Co-ordination Properties of Cyclopeptides. Formation and Stability of Zinc(II) and Copper(II) Complexes of Histidine-containing Cyclopeptides, or Imidazole *

Giuseppe Arena,[a] Giuseppe Impellizzeri,[a] Giuseppe Maccarrone,[a] Giuseppe Pappalardo[b] and Enrico Rizzarelli[a,b]

[a] *Dipartimento di Scienze Chimiche, Università di Catania, 95125 Catania, Italy*

[b] *Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico Farmaceutico del CNR, 95125 Catania, Italy*

In order to obtain an improved understanding of the complexing properties of cyclopeptides involved in biological processes, the interaction of zinc(II) with cyclo(L-histidyl-L-histidyl) was studied by potentiometric and calorimetric techniques in aqueous solution. Comparison between the thermodynamic parameters of the complexes formed with those for analogous species formed with cyclo(glycyl-L-histidyl) allowed evidence to be obtained for the formation of chelate rings of unusual size. The thermodynamic quantities associated with copper(II) complex formation with cyclo(-Gly-His-) were determined. The role of the different stereochemical requirements of copper(II) and zinc(II) in the formation of large chelate rings was assessed by means of previously reported data concerning the copper(II)–cyclo(-His-His-) complexes.

Cyclopeptides have been known since the structure of Gramicidin S was discovered.[1] They are important for their biological functions such as hormones, toxins, antibiotics and regulators of ion transport.[1,2] Cyclohistidylproline was discovered in 1976,[3] and until now its biological properties, which include inhibition of the prolactin secretion, temperature regulation, sleep prolongation and modification of behavioural responses of experimental animals, have been demonstrated,[4] but its role still remains largely unexplained. Certain L-histidine-containing cyclopeptides have been shown to possess anti-oxidant activity *in vitro*[5–8] and *in vivo*.[9] They catalyse the oxidation of dopa (3,4-dihydroxyphenylalanine) and it has been proposed that this oxidation efficiency increased in the presence of copper(II).[10] Even though some studies on the complexing features towards transition-metal ions have been reported,[11–13] only few quantitative investigations on the formation, stability and co-ordination features of metal complexes with histidine-containing cyclodipeptides have been published.[14–17] Recently, a detailed thermodynamic and spectroscopic study of the complexes of cyclo(L-histidyl-L-histidyl), cyclo(-His-His-), with copper(II)[17] was carried out in order to obtain further information on the co-ordination ability of copper(II) at the imidazole moiety. Furthermore, on the basis of the speciation obtained in the above work, the superoxide dismutase-like activity of the copper(II) complexes of cyclo(-His-His-) was correctly determined and correlated with the structural features of the metal complexes.[18] Cyclo(L-histidyl-L-histidyl) was shown to chelate copper(II) by means of the two imidazole residues, both at 1 : 1 and 1 : 2 metal to ligand ratios, as found in the solid state for $[Cu\{cyclo(-His-His-)\}_2(NO_3)_2]$.[19] The thermodynamic parameters suggested that the formation of unusually sized chelate rings in aqueous solution was due to the favourable geometric disposition of the two imidazole rings stabilized by their non-covalent interactions both with the dioxopiperazine ring and with one another.[17]

In order to ascertain whether this tendency to form large chelate rings is metal-dependent and to what extent the different (geometric and electronic) co-ordination requirements are discriminating factors in the formation of metal complexes, we report a detailed thermodynamic investigation of zinc(II)–cyclo(-His-His-) complex formation in aqueous solution at 25 °C and $I = 0.1$ mol dm^{-3} (KNO_3). Potentiometric and calorimetric measurements were also carried out on zinc(II)–imidazole (Him) and cyclo(glycyl-L-histidyl), cyclo(-Gly-His-), under the same experimental conditions. These systems were used as references to obtain thermodynamic evidence for the formation of macrochelate rings. Furthermore, for a homogeneous and complete picture of the complexing features of these ligands, the formation and the stability of copper(II) complexes with cyclo(-Gly-His-) were also investigated. These data, together with those previously determined for the copper(II)–cyclo(-His-His-) complex,[17] were used to compare the characteristics of the copper(II) complexes with those of the analogous zinc(II) species.

