Thermodynamics of Metal Complexes with Ligand–Ligand Interaction. Mixed Complexes of Copper(II) and Zinc(II) with Adenosine 5'-Triphosphate and L-Histidine or Histamine †

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Mixed-ligand complexes of the type $[M(ATP)(L)]^{3-}$ [ATP = adenosine 5'-triphosphate, L = L-histidinate ($hisO^-$)] and $[M(ATP)(L)]^{2-}$ [L = histamine (hm)], with M = Cu^{2+} or Zn^{2+}, have been studied by potentiometric and calorimetric titrations at 25 °C and I = 0.1 mol dm^{-3}. Detailed analysis of the thermodynamic parameters concerning the simple complexes of L-histidine and histamine has been carried out and has allowed us to determine details of the bonding of the main species present in aqueous solution. The two unprotonated mixed complexes show equal ΔG° values both in the case of zinc(II) and copper(II) systems but different ΔH° and ΔS° contributions. The differences in enthalpy and entropy changes reveal the presence of a ligand–ligand interaction between the purine moiety of ATP and the imidazole ring of histamine in the $[Zn(ATP)(hm)]^{2-}$ complex. Further support for this is gained by comparing the differences between the ΔH° and ΔS° values for the formation of $[Cu(ATP)(hm)]^{2-}$ and $[Zn(ATP)(hm)]^{2-}$ and those for $[Cu(ATP)(hisO)]^{3-}$ and $[Zn(ATP)(hisO)]^{3-}$.

To date mainly simple complexes of divalent metal ions with nucleotides have been studied in solution.[1-5] Only recently have M^{II}–Nu (Nu = nucleotide) complexes with biofunctional ligands been reported.[6-9] In fact there is evidence of involvement of these mixed complexes in many biological systems.[9-11] Furthermore, in such ternary complexes an interesting 'secondary' bonding has been described: the base of the nucleotide interacts with the aromatic moiety of the other ligand, forming a stacking adduct.[12-15] Recently, we have studied the formation, the stability, and the structure of ternary complexes of copper(II) and zinc(II) with adenosine 5'-triphosphate (ATP) and some amino acids in aqueous solution.[16,17] By means of calorimetric measurements it was possible to determine the effect of stacking interaction on the thermodynamic parameters of complex formation. Here we report the thermodynamics of mixed complexes of copper(II) and zinc(II) with ATP and L-histidinate ($hisO^-$) or histamine (hm). Aromatic-ring stacking interactions between the purine base of nucleotides and suitable aromatic side-chain residues, like the imidazole group, have been reported.[18] The aim of this work is to assess the role played by the metal ions in the occurrence of stacking interaction. In order to have homogeneous data, we have also determined the thermodynamic parameters concerning the binary complexes of L-histidine and histamine under the same experimental conditions (the binary ATP systems have already been reported).[17]

Many structures have been proposed[19,20] for L-histidine complexes with metal ions. On the basis of ΔH° and ΔS° values, and by the contemporary investigation of the corresponding histamine complexes, it has been possible to elucidate the bonding characteristics of most of the species present in aqueous solutions of copper(II) and zinc(II) with this amino acid.

Experimental

Chemicals.—ATP was a Merck product; its purity was checked as previously reported.[17] L-Histidine dihydrochloride and histamine dihydrochloride were obtained from Fluka. Their purity was determined alkalimetrically (using KOH) and was always higher than 99.5%. $Zn(NO_3)_2$ and $Cu(NO_3)_2$ were prepared from zinc oxide and basic copper(II) carbonate respectively by adding a slight excess of HNO_3. The stock solutions were determined by titration with ethylenediaminetetra-acetate. The ionic strength was adjusted to 0.1 mol dm^{-3} by adding KNO_3 (Fluka). Other details were previously reported.[17]

Potentiometric Measurements.—The potentiometric apparatus was as previously described.[17] Solutions (25—50 cm^3) containing a metal ion and two ligands were titrated with standard KOH until a precipitate was observed. Some titrations were also performed by titrating solutions containing the metal ion and histamine or L-histidine with ATP. The solutions were freshly prepared to avoid the ATP hydrolytic reaction. Also the solutions of copper(II)–histidine were prepared freshly for each experiment to avoid the formation of other decomposition compounds of undetermined nature.

Experimental details are reported in Table 1. Other details have been reported previously.[17]

Calorimetric Measurements.—The calorimetric measurements were performed at 25.000 ± 0.001 °C employing an LKB precision calorimeter model 8700 and a 100 cm^3 titration vessel (LKB model 8726-1). In order to determine the formation heats, the following measurements were performed.

(*a*) The protonation heats of histamine and L-histidine were measured using 80—95 cm^3 of the ligand solutions, neutralized in the case of the amino acid up to 95% with KOH, and titrated with standard HNO_3.

(*b*) The formation heats of the histamine or L-histidine binary complexes were determined on solutions (80—95 cm^3) containing the ligands by titrating with a standard metal ion solution.

(*c*) Ternary complex formation heats were determined by the same procedure as for the binary systems, except that the initial solution contained ATP also.

The reaction heats, corrected for the dilution heats deter-

† *Non-S.I. unit employed*: cal = 4.184 J.

mined in separate experiments, were calculated and experimental details are reported in Table 2.

Calculations.—The calculations concerning the potential, $E^{\ominus}$, of the electrodic system, the purity of the ligands, and the excess amount of HNO_3 in the metal ion stock solutions were performed by the least-squares computer program ACBA,[21] which minimizes the error squares sum in the titre. The calculations concerning the formation constants of the ternary complexes were performed by two least-squares computer programs: (*i*) SCOGSB,[22] which minimizes the error squares sum in titre and (*ii*) MINIQUAD 76A,[23] which minimizes the error squares sum in the analytical concentrations. In performing the calculations, we took into consideration two problems.

