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Stability Constants of Complex Formations between Divalent Metal Ions and Cyclic Dipeptides: Cyclo(glycyl-L-histidyl) and Cyclo(L-methionyl-L-histidyl)

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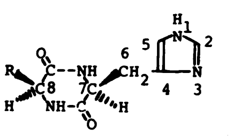
Synopsis. The values($\log K_1$ and $\log K_2$) of the complex formations between divalent metal ions and two cyclic dipeptides of this title were determined by Bjerrum's method. It is apparent from ^{1}H NMR data that metal ions link exclusively to the nitrogen atom of the imidazolyl group of cyclo(L-methionyl-L-histidyl).

The authors[1)] have studied some metal complexes with cyclic dipeptides as model compounds for metallo-proteins and -enzymes, in which the metal ions link exclusively to the functional groups of the side chains of the peptides.

This paper reports the values of the stability constants of the complex formations between divalent metal ions and cyclic dipeptides with an imidazolyl group[cyclo(glycyl-L-histidyl)=CGH and cyclo(L-methionyl-L-histidyl)=CMH].



CGH; R = H

CMH; R = $CH_2CH_2SCH_3$

9 10 11

Experimental

Materials. CGH and CMH were prepared according to methods reported earlier.[1a)] All metal salts obtained commercially were used without further purification.

Measurements. ^{1}H NMR data were obtained in D_2O at 45 °C with sodium 3-trimethylsilyl-1-propanesulfonate as an internal reference using a JEOL PS-100. In the measurements of the stability constants of the complex formations, the titrated solution contained 0.24—1.27 mmol of a cyclic dipeptide, 0.10—0.27 mmol of $Ni(NO_3)_2$, $CuSO_4$ or $ZnSO_4$, and 0.40—1.50 mmol of HCl in 0.50 dm^3, the ionic strength being adjusted to 0.2 mol dm^{-3} with KNO_3. The solution was titrated with a 0.943 mol dm^{-3} NaOH aqueous solution at 25 °C under a nitrogen atmosphere using a Hitachi-Horiba F-5 pH meter. The acid dissociation constants(K_a) used in calculations were determined by titration to be $10^{-6.25}$ and $10^{-6.31}$ for CGH and CMH, respectively. The free-ligand concentration(L) and the average coordination number($\bar{n}$) were calculated from the titer and the hydrogen-ion concentration on the assumption that 1:1 and 1:2 complexes formed. The stability constants, $K_1=[ML]/([M][L])$ and $K_2=[ML_2]/([ML][L])$, were obtained by linear fittings according to the following equation: $Y=K_1K_2X-K_1$, where X is $(2-\bar{n})[L]/(\bar{n}-1)$ and Y is $\bar{n}/\{(\bar{n}-1)[L]\}$.

Results and Discussion

Figure 1 shows that the ^{1}H NMR signals of imidazole-2 and -4 protons are equally broadened in CMH:Cu^{2+} (5000:1) and in CMH:Ni^{2+} (1000:1) systems, respectively, suggesting the coordination of the imidazolyl group to metal ions. The amide protons of the diketopiperazine (DKP) ring are replaced by deuterium in D_2O. Figure 1 also shows no broading or shift of the methylene and methyl protons (C_{10} and C_{11}) adjacent to the sulfur atom and the methine protons (C_7 and C_8), though one of the methine protons (C_7) is partially overlapped by the signal of DOH. These observation suggest that both the sulfur atom[2)] of the methionyl residue and the amide groups of DKP do not link with these metal ions. A similar tendency was also observed in the cyclo(L-histidyl-L-histidyl)-Cu^{2+}system reported earlier.[1b)] An earlier report of X-ray analysis of a Zn^{2+} complex with CMH indicates that four 1-N atoms of each imidazole of four CMH's coordinate to Zn^{2+} ion.[1c)] In the ^{1}H NMR measurement of this complex, a distinct down-field shift [δ (Zn^{2+} complex ion) $-\delta$ (free ligand)=0.33(ppm)] is observed only for the imidazole-2 proton of CMH. Thus, these metal ions(Ni^{2+}, Cu^{2+}, and Zn^{2+}) appear to interact exclusively with the imidazolyl group of CMH.

