Thermochimica Acta, 43 (1981) 103—106
Elsevier Scientific Publishing Company, Amsterdam — Printed in Belgium

Note

COMPLEXATION REACTION OF METAL IONS WITH PEPTIDE SYSTEMS. PART IX. A THERMODYNAMIC STUDY OF THE COMPLEXATION REACTION OF *N*-BENZOYL-GLYCYL-GLYCINE WITH SOME DIVALENT METAL IONS

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(Received 18 June 1980)

There are numerous examples of the in vivo interaction of transition metal ions with amino acids and peptides, and these interactions are of considerable biological importance [1]. Recently, the authors [2—5] have reported the values of stability constants and thermodynamic parameters for complexes of Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Pb(II) with *N*-benzoyl-*L*-leucine, *N*-benzoyl-*L*-phenylalanine and *N*-benzoyl-glycyl-*L*-proline. This paper reports the stability constants and the overall changes in free energy (ΔG), enthalpy (ΔH) and entropy (ΔS) of Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Pb(II) complexes with *N*-benzoyl-glycyl-glycine in 50% v/v dioxane—water medium at three temperatures (25 ± 0.1, 35 ± 0.1 and 45 ± 0.1°C) and at ionic strength 0.1 M (KNO_3). The method of Calvin—Bjerrum [6,7] as adopted by Irving and Rossotti [8] was employed to determine log K values.

EXPERIMENTAL

All the chemicals used were of Analar (BDH) or equivalent grade. Dioxane was purified by the recommended procedure [9]. *N*-benzoyl-glycyl-glycine was prepared by the method described in the literature [10]. A fresh ligand solution (0.025 M) was prepared just before use in 50% v/v dioxane—water medium. The metal nitrates were dissolved in doubly distilled CO_2-free water and the metal content estimated volumetrically by titrating against EDTA solution. The mole ratio of metal to ligand was kept at 1 : 5 in order to fulfil the maximum coordination number of the metal ion.

A Toshniwal pH meter CL 46 with glass calomel electrodes assembly, calibrated with buffers of pH 4.01 (0.05 M potassium hydrogen phthalate) and pH 7.0 (0.025 M potassium dihydrogen phosphate and 0.025 M disodium hydrogen phosphate) and having an accuracy of ±0.01 pH units, was used to measure the pH during titrations which were carried out in 50% v/v dioxane—water medium in a cell immersed in a thermostated bath maintained at 25 ± 0.1, 35 ± 0.1 and 45 ± 0.1°C.

The three solutions (total volume 50 ml in each case) were prepared such that the concentrations of the common ingredients were identical in all systems: (A) 2.5 ml of 1.0×10^{-2} M HNO_3; (B) 2.5 ml of 1.0×10^{-2} M HNO_3 + 5.0 ml of 2.5×10^{-2} M ligand; (C) 2.5 ml of 1.0×10^{-2} M$\cdot HNO_3$ + 5.0 ml of 2.5×10^{-2} M ligand + 2.5 ml of 1.0×10^{-2} M metal ion solution. An appropriate quantity of potassium nitrate solution (1.0 M) was added to maintain the desired ionic strength (0.1 M). Solutions A, B and C were titrated against potassium hydroxide (0.05 M) solution prepared in aqueous dioxane (50% v/v). The three curves were obtained from the plots of pH vs. volume of alkali required and are referred to as (i) acid, (ii) ligand, and (iii) complex titration curves. The shapes of the curves were as usual.

RESULTS AND DISCUSSION

Values of formation functions $\bar{n}_A$, $\bar{n}$ and pL were calculated using the standard expressions [8]. Calculations of practical stability constants of proton complexes were made by plotting $\bar{n}_A$ vs. pH. It was observed that the ligand titration curve does not rise to the left of the acid titration curve, in contrast to that observed for the corresponding unprotected dipeptides. This indicates that the benzoyl group protecting the amino group partially hinders zwitterion formation. Hence, only a single protonation constant pK_1^H (carboxylic group) was observed. The protonation constants at three different temperatures were calculated by various computational methods [6,11] and are summarized in Table 1.

