967, **46**, 646.
[6] B. Sarkar and T. P. A. Kruck, in 'The Biochemistry of Copper,' eds. J. Peisach, P. Aisen, and W. E. Blumberg, Academic Press, New York, 1966, p. 183.
[7] P. Z. Neuman and A. Sass-Kortsak, *Vox Sanguinis*, 1963, **8**, 11.
[8] D. R. Williams, *J.C.S. Dalton*, 1972, 790.
[9] A. D. Jones and D. R. Williams, *Inorg. Nuclear Chem. Letters*, 1971, **7**, 369.
[10] A. C. Baxter and D. R. Williams, *J.C.S. Dalton*, 1974, 1117.
[11] D. R. Williams, *J.C.S. Dalton*, 1973, 1064.
[12] I. G. Sayce, *Talanta*, 1968, **15**, 1397.
[13] A. Sabatini, A. Vacca, and P. Gans, *Talanta*, 1974, **21**, 53.
[14] D. R. Williams and P. A. Yeo, *J.C.S. Dalton*, 1972, 1988.
[15] A. D. Jones and D. R. Williams, *J. Chem. Soc.* (*A*), 1970, 3138.

(RWCALCOR [14]) was extended to include heats of forming the binary complexes so that the only two unknown parameters in each titration were the heats of forming the 1 : 1 : 1 ternary complex and its protonated form. (For some systems this involved applying 14 correction terms to each experimental heat!) These two unknowns were extracted from the heat-corrected data using a simple least-squares

TABLE 2

Gibbs free-energy changes, enthalpies, and entropies for the formation of asparaginate–, histidinate–, and threoninate–copper(II)–proton ternary complexes at 25 °C and I = 3.00M ($Na[ClO_4]$). $\Delta G^{\ominus}$ And $\Delta H^{\ominus}$ are in kJ mol^{-1}, $\Delta S^{\ominus}$ in J K^{-1} mol^{-1}. The errors are three standard deviations in the computed thermodynamic parameters and n denotes the number of experimental measurements

	$A_pA'_{p'}B_qH_r$						
	AsnO	HisO	ThrO	Cu^{II}	H^+		n
$-\Delta G^{\ominus}$	1	1	0	1	0	106.15 ± 0.07	266
	1	1	0	1	1	133.11 ± 0.17	
	1	0	1	1	0	94.04 ± 0.15	198
	0	1	1	1	0	106.22 ± 0.09	208
	0	1	1	1	1	133.68 ± 0.16	
$-\Delta H^{\ominus}$	1	1	0	1	0	67.5 ± 2.5	20
	1	1	0	1	1	88.2 ± 5.0	
	1	0	1	1	0	50.0 ± 2.5	16
	0	1	1	1	0	67.4 ± 3.0	21
	0	1	1	1	1	103.5 ± 5.0	
$\Delta S^{\ominus}$	1	1	0	1	0	129.7 ± 9.0	20
	1	1	0	1	1	150.7 ± 17.5	
	1	0	1	1	0	147.7 ± 12.0	16
	0	1	1	1	0	130.3 ± 10.0	21
	0	1	1	1	1	101.3 ± 22.5	
Threonine binary complexes							
$-\Delta G^{\ominus}$	0	0	1	1	0	49.08 ± 0.04	141
	0	0	2	1	0	91.53 ± 0.07	
$-\Delta H^{\ominus}$	0	0	1	1	0	18.0 ± 1.5	32
	0	0	2	1	0	47.0 ± 3.0	
$\Delta S^{\ominus}$	0	0	1	1	0	104.2 ± 5.0	32
	0	0	2	1	0	149.4 ± 10.0	

approach. The experimental points for a typical thermogram and the calculated curve are shown in Figure 1 alongside a species-distribution plot. The $\Delta H^{\ominus}$ and $\Delta S^{\ominus}$ results are listed in Table 2.

RESULTS AND DISCUSSION

The thermodynamic parameters for ligand protonation and for forming simple binary complexes have been reported previously [8,10] with the exception of the H^+–Cu^{II}–Thr system whose values are given in Tables 1 and 2.* The formation constants for the three ternary systems Cu^{II}–AsnO–HisO, –AsnO–HisO, and –HisO–ThrO are in Table 1.