(*a*) As potassium and sodium ions form weak complexes with ATP, we considered a five mass-balance equation system for ATP ternary complexes, also using as input data the concentration of the alkali metal ion and the formation constant of its ATP complex, already studied.[24]

(*b*) Since the ionic strength of some solutions is greater than 0.1 mol dm^{-3} without the addition of KNO_3, we used a modified version of MINIQUAD,[25] in which the changes in the ionic strength are also considered. When performing the calculations with SCOGSB, the standard deviation was always <0.01 cm^3, whereas the standard deviation in the analytical concentration was always $<1\%$ when using MINIQUAD.

The heats of the ligand protonation, as well as of binary and ternary complex formations, were calculated by the least-squares computer program DOEC,[26] which minimizes the error squares sum in the reaction heat, Q. Also in this case the changes in the ionic strength and the formation of alkali metal complexes with ATP were taken into consideration. The standard deviation in Q was always less than 0.05 cal.

In examining the potentiometric data, the use of statistical methods was necessary in order to choose the best of all the possible models. To this end, the statistical factor R (see ref. 27) was used, according to Vacca *et al.*[28]

Throughout the paper, the errors are expressed as three times the standard deviation (3σ) or as the uncertainty range (maximum deviation from the mean).

The thermodynamic parameters of protonation and complexation of ATP, reported elsewhere,[17,24] are listed in Table 3.

Table 1. Experimental details of potentiometric measurements at 25 °C and I = 0.1 mol dm^{-3} [a]

M	L	c_M^0 [b]	c_{ATP}^0 [b]	c_L^0 [b]
Zn^{2+}	$hisO^-$	4.1	7.8	3.9
		4.1	3.9	3.9
		8.1	7.9	7.7
		8.1	7.8	7.7
		8.1	15.4	7.7
Cu^{2+}	$hisO^-$	4.0	7.2	3.9
		4.0	3.9	3.9
		8.0	15.7	7.7
		8.0	7.9	7.7
Zn^{2+}	hm	4.1	3.9	3.8
		4.1	3.9	3.8
		8.1	7.9	7.6
		8.1	15.8	7.6
Cu^{2+}	hm	4.0	4.0	3.8
		4.0	7.2	3.8
		8.0	15.9	7.6
		8.0	7.9	7.6

[a] Initial volume 25—50 cm^3; titrant, KOH (0.25 mol dm^{-3}); pH range 3—7 for Zn^{2+} complexes, 3—6 for Cu^{2+} complexes. [b] Initial analytical concentrations (mmol dm^{-3}).

Results and Discussion

Simple Complexes.—The stability of copper(II) and zinc(II) complexes with histamine or L-histidine has been widely studied and the corresponding formation constants have been reported.[29] On the basis of potentiometric data obtained under the same experimental conditions,[30-32] we have determined calorimetrically the corresponding values of enthalpy and entropy changes, reported in Table 4. Thermodynamic data for these systems have already been reported, particularly for copper(II), under different experimental conditions.[33-39] The comparison of our data with data obtained by others under

Table 2. Experimental details of calorimetric measurements at 25 °C and I = 0.1 mol dm^{-3} (KNO_3) [a]

M	L	c_L^0 [b]	c_{ATP}^0 [b]	Titrant [b]	pH [c]
—	$hisO^-$, hm	3—10	—	HNO_3 (150)	10—2
Zn^{2+} [d]	$hisO^-$	2—15	—	$Zn(NO_3)_2$ (123.4)	9—5.5
Cu^{2+} [e]	$hisO^-$	2—15	—	$Cu(NO_3)_2$ (124.0)	11—4
Zn^{2+} [f]	hm	2—10	—	$Zn(NO_3)_2$ (123.0)	7—4.5
Cu^{2+} [g]	hm	2—10	—	$Cu(NO_3)_2$ (124.0)	12—4.5
Zn^{2+}	$hisO^-$	10—30	13.5—26	$Cu(NO_3)_2$ (120—250)	
Cu^{2+}	$hisO^-$	7—26	7—30	$Cu(NO_3)_2$ (120—250)	
Zn^{2+}	hm	9—18	11—25	$Zn(NO_3)_2$ (120—250)	
Cu^{2+}	hm	7—17	12—29	$Cu(NO_3)_2$ (120—250)	

[a] Initial volume 85—90 cm^3. [b] Concentrations in mmol dm^{-3}. [c] The pH values were adjusted, for each solution, by adding KOH. [d] c_{Zn}/c_{hisO} = 0.02—1.5. [e] c_{Cu}/c_{hisO} = 0.02—1.5. [f] c_{Zn}/c_{hm} = 0.02—1.1. [g] c_{Cu}/c_{hm} = 0.02—1.5.

Table 3. $\Delta G^{\ominus}$, $\Delta H^{\ominus}$, and $\Delta S^{\ominus}$ values [a] for the protonation [b] and the zinc(II) and copper(II) complex formation [c] of ATP at 25 °C and I = 0.1 mol dm^{-3}

Reaction	$-\Delta G^{\ominus}$/kcal mol^{-1}	$\Delta H^{\ominus}$/kcal mol^{-1}	$\Delta S^{\ominus}$/cal K^{-1} mol^{-1}
$H^+ + ATP^{4-} \rightleftharpoons HATP^{3-}$	9.69	−0.2	32
$2H^+ + ATP^{4-} \rightleftharpoons H_2ATP^{2-}$	15.25	−3.8	38
$Cu^{2+} + ATP^{4-} \rightleftharpoons [Cu(ATP)]^{2-}$	8.65	0.84	32.5
$Cu^{2+} + 2ATP^{4-} \rightleftharpoons [Cu(ATP)_2]^{6-}$	11.6	−1.7	32
$Cu^{2+} + ATP^{4-} + H^+ \rightleftharpoons [Cu(ATP)H]^-$	13.66	−3.7	33
$2Cu^{2+} + ATP^{4-} \rightleftharpoons [Cu_2(ATP)]$	11.94	5.1	57
$Zn^{2+} + ATP^{4-} \rightleftharpoons [Zn(ATP)]^{2-}$	7.13	3.9	37
$Zn^{2+} + 2ATP^{4-} \rightleftharpoons [Zn(ATP)_2]^{6-}$	9.7	1.2	37
$Zn^{2+} + ATP^{4-} + H^+ \rightleftharpoons [Zn(ATP)H]^-$	12.57	0.9	45
$2Zn^{2+} + ATP^{4-} \rightleftharpoons [Zn_2(ATP)]$	9.65	6.9	56

[a] The values were corrected for the formation of Na^+- and K^+-ATP complexes. [b] From ref. 24. [c] From ref. 17.