Experimental

Materials.—Copper(II) nitrate was prepared from copper(II) basic carbonate by addition of a slight excess of HNO_3 and its concentration was determined by ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetate titration with the appropriate indicator. The excess of HNO_3 was determined by Gran's method, and by use of the ACBA computer program (see *Calculations*). Zinc(II) nitrate was obtained from ZnO previously calcined at 1100 °C, by adding a slight excess of HNO_3. The concentration of the zinc(II) stock solution was determined in the same manner as for the copper(II) solution.

The concentrations of stock solutions of HNO_3 and KOH were determined by titration with tris(hydroxymethyl)-aminomethane primary standard (Tris), and potassium hydrogenphthalate, respectively. All solutions were prepared with doubly distilled water. Other details were as previously reported.[17]

Synthesis of Cyclic Dipeptides.—The compound cyclo(-His-His-) was synthesised by cyclization of L-histidine methyl ester dihydrochloride in MeOH at 37 °C.[20] Cyclo(-Gly-His-) was

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Non-SI unit employed: cal = 4.184 J.

synthesized by adding triethylamine to a stirred suspension of L-histidine methyl ester dihydrochloride in dry chloroform. Benzyloxycarbonylglycyl 4-nitrophenyl ester was then added and the mixture stirred at room temperature overnight. The reaction mixture was extracted with water then with ammonia and finally with water until the washings were practically neutral. The organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and crystallized from ethyl acetate. The *N*-benzyloxycarbonylglycylhistidine methyl ester obtained was dissolved in absolute ethanol and hydrogenolysed over 10% palladium-on-charcoal catalyst. The *N*-deprotected dipeptide was then heated under reflux in anhydrous methanol and the desired cyclo(-Gly-His-) precipitated on cooling. Crystallization of the product from water–acetone gave colourless prisms.[21]

Potentiometric Titrations.—Computer-controlled potentiometric titrations were performed by two distinct Metrohm digital pH meters (model 654) equipped with model 109 glass electrodes and model 404 saturated calomel electrodes. The titration cell was thermostatted at 25.0 ± 0.1 °C, and all solutions were kept under an atmosphere of nitrogen, which was previously bubbled through a solution of the same ionic strength and temperature as the solution under study.

Titrations of HNO_3 with KOH were performed before and after each set of experiments to convert reading values into pH. The ionic strength was kept at 0.1 mol dm^{-3} (KNO_3). The experimental details are shown in Table 1.

Calorimetric Measurements.—The calorimetric data were obtained by titration using a Tronac isoperibol apparatus (model 450) equipped with a reaction Dewar (25 cm^3) at 25.000 ± 0.001 °C. The calorimetric apparatus was calibrated by titrating Tris or $HClO_4$ solutions with HCl or NaOH, respectively.[22,23] In all cases the titration data, corrected for all non-chemical energy terms, determined in separate experiments, were refined simultaneously to obtain the final ΔH° values. The experimental details are shown in Table 1.

Other experimental details were as previously reported.[17]

Calculations.—The calculations concerning the electrode system, E_j and slope were performed by the ACBA computer program,[24] which refines the parameters of acid–base titrations using a non-linear least-squares method minimizing the function $U = \Sigma(V_{i,\text{exptl}} - V_{i,\text{calc}})^2$, where V_i is the volume of the titrant added. All other potentiometric data were handled by the SUPERQUAD program.[25] This program minimizes the error-square sum based on the measured electrode potentials. For the analysis of residuals the procedure recommended by Vacca *et al.*[26] was followed. The enthalpies of formation were computed by means of the DOEC least-squares program,[27] which minimizes the function $U = \Sigma(Q_{j,\text{calc}} - Q_{j,\text{exptl}})^2$ where Q_j is the heat of reaction at the jth point and is related to ΔH° by $-Q_j = \Sigma\delta n_i \Delta H^\circ{}_i$ where δn_i and $\Delta H^\circ{}_i$ are the number of moles and the enthalpy of the ith species, respectively.