Previous researchers (Freeman and Martin [16], 0.1M-KNO_3, 25 °C) reported [Cu(HisO)(ThrO)] (log β 17.56), $[Cu(HHisO)(ThrO)]^+$ (log β 21.90), and $[Cu(HisO)(ThrO)(OH)]^-$ (log β 7.00), observing that the constants for the species were larger than those of the parents and that D as against L amino-acid stereospecificity was absent. Our work failed to detect $[Cu(HisO)(ThrO)(OH)]^-$ but β values were obtained for the other two ternary complexes in agreement with Freeman and Martin (after allowing for a change in the ionic-background salt). Other workers (Kruck and Sarkar,[17] 0.15M-NaCl, 25 °C) studied: (*i*) the Cu^{II}–His–Gln system, which may be considered analogous to the present Cu^{II}–HisO–AsnO study, and reported β for the complexes [Cu(GlnO)(HisO)] (log β 17.624) and $[Cu(GlnO)(HHisO)]^+$ (log β 21.654) but not $[Cu(GlnO)(HisO)(OH)]^-$ (cf. Freeman and Martin) {We found the complexes [Cu(AsnO)(HisO)] and $[Cu(AsnO)(HHisO)]^+$ with comparable β values.}; (*ii*) $[Cu(HisO)(Ser)]^+$ (log β 17.540) and $[Cu(HHisO)(SerO)]^+$

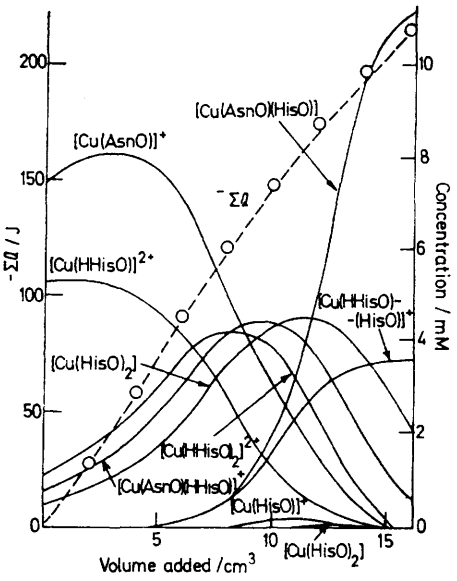


FIGURE 1 Experimental thermogram and pH–complex distribution profile for the copper(II)–asparaginate–histidinate–proton system. The broken line was calculated on the basis of the parameters reported in Tables 1 and 2; (○), experimental data

(log β 21.703), our homologous Thr complexes having somewhat larger log β values.

The two systems exhibiting protonated ternary complexes both contain histidinate (HisO), thus suggesting that the donor group protonated belongs to HisO (see structures later). Understandably, the chelating ability of all three ligands studied was pH dependent and the continuity of stepwise complexing was obeyed in that, for example, $Cu^{2+} \longrightarrow [Cu(AsnO)(HisO)]$ *via* $[Cu(HisO)]^+$ and $[Cu(HHisO)]^{2+}$, all complexes being present in significant amounts in the pH range studied (see Figure 1).

Ternary Complexes as against Parent Binaries.—It has been firmly established that formation constants for ternary complexes are different to those calculated on the basis of β values for the parent binary complexes. There have been numerous reports of methods for statistically calculating ternary β values from those of the parent

* Asn = Asparagine, Gln = glutamine, His = histidine, Ser = serine, and Thr = threonine; AsnO = asparaginate and HHisO = histidinate protonated at the primary amine nitrogen atom.

[16] H. C. Freeman and R.-P. Martin, *J. Biol. Chem.*, 1969, **244**, 4823.

[17] T. P. A. Kruck and B. Sarkar, *Canad. J. Chem.*, 1973, **51**, 3555.

binary complexes;[16-23] nevertheless suggestions as to which structural properties actually cause this enhanced ternary-complex stability have been strictly limited to occasional glances at central-metal-ion asymmetry causing increased entropy contributions to $\Delta G^{\ominus}$.[17] Our results prefer the former explanation rather than the latter because it explains the $-\Delta H^{\ominus}$,$\Delta S^{\ominus}$ (*b*,*a*) pattern in Table 3, whereas the bond-strain suggestion would involve a *b*,*b* or *a*,*a* pattern. However, there is a need for more experimental data to verify our postulate.