Table 4. Thermodynamic parameters for proton–, copper(II)–, zinc(II)–histidinate and –histamine complexes at 25 °C and I = 0.1 mol dm^{-3} (KNO_3)

Reaction	log β [a]	$-\Delta G^{\ominus}$/kcal mol^{-1}	$-\Delta H^{\ominus}$ [b]/kcal mol^{-1}	$\Delta S^{\ominus}$[b]/cal K^{-1} mol^{-1}
$H^+ + hisO^- \rightleftharpoons HhisO$	9.09	12.40	10.53(5)	6.3(2)
$2H^+ + hisO^- \rightleftharpoons H_2hisO^+$	15.12	20.63	17.48(8)	10.6(4)
$3H^+ + hisO^- \rightleftharpoons H_3hisO^{2+}$	16.9	23.1	18.2(2)	16.4(7)
$H^+ + hm \rightleftharpoons Hhm^+$	9.79	13.36	12.15(8)	4.1(4)
$2H^+ + hm \rightleftharpoons H_2hm^{2+}$	15.86	21.64	19.67(11)	6.6(5)
$Cu^{2+} + hisO^- \rightleftharpoons [Cu(hisO)]^+$	10.15	13.85	10.6(1)	10.9(4)
$Cu^{2+} + hisO^- + H^+ \rightleftharpoons [Cu(hisO)H]^{2+}$	14.17	19.33	13.8(2)	18.5(7)
$Cu^{2+} + 2hisO^- \rightleftharpoons [Cu(hisO)_2]$	18.13	24.73	19.6(2)	17.2(7)
$Cu^{2+} + 2hisO^- + H^+ \rightleftharpoons [Cu(hisO)_2H]^+$	23.87	32.6	25.4(3)	24(1)
$Cu^{2+} + 2hisO^- + 2H^+ \rightleftharpoons [Cu(hisO)_2H_2]^{2+}$	27.10	37.0	27(1)	34(4)
$2Cu^{2+} + 2hisO^- \rightleftharpoons [Cu_2(hisO)_2H_{-2}] + 2H^+$	8.03	10.95	3.6(9)	25(4)
$Cu^{2+} + 2hisO^- \rightleftharpoons [Cu(hisO)_2H_{-1}]^- + H^+$	6.80	9.28	9(1)	1(4)
$Cu^{2+} + hm \rightleftharpoons [Cu(hm)]^{2+}$	9.56	13.04	12.1(2)	3.2(4)
$Cu^{2+} + hm + H^+ \rightleftharpoons [Cu(hm)H]^{3+}$	12.86	17.53	17.9(4)	−1(2)
$Cu^{2+} + 2hm \rightleftharpoons [Cu(hm)_2]^{2+}$	16.12	21.98	22.2(3)	−0.7(7)
$Cu^{2+} + 2hm + H^+ \rightleftharpoons [Cu(hm)_2H]^{3+}$	21.9	29.8	29.0(4)	3(2)
$2Cu^{2+} + 2hm \rightleftharpoons [Cu_2(hm)_2H_{-2}]^{2+} + 2H^+$	7.44	10.15	8.8(5)	4(2)
$Cu^{2+} + 2hm \rightleftharpoons [Cu(hm)_2H_{-1}]^+ + H^+$	5.38	7.34	9.8(6)	−8(3)
$Zn^{2+} + hisO^- \rightleftharpoons [Zn(hisO)]^+$	6.53	8.91	4.81(2)	13.7(7)
$Zn^{2+} + hisO^- + H^+ \rightleftharpoons [Zn(hisO)H]^{2+}$	11.56	15.77	11.4(3)	15(2)
$Zn^{2+} + 2hisO^- \rightleftharpoons [Zn(hisO)_2]$	11.92	16.26	10.9(3)	18(2)
$Zn^{2+} + hm \rightleftharpoons [Zn(hm)]^{2+}$	5.23	7.13	5.71(2)	4.7(7)
$Zn^{2+} + hm + H^+ \rightleftharpoons [Zn(hm)H]^{3+}$	11.44	15.61	14.5(3)	4(2)
$Zn^{2+} + 2hm \rightleftharpoons [Zn(hm)_2]^{2+}$	10.18	13.89	10.4(3)	12(1)

[a] From refs. 30—32. [b] Values in parentheses are 3σ.

the same experimental conditions [36,37] shows an excellent agreement as regards protonation values, while some differences are observed in the complexation values. In our opinion, this discrepancy is due to neglect of the protonated complexes in the speciation reported previously.[36,37]

The species pertinent to the equilibrium $Zn + L \rightleftharpoons [Zn(L)]$ are favoured both enthalpically and entropically (see Table 4). The larger stability of the L-histidinate complex with respect to the corresponding histamine complex is due to the entropic contribution, while with $[Zn(hm)]^{2+}$ the enthalpic contribution is slightly greater. This comparison suggests that the $hisO^-$ behaves as a tridentate ligand, since the differences in $\Delta H^{\ominus}$ and $\Delta S^{\ominus}$ values with respect to histamine may be ascribed to the co-ordination of the carboxylic oxygen. This co-ordination gives rise to an endothermic contribution and a higher $\Delta S^{\ominus}$ value, owing to the partial neutralization of the metal ion charge.