Results and Discussion

The reaction of the Him, cyclo(-L-His-L-His-) and cyclo(-Gly-L-His-) ligands with zinc(II) and copper(II) is represented in equation (1) where L is the appropriate ligand with charges

$$pM + qL + rH \rightleftharpoons M_pL_qH_r \quad (1)$$

omitted for simplicity. The stability constants are defined by equation (2). The equilibria (3)–(5) were considered to fit the experimental titration curves for the above reactions.

$$\beta_{pqr} = [M_pL_qH_r]/[M]^p[L]^q[H]^r \quad (2)$$

$$M + L \rightleftharpoons [ML] \quad (3)$$

$$M + 2L \rightleftharpoons [ML_2] \quad (4)$$

$$M + 3L \rightleftharpoons [ML_3] \quad (5)$$

A simple model has been proposed for the zinc(II)–cyclo(-His-His-) system by Kojima,[28] who took into account the [ML] and $[ML_2]$ species. Whereas that model is in accord with our results, the log K_1 value differs markedly from that determined in the present investigation. This may be due both to the very low concentrations employed and to the limited M:L ratios investigation by Kojima[28] (Table 2).

The zinc(II)–Him system has been extensively studied.[29–37] The protonation value is very close to that reported by Sigel and Saha[38] under the same experimental conditions. These authors concluded that only $[Zn(Him)]^{2+}$ formed under their experimental conditions (M:L = 1:1). This probably explains the discrepancy between their value and the values obtained in the present investigation at a larger metal:ligand ratio. Bauman and Wang[39] reported a ΔH° value for $[Zn(Him)]^{2+}$ of −3.8 kcal mol^{-1}. The difference between this and our value (Table 2) may be due to the fact that the 'Zn^{II} titration was terminated at low $\bar{n}$ value because of the precipitation of zinc imidazolate at higher $\bar{n}$ during the enthalpic titration'.[39] As shown in Table 2, the formation of $[Zn(Him)_2]^{2+}$ is more entropically and less enthalpically favoured than is that of $[Zn(Him)]^{2+}$. This trend recalls that found for other zinc(II) complexes in which the octahedral geometry present in the mono complex changes into the tetrahedral geometry preferred by zinc(II) in the bis complex, with a consequent increase in the metal desolvation process accounting for the more positive ΔS° and less negative enthalpy values.[40]

No thermodynamic data have until now been reported on metal-complex formation with either cyclo(-Gly-His-) or cyclo(-His-His-). The complex $[Zn\{cyclo(-Gly-His-)\}]^{2+}$ is less stable than $[Zn(Him)]^{2+}$ due to a less favourable enthalpy contribution, while the entropy term is less unfavourable (Table 2). This behaviour is similar to that found in the proton complex formation.[17,21] In the latter case, it has previously been shown[21] that the unprotonated cyclodipeptide exists in a folded conformation with the imidazole residue projected towards the dioxopiperazine ring, while in its protonated species this non-covalent interaction is lost due to the arrangement of the protonated imidazole moiety far away from this ring. Since non-covalent interactions are enthalpically favoured and entropically disfavoured,[21,41,42] the basicity decrease of the imidazole nitrogen in cyclo(-Gly-His-) compared to that of imidazole itself can be understood. In analogy with the protonation process, the interaction of the metal ion with the imidazole nitrogen again involves a change of disposition of the imidazole residue with a consequent unfavourable enthalpy contribution to the complex formation.

As expected, the formation of $[Cu\{cyclo(-Gly-His-)\}]^{2+}$ is enthalpically favoured. Its stability constant is smaller than that found for $[Cu(Him)]^{2+}$ (Table 2) and, as found for the analogous zinc(II) complex, this is due to a less favourable enthalpy contribution which can be explained in the same way. Copper(II) forms a bis complex with cyclo(-Gly-His-), again showing a stability constant smaller than that of $[Cu(Him)_2]^{2+}$. This results from a more favourable enthalpy change and a more negative entropy contribution. This is surprising since also in this step the binding of cyclo(-Gly-His-) involves an unfavourable enthalpy contribution due to displacement of the imidazole residue from the dioxopiperazine ring. The reason for this is not well understood.