TABLE 3

Enhancement of the stability of ternary complexes compared to their parent binary complexes

System	$-\Delta G^{\ominus}$ Expt.	$-\Delta G^{\ominus}$ Calc.	$-\Delta G^{\ominus}$ Difference	$-\Delta H^{\ominus}$ Expt.	$-\Delta H^{\ominus}$ Calc.	$-\Delta H^{\ominus}$ Difference	$T\Delta S^{\ominus}$ Expt.	$T\Delta S^{\ominus}$ Calc.	$T\Delta S^{\ominus}$ Difference
[Cu(AsnO)(HisO)]	106.14	100.5, 98.7	*a*	67.5	67.5, 77.9	*b*	38.7	33.0, 20.8	*a*
[Cu(AsnO)(HHisO)]$^{+}$ [d]	133.09	130.2	*a*	88.2	101.0	*b*	44.9	29.2	*a*
[Cu(AsnO)(ThrO)]	94.04	92.0, 90.2	*a*	50.0	56.5, 52.0	*b*	44.0	35.5, 38.2	*a*
[Cu(HisO)(ThrO)]	106.22	100.0, 100.1	*a*	67.4	72.9, 58.0	*c*	38.8	27.1, 42.1	*c*
[Cu(HHisO)(ThrO)]$^{+}$ [d]	133.68	131.5	*a*	103.5	96.0	*a*	30.2	35.5	*b*

[a] Expt. > Calc. [b] Expt. < Calc. [c] Expt. equal to, or between, Calc. values. [d] Since neither [Cu(AsnO)]$^{+}$ nor [Cu(ThrO)]$^{+}$ form protonated binary complexes it was only possible to calculate $\Delta G^{\ominus}$, $\Delta H^{\ominus}$, and $T\Delta S^{\ominus}$ *via* the Cu + HHisO route; units are kJ mol^{-1} and JK^{-1} mol^{-1}.

exhibit this enhancement and we have apportioned the Gibbs free-energy change into its enthalpy and entropy contributions in Table 3. The approach used is to assume that there are two possible routes to forming, for example, [Cu(AsnO)(HisO)] as in equations (1) and (2)

$$Cu^{2+} + AsnO \xrightarrow{K_1^{AsnO}} [Cu(AsnO)]^{+} \xrightarrow{K_2^{HisO}} [Cu(AsnO)(HisO)] \quad (1)$$

$$Cu^{2+} + HisO \xrightarrow{K_1^{HisO}} [Cu(HisO)]^{+} \xrightarrow{K_2^{AsnO}} [Cu(AsnO)(HisO)] \quad (2)$$

where the constants refer to parent binary complexes. Thus we obtain expressions (3) and (4); $\Delta H^{\ominus}_{calc.}$ and

$$\Delta G\{[Cu(AsnO)(HisO)]\}^{\ominus}\ (calc.) = -RT[\log \beta_1^{AsnO} + (\log \beta_2^{HisO} - \log \beta_1^{HisO})] \quad (3)$$

$$\Delta G\{[Cu(AsnO)(HisO)]\}^{\ominus}\ (calc.) = -RT[\log \beta_1^{HisO} + (\log \beta_2^{AsnO} - \log \beta_1^{AsnO})] \quad (4)$$

$T\Delta S^{\ominus}_{calc.}$ were computed likewise and are recorded in Table 3.

One fact is clear. An enhanced $-\Delta G^{\ominus}$ arises from a lower than expected $-\Delta H^{\ominus}$ and an elevated $T\Delta S^{\ominus}$ or *vice versa* (see difference column in Table 3). The origins of these parallel and apparently related effects in $\Delta H^{\ominus}$ and $\Delta S^{\ominus}$ may now be traced to two possible sources. Ternary-complex formation sometimes liberates more water from the solvation sphere of the copper ion (and sometimes less), thus increasing $\Delta S^{\ominus}$ but requiring $-\Delta H^{\ominus}$ to decrease because more aquation bonds are ruptured. Alternatively, ternary-complex formation causes increased complex-bond strain. However, this would be evident in a lower $-\Delta H^{\ominus}$ (a weaker complex bond) and a lower $\Delta S^{\ominus}$ (less degrees of freedom in the system). We

Species Distributions—COMPLOT [10] models were computed for blood-plasma concentrations of the amino-acids and copper for the three binary systems. One of these models, the copper(II)–asparaginate–histidinate, is shown in Figure 2. In all three systems as the pH was