The formation of the bis-complexes is enthalpically and entropically favoured. However, unlike mono-complex formation, the reaction $[Zn(L)] + L \rightleftharpoons [Zn(L)_2]$ is more exothermic in the case of $[Zn(hisO)_2]$ than for $[Zn(hm)_2]^{2+}$. This different behaviour may be explained supposing that, as is likely, in all these complexes the zinc(II) ion achieves tetrahedral co-ordination. Thus, in the considered reaction, if we assume that in $[Zn(hisO)_2]$ both histidinate molecules co-ordinate as does histamine, the co-ordination of the second molecule requires the removal of the carboxylic oxygen bond of the mono-complex. This conclusion about the structure of the $[Zn(hisO)_2]$ complex is in accordance with the reports of Williams [40] and Brookes and Pettit.[41] Also, Morris and Martin [42] proposed that this complex possesses a significant amount of six-co-ordinate character. The results of Cotton and co-workers [43] and Harding and Cole [44] show that in this species in the solid state, zinc(II) is tetrahedral and the two carboxylic oxygens approach the metal closely enough (2.8—2.9 Å) to be considered as loosely co-ordinated.[45]

Both the copper(II) mono-complexes are enthalpically and entropically stabilized. Analogously to zinc(II) species, the formation of the histamine complex is accompanied by a larger enthalpy and a lesser entropy contribution with respect to histidine. As in the case of zinc(II) complexes and on the basis of similar considerations, it can be proposed that also in this species histidine behaves as a tridentate ligand. This conclusion is in agreement with what was suggested by Martin and co-workers.[46] on the basis of spectroscopic measurements and by Williams [38] on the basis of thermodynamic data {Williams reports a greater exothermicity in the formation of $[Cu(hisO)]^+$ with respect to $[Cu(hm)]^{2+}$}. This greater exothermicity, not easily explainable, was not found by us nor by Meyer and Bauman,[35] but it is contradictory to recent proposals on the basis of e.s.r. data,[47] according to which a histamine-like co-ordination would be present in $[Cu(hisO)]^+$.

Also the bis-complex formation shows the same behaviour as for the mono-complexes, *i.e.* $[Cu(hisO)_2]$ is less enthalpically and more entropically stabilized with respect to $[Cu(hm)_2]^{2+}$. As regards $[Cu(hisO)_2]$, our data seem to suggest that both the histidine molecules are tridentate, giving rise to a distorted octahedral complex. Every conceivable structure has been suggested in the past for $[Cu(hisO)_2]$; however, our structure is in agreement with the conclusions of Morris and Martin [42] and Barnes and Pettit,[37] as well as with a recent c.d. investigation,[48,49] but disagrees with recent proposals on the basis of stability constant values only,[50] and on the basis of n.m.r. data.[51] Unfortunately, no data can be obtained from solid-state investigation, due to the failure to prepare crystals of $[Cu(hisO)_2]$. Recently the structure of diaqua(L-histidinato)(D-histidinato)copper(II) tetrahydrate has been reported.[52] As regards the bis(histamine) complex, on the basis of the negative $\Delta S^{\ominus}$ of formation, it is reasonable to propose that the copper(II) ion preserves some degree of axial interaction with the solvent molecules, while four nitrogen atoms should occupy the in-plane co-ordination positions. On the other hand, an octahedral structure has been determined by an *X*-ray investigation of $[Cu(hm)_2(ClO_4)_2]$.[53] Conclusions from comparison between solid-state and solution data should be drawn with great care.

Table 5. Thermodynamic parameters of reactions occurring in the studied binary systems. Some other reactions are reported for comparison [a]

Reaction	$\Delta G^{\ominus}$/kcal mol^{-1}	$\Delta H^{\ominus}$/kcal mol^{-1}	$\Delta S^{\ominus}$/cal K^{-1} mol^{-1}	Ref.
$Cu^{2+} + H_3hisO^{2+} \rightleftharpoons [Cu(hisO)H]^{2+} + 2H^+$	3.8	4.4	2.1	*b*
$Cu^{2+} + H_2hm^{2+} \rightleftharpoons [Cu(hm)]^{2+} + 2H^+$	8.6	7.6	−3.4	*b*
$Cu^{2+} + H_2impa^{+} \rightleftharpoons [Cu(impa)]^{+} + 2H^+$	9.7	5.2	−15.1	35
$Cu^{2+} + H_2trpO^{+} \rightleftharpoons [Cu(trpO)]^{+} + 2H^+$	4.7	5.9	4.0	17
$Zn^{2+} + H_3hisO^{2+} \rightleftharpoons [Zn(hisO)H]^{2+} + 2H^+$	7.2	6.8	−1.4	*b*
$Zn^{2+} + H_2hm^{2+} \rightleftharpoons [Zn(hm)]^{2+} + 2H^+$	14.6	14.0	−1.9	*b*
$Zn^{2+} + H_2trpO^{+} \rightleftharpoons [Zn(trpO)]^{+} + 2H^+$	9.6	8.9	−2.5	17
$Cu^{2+} + H_2hm^{2+} \rightleftharpoons [Cu(hm)H]^{3+} + H^+$	4.0	1.7	−7.6	*b*
$Cu^{2+} + NH_4^{+} \rightleftharpoons [Cu(NH_3)]^{2+} + H^+$	6.8	7.5	2.5	*c*
$Cu^{2+} + Him^{+} \rightleftharpoons [Cu(im)]^{2+} + H^+$	5.6	2.8	−9.5	*c*
$Zn^{2+} + H_2hm^{2+} \rightleftharpoons [Zn(hm)H]^{3+} + H^+$	6.0	5.2	−2.6	*b*
$Zn^{2+} + NH_4^{+} \rightleftharpoons [Zn(NH_3)]^{2+} + H^+$	9.4	9.8	1.3	*c*
$Zn^{2+} + Him^{+} \rightleftharpoons [Zn(im)]^{2+} + H^+$	2.5	0.6	−6.5	*c*

[a] $impa^- = \beta$-(4-Imidazolyl)propionate, im = imidazole, $trpO^- =$ tryptophanate. [b] This work. [c] J. J. Christensen, D. J. Eatough, and R. M. Izatt, 'Handbook of Metal Ligand Heats and Related Thermodynamic Quantities,' 2nd edn., Marcel Dekker, New York, 1975.