The stability constant for $[Zn\{cyclo(-His-His-)\}]^{2+}$ is higher than that of $[Zn\{cyclo(-Gly-His-)\}]^{2+}$ but smaller than that of $[Zn(Him)_2]^{2+}$ ($\log\beta = 4.91$); in the latter species two nitrogens are involved in the co-ordination. This raises questions as to the number of nitrogen atoms of cyclo(-His-His-) involved in the co-ordination to Zn^{II}. For the analogous copper(II) species, *i.e.* $[Cu\{cyclo(-His-His)\}]^{2+}$, we have previously demonstrated by

Table 1 Summary of experimental parameters for potentiometric and calorimetric measurements at 25 °C and I = 0.1 mol dm^{-3} KNO_3

Concentration range, c/mol dm^{-3}

Cu^{2+}	Zn^{2+}	Him	cyclo(-Gly-His-)	cyclo(-His-His-)	Titrant	Concentration	pH range	No. of titrations	No. of points
Potentiometry									
0.0035–0.0060									284
			0.0063–0.0090		KOH	0.1001–0.1017	3.1–6.0	8	
	0.0050–0.0080	0.0160–0.0199				0.0998–0.1017	3.5–6.9	6	331
	0.0470–0.0055		0.0051–0.0096			0.0998–0.1017	2.7–7.2	4	203
	0.0050–0.0070			0.0051–0.0091		0.0999–0.1015	3.1–6.2	9	384
Calorimetry									
	0.0080–0.0099				Him–H_2im^+	0.4015, 0.2399	4.0–5.6	8	284
0.0047–0.0050					cyclo(-Gly-His-)–H^+	0.2001, 0.0700	2.0–4.2	4	106
	0.0037–0.0040				cyclo(-Gly-His-)–H^+	0.2001, 0.0700	2.6–4.2	4	90
				0.0058–0.066	Zn^{2+}	0.2032	4.5	6	263

Table 2 Thermodynamic parameters for the interactions of Him, cyclo(-Gly-His-) and cyclo(-His-His-) with Zn^{2+} at 25 °C and I = 0.1 mol dm^{-3} (KNO_3)*

Reaction	log K	$-\Delta G°$/ kcal mol^{-1}	$-\Delta H°$/ kcal mol^{-1}	$\Delta S°$/ cal K^{-1} mol^{-1}	Ref.
Zn^{2+} + Him $\rightleftharpoons$ $[Zn(Him)]^{2+}$	2.28(6)	3.11(8)	4.7(1)	−5.3(5)	This work
$[Zn(Him)]^{2+}$ + Him $\rightleftharpoons$ $[Zn(Him)_2]^{2+}$	2.63(6)	3.59(9)	1.6(5)	6.0(2)	This work
$[Zn(Him)_2]^{2+}$ + Him $\rightleftharpoons$ $[Zn(Him)_3]^{2+}$	2.26(6)	3.08(9)	3.7(9)	−4.0(3)	This work
Zn^{2+} + cyclo(-Gly-His-) $\rightleftharpoons$ $[Zn\{cyclo(-Gly-His-)\}]^{2+}$	1.71(1)	2.34(1)	2.4(2)	−0.2(9)	This work
Zn^{2+} + cyclo(-His-His-) $\rightleftharpoons$ $[Zn\{cyclo(-His-His-)\}]^{2+}$	2.55(3)	3.48(4)	4.9(2)	−4.7(8)	
	3.8	—	—	—	28
$[Zn\{cyclo(-His-His-)\}]^{2+}$ + cyclo(-His-His-) $\rightleftharpoons$ $[Zn\{cyclo(-His-His-)\}_2]^{2+}$	2.87(2)	3.91(3)	6.0(3)	−7.3(9)	
	2.9	—	—	—	28

* Uncertainties given in parentheses as 3σ.