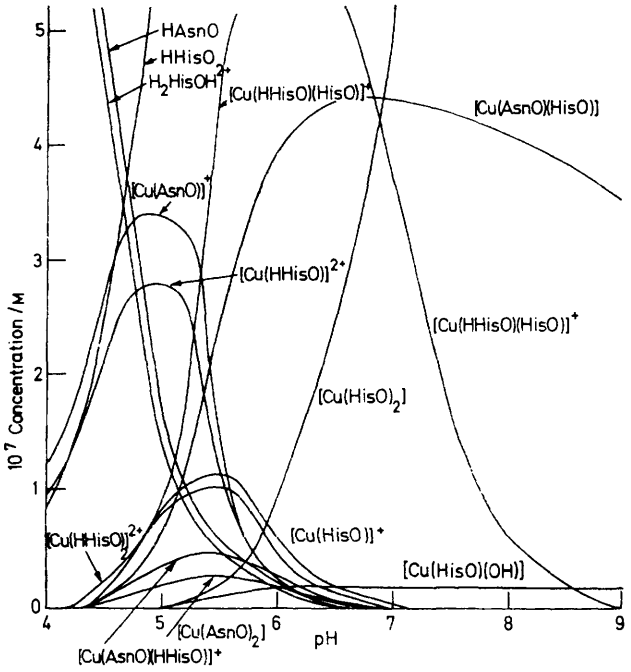


FIGURE 2 COMPLOT model of the copper(II)–asparaginate–histidinate system. Total plasma concentrations used were 1.4, 44, and 81μM respectively. The concentrations of HHisOH^{+} and HAsnO would appear off the top of the plot

raised continuity of complexing occurred. In the simpler system this was $[Cu(ThrO)]^{+} \longrightarrow [Cu(AsnO)]^{+} \longrightarrow [Cu(AsnO)(ThrO)] \longrightarrow [Cu(ThrO)_2] \longrightarrow [Cu(AsnO)_2]$

[18] D. D. Perrin and V. S. Sharma, *J. Chem. Soc.* (*A*), 1968, 448.
[19] H. Sigel, 'Metal Ions in Biological Systems,' ed. H. Sigel, Dekker, New York, 1974, vol. 2, p. 64.
[20] D. D. Perrin, I. G. Sayce, and V. S. Sharma, *J. Chem. Soc.* (*A*), 1967, 1755.
[21] I. Nagypál, A. Gergely, and E. Farkas, *J. Inorg. Nuclear Chem.*, 1974, **36**, 699.
[22] J. Bjerrum, D. N. Hume, H. Diebler, Y. D. Fridman, and A. E. Martell, *Proc. 3rd Symp. Co-ordination Chem.*, Debrecen, Hungary, 1970, Akademiai Kiado Press, Budapest, 1971.
[23] R.-P. Martin and J. P. Scharff, 'An Introduction to Bioinorganic Chemistry,' ed. D. R. Williams, C. C. Thomas Publ., Springfield, Illinois, 1975.

and in the more complex system of Figure 2 the following pattern is discernible: $[Cu(AsnO)]^+ \longrightarrow [Cu(HHisO)]^{2+} \longrightarrow [Cu(HisO)]^+ \longrightarrow [Cu(HHisO)_2]^{2+} \longrightarrow [Cu(AsnO)(HHisO)]^+ \longrightarrow [Cu(AsnO)_2] \longrightarrow [Cu(HHisO)(HisO)]^+ \longrightarrow [Cu(AsnO)(HisO)] \longrightarrow [Cu(HisO)_2] \longrightarrow [Cu(HisO)(OH)]$.

We are particularly interested in species distributions for blood-plasma pH. The free copper(II) concentration was computed to be 10^{-11}—10^{-12}M and the major species present quoted as a percentage of the total copper were $[Cu(HisO)_2]$ (55), [Cu(AsnO)(HisO)] (30), $[Cu(HHisO)(HisO)]^+$ (15); [Cu(AsnO)(ThrO)] (48), $[Cu(ThrO)_2]$ (42), $[Cu(AsnO)_2]$ (8); [Cu(HisO)(ThrO)] (52), $[Cu(HisO)_2]$ (35), and $[Cu(HHisO)(HisO)]^+$ (11). It is remarkable that such a high percentage of the copper appears in electrically uncharged form at plasma pH. Such neutral complexes have been correlated with membrane solubility [24] and thus it appears that binary bis and ternary 1 : 1 : 1 ligand complexes of copper are ideally suited for the role of copper-ion transport into cell membranes. This observation is in agreement with the postulates of Sarkar and Kruck.[6]