Table 6. Thermodynamic parameters [a] for the possible co-ordination modes in protonated simple complexes of copper(II) and zinc(II) with L-histidine or histamine

Co-ordination mode	Reaction [b]	log *K*	$-\Delta G^{\ominus}$/ kcal mol^{-1}	$-\Delta H^{\ominus}$/ kcal mol^{-1}	$\Delta S^{\ominus}$/ cal K^{-1} mol^{-1}	Ref.
Impa-like (1)	$Cu^{2+} + HhisO \rightleftharpoons [Cu(hisO)H]^{2+}$	5.1	6.9	3.3	12.2	*c*
	$Cu^{2+} + impa^- \rightleftharpoons [Cu(impa)]^{+}$	4.5	6.1	3.6	8.2	35
Glycine-like (2)	$Cu^{2+} + HhisO \rightleftharpoons [Cu(hisO)H]^{2+}$	8.1	11.1	6.9	14.2	*c*
	$Cu^{2+} + trpO^- \rightleftharpoons [Cu(trpO)]^{+}$	8.3	11.3	5.9	18.0	17
Histamine-like (3)	$Cu^{2+} + HhisO \rightleftharpoons [Cu(hisO)H]^{2+}$	12.4	16.9	13.1	12.7	*c*
	$Cu^{2+} + hm \rightleftharpoons [Cu(hm)]^{2+}$	9.6	13.0	12.1	3.2	*c*
Glycine-like (2)	$Zn^{2+} + HhisO \rightleftharpoons [Zn(hisO)H]^{2+}$	5.5	7.5	4.5	11	*c*
	$Zn^{2+} + trpO^- \rightleftharpoons [Zn(trpO)]^{+}$	4.7	6.4	2.9	12	17
Histamine-like (3)	$Zn^{2+} + HhisO \rightleftharpoons [Zn(hisO)H]^{2+}$	9.8	13.3	10.7	9	*c*
	$Zn^{2+} + hm \rightleftharpoons [Zn(hm)]^{2+}$	5.2	7.1	5.7	5	*c*
Imidazole-like (1)	$Cu^{2+} + Hhm^{+} \rightleftharpoons [Cu(hm)H]^{3+}$	3.1	4.2	5.8	−5	*c*
	$Cu^{2+} + im \rightleftharpoons [Cu(im)]^{2+}$	4.3	5.9	7.2	−4	*d*
Ammonia-like (2)	$Cu^{2+} + Hhm^{+} \rightleftharpoons [Cu(hm)H]^{3+}$	6.8	9.3	10.4	−3.5	*c*
	$Cu^{2+} + NH_3 \rightleftharpoons [Cu(NH_3)]^{2+}$	4.1	5.4	5.0	2.1	*d*
Imidazole-like (1)	$Zn^{2+} + Hhm^{+} \rightleftharpoons [Zn(hm)H]^{3+}$	1.7	2.3	2.4	0	*c*
	$Zn^{2+} + im \rightleftharpoons [Zn(im)]^{2+}$	2.3	3.1	4	−3	*d*
Ammonia-like (2)	$Zn^{2+} + Hhm^{+} \rightleftharpoons [Zn(hm)H]^{3+}$	5.4	7.3	7.0	2	*c*
	$Zn^{2+} + NH_3 \rightleftharpoons [Zn(NH_3)]^{2+}$	2.3	3.1	2.6	2	*d*
Both histidine molecules glycine-like (4)	$Cu^{2+} + 2HhisO \rightleftharpoons [Cu(hisO)_2H_2]^{2+}$	15.0	20.5	13	25	*c*
	$Cu^{2+} + 2trpO^- \rightleftharpoons [Cu(trpO)_2]$	15.4	21.0	13	26	17
Tridentate	$[Cu(hisO)H]^{2+} + hisO^- \rightleftharpoons [Cu(hisO)_2H]^{+}$	9.7	13.3	11.6	6	*c*
	$[Cu(thrO)]^{+} + hisO^- \rightleftharpoons [Cu(thrO)(hisO)]$	10.0	13.6	11.8	6	64
Bidentate	$[Cu(hm)H]^{3+} + hm \rightleftharpoons [Cu(hm)_2H]^{3+}$	9.0	12.3	11.1	4	*c*
	$Cu^{2+} + hm \rightleftharpoons [Cu(hm)]^{2+}$	9.6	13.0	12.1	3	*c*

[a] $\log K(1) = \log \beta_{111} - \log K_1^H$, $\log K(2) = \log \beta_{111} - \log K_2^H$, $\log K(3) = \log \beta_{111} - \log K_3^H$, $\log K(4) = \log \beta_{1222} - 2\log K_2^H$; $\beta_{pqr} = [M_pL_qH_r]/[M]^p[L]^q[H]^r$. [b] $thrO^- =$ Threoninate. [c] This work. [d] See footnote (*c*) of Table 5.

Protonated Simple Complexes.—The structure of protonated histidine complexes has been interpreted in a number of different ways since the amino acid can co-ordinate in three different ways: glycine-like, histamine-like, or as β-(4-imidazolyl)propionic acid. Values of thermodynamic parameters of reactions involving these and other ligands are reported in Tables 5 and 6 for the sake of comparison.