Table 3 Thermodynamic parameters for the interactions of Him, cyclo(-Gly-His-) and cyclo(-His-His-) with Cu^{2+} at 25 °C and I = 0.1 mol dm^{-3} (KNO_3)*

Reaction	log K	$-\Delta G°$/ kcal mol^{-1}	$-\Delta H°$/ kcal mol^{-1}	$\Delta S°$/ cal K^{-1} mol^{-1}	Ref.
Cu^{2+} + Him $\rightleftharpoons$ $[Cu(Him)]^{2+}$	4.32	5.90	6.94	−3.5	17
$[Cu(Him)]^{2+}$ + Him $\rightleftharpoons$ $[Cu(Him)_2]^{2+}$	3.29	4.48	6.5	−6.4	17
$[Cu(Him)_2]^{2+}$ + Him $\rightleftharpoons$ $[Cu(Him)_3]^{2+}$	2.70	3.68	6.7	−10.3	17
$[Cu(Him)_3]^{2+}$ + Him $\rightleftharpoons$ $[Cu(Him)_4]^{2+}$	1.90	2.64	3.5	−2.8	17
Cu^{2+} + cyclo(-Gly-His-) $\rightleftharpoons$ $[Cu\{cyclo(-Gly-His-)\}]^{2+}$	3.35	4.57(1)	5.05(1)	−1.60(1)	This work
$[Cu\{cyclo(-Gly-His-)\}]^{2+}$ + cyclo(-Gly-His-) $\rightleftharpoons$ $[Cu\{cyclo(-Gly-His-)\}_2]^{2+}$	2.67	3.65(2)	7.13(1)	11.67(1)	This work
Cu^{2+} + cyclo(-His-His-) $\rightleftharpoons$ $[Cu\{cyclo(-His-His-)\}]^{2+}$	5.99	8.17	9.88	−5.7	17
$[Cu\{cyclo(-His-His-)\}]^{2+}$ + cyclo(-His-His-) $\rightleftharpoons$ $[Cu\{cyclo(-His-His-)\}_2]^{2+}$	4.55	6.21	7.1	−2.9	17

* Uncertainties given in parentheses as 3σ.

means of ESR measurements[18] that both cyclo(-His-His-) nitrogens are co-ordinated, thus leading to the formation of a macrochelate, as found in the solid state.[19] The comparison of the $\Delta H°$ values associated with the formation of $[Zn\{cyclo(-His-His-)\}]^{2+}$ and of $[Zn\{cyclo(-Gly-His-)\}]^{2+}$ shows this to be very likely the case also for Zn^{II}. The $\Delta H°$ value for the former is higher than that for the latter, where only one nitrogen is co-ordinated; the negative entropy contribution is also consistent with the formation of a macrochelate. In contrast with our conclusion, on the basis of NMR results, it has been previously suggested that cyclo(-His-His-) acts as a monodentate ligand[43] in $[Zn\{cyclo(-His-His-)\}]^{2+}$. Given the exothermicity of the reaction, as indicated by the present results, we are inclined to believe that the experimental conditions employed for the NMR experiments (50 °C) may have caused the detachment of a histidine nitrogen.

The complex $[Zn\{cyclo(-His-His-)\}_2]^{2+}$ is more stable than $[Zn\{cyclo(-His-His-)\}]^{2+}$ due to the more favourable enthalpy change. This behaviour is different from that found in the analogous copper(II) complexes, in which the $\Delta H°$ value for the formation of $[Cu\{cyclo(-His-His)-\}_2]^{2+}$ is less favourable than that of $[Cu\{cyclo(-His-His-)\}]^{2+}$; however, this is consistent with the well known tendency of Zn^{II} to switch from an octahedral to a tetrahedral geometry, as discussed above for $[Zn(Him)_2]^{2+}$. The enthalpy value for the formation of $[Zn\{cyclo(-His-His-)\}]^{2+}$ would thus also 'contain' the endothermic contribution associated with the change of geometry; this would also explain the higher entropy contribution in the first complexation step.

In conclusion a detailed thermodynamic study allows us to reveal both the formation of chelate rings of unusual size as well as the different enthalpy and entropy contributions to the

stabilization of such macrochelate rings. The ligand features prevail on the geometric and electronic requirements of the two metal ions, leading to the formation of macrochelate rings in both cases.

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