Structures of Ternary Complexes.—The most important details arising from this study are thermodynamic conclusions which suggest the structures of the complexes present in aqueous solution. Spectral investigations of structure perceive only those aspects of the structure that are involved in electronic transitions. On the other hand enthalpies and entropies of complex formation reflect all bond strengths, ring strains, and configurations. In order to recognise these characteristics in $\Delta H^\ominus$ and $\Delta S^\ominus$ patterns one ought to approach the question of the ternary structures *via* those of their respective parent binary complexes.

A premier question is whether the ligands concerned are bidentate or tridentate to copper(II). Table 4 lists

TABLE 4

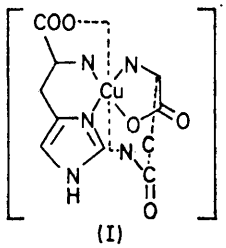
Values of $\Delta H_1^\ominus$ (kJ mol^{-1}) and $\Delta S_1^\ominus$ (J K^{-1} mol^{-1}) for forming 1 : 1 complexes with Cu^{II} and suggested number of bonds from the ligand to the metal ion

System	$-\Delta H_1^\ominus$	$\Delta S_1^\ominus$	Bonding	Ref.
$[Cu(HisO)]^+$	43.9	45.9	Tridentate	8
$[Cu(AsnO)]^+$	27.5	73.9	Bi- or tri-dentate?	10
$[Cu(PhAlO)]^+$ *	19.2	93.7	Bidentate	14
$[Cu(ThrO)]^+$	18.0	104.2	Bidentate	Table 2
$[Cu(GlnO)]^+$	16.5	118.0	Bidentate	10

* PhAlaO = *N*-Phenylalaninate.

$\Delta H_1^\ominus$ and $\Delta S_1^\ominus$ for the present ligands (asparaginate, histidinate, and threoninate) and related reference ligands. Phenylalanate has but two donor groups (NH_2 and CO_2^-) and so can only be bidentate. Its $\Delta H_1^\ominus$ and $\Delta S_1^\ominus$ of complex formation are similar to those of threoninate and glutaminate and so these are assumed to be bidentate also. Histidinate, on the other hand, is customarily tridentate to octahedral metal ions [25] and its somewhat strained tridentate nature in Jahn–Teller distorted octahedral Cu^{II} complexes has already been the topic of intense investigation.[8] The increased ligand–metal ion bond strengths arising from two chelate rings are shown by the heat of formation of the 1 : 1 histidinate–copper(II) complex being double that for the bidentate ligand–copper(II) complexes. Further, the reduced degrees of freedom when the two chelate rings are formed correspondingly reduces the entropy of formation by half that of the bidentates. Copper(II)–asparaginate has $\Delta H_1^\ominus$ and $\Delta S_1^\ominus$ values that are intermediate between tri- and bi-dentate complexing. This suggests that the amino-acid side group $[CO(NH_2)]$ is either weakly localised in the vicinity of one of the long axial bonds of Cu^{II} or that there is a mixture of bi- and tri-dentate AsnO complexes present, our calorimetric results being the average of the two species. We shall now discuss each of the five ternary complexes in turn.

[Cu(AsnO)(HisO)], (I).—The histidinate is shown bonded * as argued in ref. 8 with two planar amine–Cu^{II} bonds and a longer axial carboxylate–Cu^{II} bond. The asparaginate is shown as just discussed, a transient tridentate ligand having the basic planar bonding to its



(I)

amino-acid groups. The question as to whether the NH_2 groups are *cis* or *trans* to each other is still open. However, we favour *cis* on the grounds of the repulsion of two negatively charged CO_2^- groups, the HisO carboxylate being axial and the AsnO planar. Were the bond configurations to be truly symmetrical Jahn–Teller octahedral, the distances between the carboxylate groups for both the *cis*- and *trans*-NH_2 suggestions would be similar. However, molecular models suggest that the HisO carboxylate–Cu^{II} bond is not at 90° to the plane but nearer to 70°. Thus, less intercarboxylate repulsion occurs for the *cis*-NH_2 model. Another open question is whether the AsnO side group bonded in an extended axial position is through the NH_2 or C=O. As shown in (I) we tentatively suggest a Cu–N bond in deference for Cu^{II} preferring N rather than O donors. The overall test that the basic structure is as drawn is that $\Delta H_1^\ominus$ (calc.) and $\Delta S_1^\ominus$ (calc.), calculated using the assumption that binary structures survive in the ternary complexes, are in agreement with the experimentally observed values in Table 3.