As regards the species $[M(hisO)H]^{2+}$, two kinds of comparisons have been considered. The first refers to the substitution reaction of protons by the metal ion in two co-ordination sites of the ligand. This comparison has the advantage of comparing exactly the same process in different ligands, but it has the disadvantage of considering a global process occurring in several steps in different molecules. Small differences in each step due to the difference of the compared molecules might be significant overall. The other comparison considers a more limited process with fewer elementary steps and thus does not suffer from this disadvantage. On the other hand, the thermodynamic values compared do not correspond to any real reaction and are calculated starting from the knowledge of what site is involved in each protonation step. In this procedure it is necessary to assume that the species charge does not influence the thermodynamic parameters of protonation.

In this case, the two different methods of comparison agree with each other in suggesting a substituted glycine-like co-ordination in $[Cu(hisO)H]^{2+}$, particularly suggested by the first comparison (Table 5). This conclusion is in agreement with the views of Martin and co-workers [46] and Brookes and Pettit,[41] as well as with the results of a recent c.d. investigation.[48]

As regards $[Zn(hisO)H]^{2+}$, the comparisons do not give so straightforward an indication of the chelation of histidine to

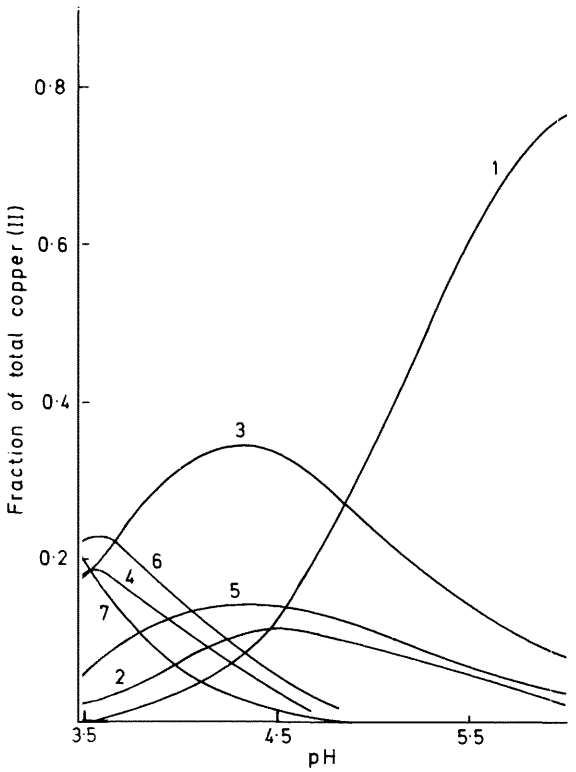

Figure 1. Species distribution diagram for the system Cu^{2+}–ATP^{4-}–$hisO^{-}$: (1) $[Cu(ATP)(hisO)]^{3-}$, (2) $[Cu(ATP)(hisO)H]^{2-}$, (3) $[Cu(ATP)]^{2-}$, (4) $[Cu(ATP)H]^{-}$, (5) $[Cu(hisO)]^{+}$, (6) $[Cu(hisO)H]^{2+}$, (7) free Cu^{2+}. In Figures 1—4: $c_M = c_L = 5$, $c_{ATP} = 7.5$ mmol dm^{-3} (M = Cu^{2+} or Zn^{2+}, L = $hisO^{-}$ or hm)

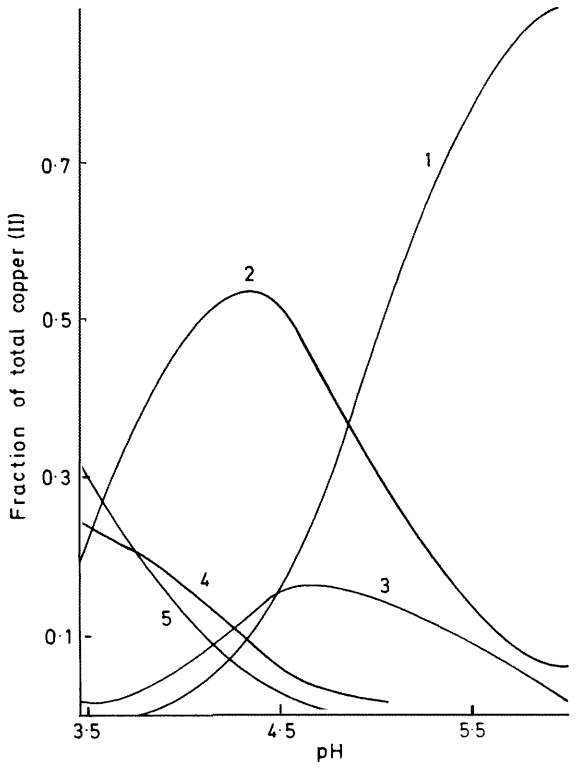

Figure 2. Species distribution diagram for the system Cu^{2+}–ATP^{4-}–hm: (1) $[Cu(ATP)(hm)]^{2-}$, (2) $[Cu(ATP)]^{2-}$, (3) $[Cu(ATP)(hm)H]^{-}$, (4) $[Cu(ATP)H]^{-}$, (5) free Cu^{2+}

zinc(II), also because we have not found the corresponding data for β-(4-imidazolyl)propionic acid. Nevertheless, a glycine-like co-ordination is suggested also in this complex by the first comparison procedure.