The metal—ligand stability constants were obtained by analysis of the formation curves obtained by plotting $\bar{n}$ vs. pL. These plots for all metal ions indicate that the value of $\bar{n}$ approaches 1 in the pH range 4.5—6.00, below the pH region of hydrolysis of metal ions. This suggests that Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Pb(II) form only 1 : 1 complexes with *N*-benzoyl-glycyl-glycine. The absence of 1 : 2 chelates may be due to the steric hindrance offered to the incoming second ligand molecule by the coordinated ligand of the 1 : 1 chelate. The Bjerrum half integral method [7], interpolation at various $\bar{n}$ values, the graphical method [11], extended to dioxane—water mixtures by Van Uitert and Haas [12], were used to calculate $\log K_1$ values. The values of $\log K_1$ were also determined at three different concentrations of metal ion while keeping the ligand concentration constant. The $\log K_1$ values were found to be identical within the experimental error at all concentrations of the metal ion, thereby indicating the formation of mononuclear complexes. The mean values of the concentration stability constants ($\log K_1$) are summarized in Table 1. Benzoylation of the α-amino group of glycyl-glycine to form *N*-benzoyl-glycyl-glycine markedly reduced the affinity of the ligand for the metal ions under study. The observed $\log K_1$ values of metal complexes of *N*-benzoyl-glycyl-glycine under study are comparable to those of the corresponding metal complexes of acetates. This indicates that the benzoyl derivative shows almost the same affinity for metal ions as acetates and the amide groups do not appear to contribute to the stability of these complexes. The order of stability is Cu(II) > Co(II) > Zn(II) > Ni(II) > Pb(II) > Cd(II). The greater stability of

TABLE 1

Protonation constants of *N*-benzoyl-glycyl-glycine, and stability constants of its complexes at three temperatures

Metal ion	Constant	Temperature (°C)			$-\Delta G$ (kcal mole^{-1})			ΔH (kcal mole^{-1}) at 35°C	ΔS (cal mole^{-1}deg^{-1}) at 35°C
		25	35	45	25	35	45		
H^+	log $^{P}K_1^{H}$ *	5.05	4.85	4.65					
Co(II)	log K_1	2.92	2.86	2.83	3.98	4.03	4.12	−1.93	6.82
Ni(II)	log K_1	2.86	2.79	2.77	3.90	3.93	4.03	−1.92	6.53
Cu(II)	log K_1	3.26	2.94	2.93	4.45	4.14	4.26	−6.94	−9.09
Zn(II)	log K_1	2.89	2.83	2.81	3.94	3.99	4.09	−1.71	7.04
Cd(II)	log K_1	2.84	2.79	2.76	3.87	3.93	4.02	−1.72	7.18
Pb(II)	log K_1	2.85	2.81	2.76	3.89	3.96	4.02	−1.95	6.53

* Carboxylic functional group.

Co(II) than Ni(II) may be attributed to the additional stabilization due to Jahn—Teller distortion present in the case of Co(II), similar to Cu(II), and a favourable entropy effect, while partial oxidation of the Co(II) complexes is not completely ruled out. The value of log K_1 decreases with increase of temperature.

The values of overall changes in free energy (ΔG), enthalpy (ΔH) and entropy (ΔS) accompanying complexation were determined using the temperature coefficient and Gibb's Helmholtz equation [13] (Table 1). The error in ΔG and ΔH values lies in the range 0.2—0.5 kcal mole^{-1} and that for ΔS is 0.5 cal mole^{-1} deg^{-1}. ΔG values for all the metal complexes except Cu(II) complexes are more negative with increase of temperature, showing that complex formation is a spontaneous process. The enthalpy change (ΔH) being negative in all cases is favourable for the formation of these complexes; the entropy change (ΔS) being positive in the case of Co(II), Ni(II), Zn(II), Cd(II) and Pb(II) complexes is favourable, whereas for Cu(II) complexes the reverse is true.

ACKNOWLEDGEMENT

We are thankful to the CSIR, New Delhi, India, for the award of a fellowship to R.K.

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