$[Cu(AsnO)(HHisO)]^+$, (II).—Only ternary complexes that contain histidinate form protonated species. This shows that the site of protonation is at one of the three donor groups of HisO. Furthermore, the binary Cu^{II}–AsnO system does not have protonated species. The

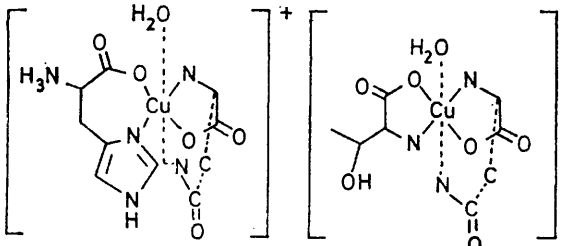
* Full lines represent planar bonds, broken lines axial.

[24] J. N. Cape, D. H. Cook, and D. R. Williams, *J.C.S. Dalton*, 1974, 1849.

[25] D. R. Williams, *J. Chem. Soc.* (*A*), 1970, 1550.

proton is thus assumed to be attached to the primary amine of HisO as deduced in ref. 8, the axial carboxylate group moving inwards towards the central metal ion to adopt a planar bonding position *trans* to the AsnO carboxylate. The enthalpy for the reaction [Cu(AsnO)(HisO)] + H^+ ⟶ [Cu(AsnO)(HHisO)]$^+$ (20.7 kJ mol^{-1}) is comparable to that of [Cu(HisO)]$^+$ + H^+ ⟶ [Cu(HHisO)]$^{2+}$ (23.1 kJ mol^{-1}).

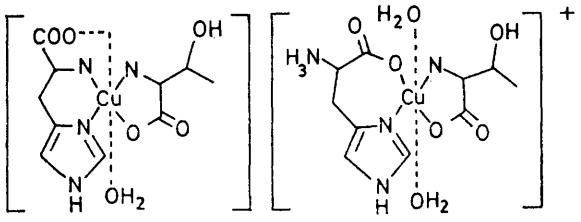
[Cu(AsnO)(ThrO)], (III).—The Cu^{II}–asparaginate bonding is as just described and threoninate is bidentate as deduced from Table 4, the OH group hanging free and not bonded to the Cu^{II}. The principle of repulsion between like groupings suggests that the carboxylate and primary amine groups are *trans* to each other.



(II) (III)

[Cu(HisO)(ThrO)], (IV).—The aqueous structure of this complex is based on the binary parent logistics just advanced for histidinate and threoninate. In addition to the model measurements suggesting that the two NH_2 groups are *cis*, Freeman *et al.*[26] found *cis*-NH_2 groups and the angle $N(NH_2)$–Cu–$O(CO_2^-)$ = 68.3° in the crystal structure.

[Cu(HHisO)(ThrO)]$^+$.—This cationic complex has the aqueous structure (V), the proton being attached to the primary amine nitrogen of histidinate and other features being deduced as for the previous ternary complexes.



(IV) (V)

This paper has examined the relatively new field of ternary-structure determination in aqueous solution and has demonstrated that precision thermodynamic measurements can provide many of the important bonding details. This statement requires some qualification. ' Precision ' encompasses the best methods available for $\Delta G^\ominus$ determination (both data acquisition and least-squares computation) and then accurate calorimetry involving reliable ΔH corrections (for the other complexes formed simultaneously to the ternary ones) to obtain $\Delta H^\ominus$ and $\Delta S^\ominus$. The ' structures ' are then revealed through bond strengths, ring strains, and some configurational information. This ought to be contrasted with *X*-ray crystallographic determinations which reveal bond angles, dimensions, and configurations for the non-aqueous crystalline state. The two methods are complementary, giving different views of the same system under different ambient conditions.

We thank the University of St. Andrews for the award of a maintenance grant (to A. C. B.).

[4/2219 *Received*, 28*th October*, 1974]

[26] H. C. Freeman, J. M. Guss, M. J. Healy, R.-P. Martin, C. E. Nockolds, and B. Sarkar, *Chem. Comm.*, 1969, 225.