In the literature other structures have been proposed for these protonated species, namely protonation of the amino group with the imidazole nitrogen co-ordination only (leaving the carboxyl group free),[50,54] or protonation of the amino group and an imidazolylpropionic acid type of co-ordination.[38,54-58] In conclusion, the location of the proton and the co-ordination sites in $[M(hisO)H]^{2+}$ species are so controversial that it has been proposed that this species may possess more than one structure.[59] Comparable thermodynamic values (Tables 5 and 6) for the protonated histamine complexes to those of $[ML]^{2+}$ imidazole complexes suggest that metal–ligand binding for all these complexes is similar, *i.e.* co-ordination of metal ion with imidazole nitrogen. The same conclusions have been drawn on the basis of the stability constants only, both for zinc(II) and for copper(II) [50,60] as well as in a recent Raman investigation for copper(II).[61]

As regards $[Cu(hisO)_2H_2]^{2+}$, the comparison of the thermodynamic parameters with the bis(tryptophanato)copper(II) complex (Table 6), suggests that both the histidine molecules co-ordinate glycine-like. This is consistent with the proposals of Kruck and Sarkar,[58] but in disagreement with other reports.[38,50,56] Histidine behaves as a tridentate ligand in $[Cu(hisO)_2H]^{+}$. Interestingly the same structure has been found in the solid state.[62] In Table 6 we compare the addition reactions of a histidinate molecule to $[Cu(hisO)H]^{2+}$ and $[Cu(thrO)]^{+}$, respectively; very similar thermodynamic parameters are found for the two species. Therefore, similar structures may be hypothesized for $[Cu(hisO)_2H]^{+}$ and [Cu(hisO)(thrO)], which is known [63,64] to have all the five donor atoms bound to the copper(II). This conclusion is in agreement with the data of refs. 41, 42, 58, and 48, but in disagreement with those of 35, 38, 50, and 65. An e.s.r. investigation [47] has confirmed the in-plane co-ordination of three nitrogen atoms, and a hydrogen bond between a free carboxylic group and the protonated imidazole nitrogen of the other molecule. While our data disagree with the presence of an unco-ordinated carboxylic group, it may not be excluded that a hydrogen bond exists between the imidazole nitrogen and an axially co-ordinated carboxylic group. A similar structure has been proposed for mixed complexes of histidine,[66,67] and a better insight into the structure might be achieved from the thermodynamic parameters of the complex [Cu(L-hisO)(D-hisO)H]$^{+}$. As regards $[Cu(hm)_2H]^{3+}$, the data for the equilibrium reported in Table 6 clearly seem to indicate that on adding an hm molecule to $[Cu(hm)H]^{3+}$, the metal ion is bound to three nitrogen atoms, while the other imidazole nitrogen is protonated, as already suggested.[49,61]

Mixed Complexes.—Under the investigated experimental conditions, two ternary species, [M(ATP)(L)H] and [M(ATP)(L)], have been found. In Figures 1—4 we report the species distribution *vs.* pH for the ternary systems studied here. At the considered analytical concentrations, the amount of copper(II) protonated mixed species in both the systems is always less than 20% of the total copper(II) concentration and it is at a maximum at pH 4.5; the unprotonated ternary species prevail at pH > 5, with a degree of formation larger than 50%. In the corresponding zinc(II) systems the protonated mixed species are present in larger concentration (up to 30%), with respect to copper(II) systems, with a maximum at pH 6,

Table 7. Thermodynamic parameters * for the mixed complex formation at 25 °C and I = 0.1 mol dm^{-3}

Reaction	log β	$\Delta G^{\ominus}$/kcal mol^{-1}	$-\Delta H^{\ominus}$/kcal mol^{-1}	$\Delta S^{\ominus}$/cal K^{-1} mol^{-1}
$Cu^{2+} + ATP^{4-} + hisO^- \rightleftharpoons [Cu(ATP)(hisO)]^{3-}$	15.25(7)	20.8(1)	8.3(2)	42(1)
$Cu^{2+} + ATP^{4-} + hisO^- + H^+ \rightleftharpoons [Cu(ATP)(hisO)H]^{2-}$	19.6(2)	26.7(3)	10.4(2)	55(2)
$Cu^{2+} + ATP^{4-} + hm \rightleftharpoons [Cu(ATP)(hm)]^{2-}$	15.35(5)	20.9(1)	5.6(2)	51(1)
$Cu^{2+} + ATP^{4-} + hm + H^+ \rightleftharpoons [Cu(ATP)(hm)H]^-$	19.8(1)	27.1(2)	8.5(5)	62(2)
$Zn^{2+} + ATP^{4-} + hisO^- \rightleftharpoons [Zn(ATP)(hisO)]^{3-}$	10.68(8)	14.6(1)	3.1(2)	39(1)
$Zn^{2+} + ATP^{4-} + hisO^- + H^+ \rightleftharpoons [Zn(ATP)(hisO)H]^{2-}$	16.8(3)	22.9(4)	8.1(3)	50(2)
$Zn^{2+} + ATP^{4-} + hm \rightleftharpoons [Zn(ATP)(hm)]^{2-}$	10.75(8)	14.7(1)	6.2(2)	28(1)
$Zn^{2+} + ATP^{4-} + hm + H^+ \rightleftharpoons [Zn(ATP)(hm)H]^-$	17.5(3)	23.9(4)	10.0(3)	46(2)

* Values in parentheses are 3σ.

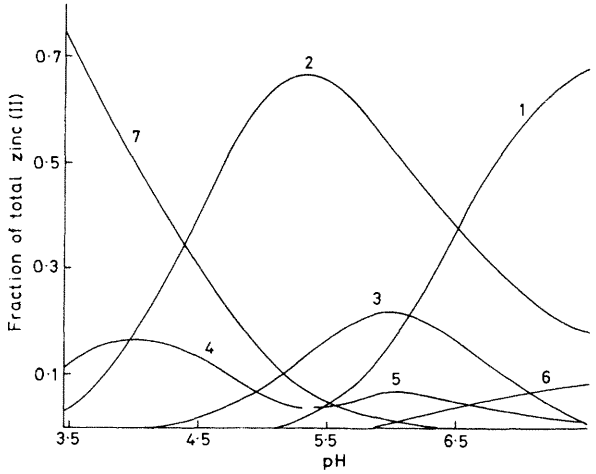

Figure 3. Species distribution diagram for the system Zn–ATP^{4-}–hisO$^-$: (1) [Zn(ATP)(hisO)]$^{-3}$, (2) [Zn(ATP)]$^{2-}$, (3) [Zn(ATP)(hisO)H]$^{2-}$, (4) [Zn(ATP)H]$^-$, (5) [Zn(hisO)]$^+$, (6) [Zn(hisO)$_2$], (7) free Zn^{2+}

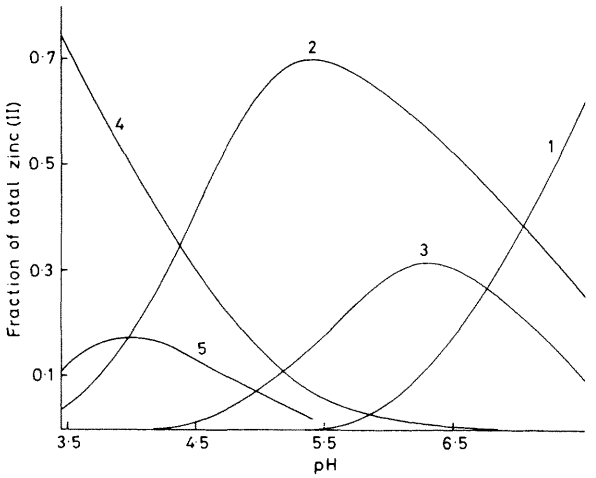

Figure 4. Species distribution diagram for the system Zn–ATP^{4-}–hm: (1) [Zn(ATP)(hm)]$^{2-}$, (2) [Zn(ATP)]$^{2-}$, (3) [Zn(ATP)(hm)H]$^-$, (4) free Zn^{2+}, (5) [Zn(ATP)H]$^-$

while the unprotonated species becomes prevalent at pH > 7.5.

The stability constants (T = 25 °C and I = 0.1 mol dm^{-3} in KCl) for ternary systems of ATP and L-histidine with a number of metal ions have been reported recently.[68] The difference between the values of these authors and our values (Table 7), in our opinion, may not be ascribed to the differences in the simple parent complexes only,[17,30,31] but also to the neglect of the protonated ternary species. This fact is shown by the Δlog K values,[69] which are also different.

We observe that the enthalpy of formation, $\Delta G^{\ominus}$, of [Cu(ATP)(hisO)]$^{3-}$ is equal to that of [Cu(ATP)(hm)]$^{2-}$, showing that the ATP co-ordination cancels out the difference of stability between the simple parent complexes. On this basis, it may be supposed that in these ternary complexes both histamine and histidine co-ordinate to copper(II), through the same donor atoms, namely the amine and the imidazole nitrogens. In these complexes, the in-plane co-ordination is completed by the bonds of ATP through the two oxygen atoms of β- and γ-phosphate groups. Assuming an approximately square-planar co-ordination for copper(II), the more exothermic enthalpy change for the formation of [Cu(ATP)(hisO)]$^{3-}$ can be ascribed to a hydrogen-bonding type interaction between the carboxylate groups of hisO$^-$ and the amine group of the base of the nucleotide. The less positive entropy change accompanying the formation of L-histidinate ternary complexes with respect to the analogous complex of histamine can be due both to the stiffening of ligands consequent upon the bridge between the two non-co-ordinating groups and to the different degree of solvent interaction with metal ion. Hydrogen-bond formation between nucleic acid bases and biofunctional ligands in metal complexes has been previously reported.[70] Even if crystallographic results indirectly indicate the nature of the binding mode in solution, the fact that the amine group at the 6-position of the nucleotide ring is favourably placed to donate a hydrogen bond to an appropriate acceptor group on another ligand co-ordinated to the metal centre reinforces our hypothesis for the [Cu(ATP)(hisO)]$^{3-}$ complex.

As regards the protonated species, the differences observed between histamine and histidine complexes follow the same trend observed in the unprotonated complexes, as can be seen from the very similar values of the thermodynamic parameters for the protonation reactions of [M(ATP)(L)]$^{2-,3-}$ complexes. Though there are several possible protonation sites in these complexes, a comparison with the protonation step values of ATP (Table 3) suggests the protonation occurs at N(1).

Also, zinc(II) ternary complexes show equal values of $\Delta G^{\ominus}$. However, in this case, the individual enthalpy and entropy contributions to the overall stability have an opposite trend with respect to the copper(II) complexes: the histamine complex is more enthalpically and less entropically favoured. Another useful comparison may be made between [Cu(ATP)(hm)]$^{2-}$ and [Zn(ATP)(hm)]$^{2-}$, where we observe a behaviour opposite to that expected. As a general rule, both for O- and for N-co-ordination, copper(II) complexes show a more exothermic and a less entropic contribution with respect to

zinc(II), but in this case the trend is the opposite. Thus, we have to conclude that an additional effect takes place, altering the common trend in the thermodynamic parameters.

In a recent paper [71] it was reported that a stacking interaction, which may occur between aromatic and heteroaromatic rings, gives rise to a favourable enthalpic and an unfavourable entropic contribution. Thus, the observed values of thermodynamic parameters for $[Zn(ATP)(hm)]^{2-}$ may be ascribed to the occurrence of a stacking interaction between the ATP purine moiety and the histamine imidazole ring. This hypothesis also explains the difference observed between $[Zn(ATP)(hm)]^{2-}$ and $[Zn(ATP)(hisO)]^{3-}$, considering that in the latter complex there is no stacking interaction, probably due to steric hindrance of the carboxylic group. Experiments with a second independent method, in particular ^1H n.m.r. measurements considering the ambiguity of some spectrophotometric results,[15] would be highly desirable to confirm the conclusions on the mixed histidinate complex of zinc(II).

We may then conclude that the knowledge of the individual enthalpic and entropic contributions to the free energy is of considerable usefulness; this is particularly true, for instance, for systems such as zinc(II)–histamine–ATP, for which an equal value of $\Delta G^{\ominus}$ conceals structural differences, easily singled out by a complete thermodynamic analysis. We feel that the above assertion is obvious; it is not satisfactory to infer bonding details for mixed complexes on the basis of stability constants only, as has been done in the past.[72]

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