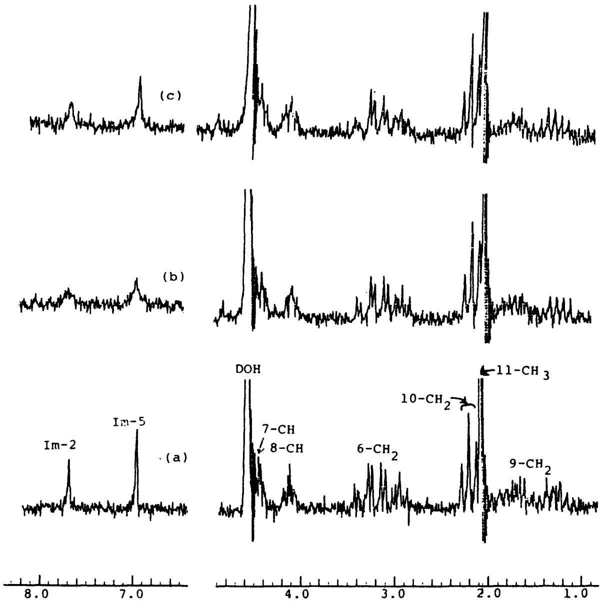


Fig. 1. ^{1}H NMR spectra of D_2O solution of the ligand (CMH) in the absence and presence of Ni^{2+} or Cu^{2+} at 45 °C. Ligand concentration = 0.052 mol dm^{-3}. (a) ligand alone, (b) ligand:Cu^{2+}=5000:1, (c) ligand: Ni^{2+}=1000:1. Im; imidazole.

The stability constants between a divalent metal ion and monodentate ligands (CGH and CMH) were obtained by Bjerrum's method. Figure 2 shows a typical example of an *X*-*Y* plot. As shown in Table 1, the obtained values of $\log K_1$ and $\log K_2$ seem to be in the order of the Irving-Williams series. Table 1 also shows that the *K* values for CMH are comparable to those for CGH having no functional group except an imidazolyl one. These results suggest that the coordination mode of CMH for metal ions is similar to that of CGH. Table 2 indicates that the *K* values for divalent metal ions and

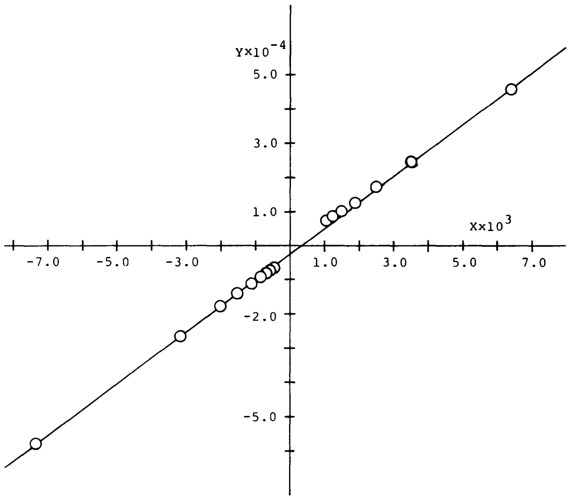


Fig. 2. A typical example of an X-Y plot. Cu: CGH=1:3.3.

Table 1. Stability constants of complexes between divalent metal ions and cyclic dipeptides

Metal	M_t:L_t*	logK_1	logK_2
	cyclo(glycyl-L-histidyl)		
Ni	1:1.1	2.48	1.86
	1:2.1	2.60	1.79
	1:3.0	2.56	1.89
Cu	1:3.3	3.48	3.39
	1:4.2	3.48	3.29
Zn	1:2.1	2.28	1.65
	1:4.4	2.21	1.53
	cyclo(L-methionyl-L-histidyl)		
Ni	1:2.2	2.61	2.31
	1:3.1	2.49	2.20
Cu	1:2.4	3.37	3.19
	1:3.2	3.40	3.28
	1:3.6	3.29	3.20
Zn	1:2.0	2.50	1.48
	1:4.2	2.43	2.31

*M_t and L_t are total concentrations of each metal ion and each ligand, respectively.

cyclic dipeptides (CGH and CMH) are proportional to the strength of the basicities of ligands as compared with those for imidazole and pyridine.

In order to consider higher coordination numbers for metal ions, attempts to obtain the values of K_3 were carried out by successive approximations. However, the values were not successfully obtained because of the relatively small values of $\bar{n}$, as shown in Fig. 3. The values from K_1 to K_4 were also determined by Scatchard's method.[3] The values of logK_1 and logK_2 are shown as follows in order to make a comparison with those obtained by Bjerrum's method: CGH (Ni, 2.47, 1.33; Cu, 3.53, 2.99) and CMH (Ni, 2.38, 1.73; Cu, 3.50, 2.91; Zn, 2.34, 2.24). The stability constants between the Zn^{2+} ion and CGH were not obtained because of bad linearity. The values of logK_1 are in good agreement with those calculated using Bjerrum's method.

Table 2. Logarithms of stability constants[a)]

Ligands		H^+	Ni^{2+}	Cu^{2+}	Zn^{2+}
Imidazole[b)]	K_1	7.11	3.0	4.20	2.52
	K_2		2.5	3.42	2.32
	K_3		2.0	2.88	2.32
	K_4		1.5	2.1	2.0
CMH	K_1	6.31	2.55	3.35	2.43
	K_2		2.26	3.22	1.89
CGH	K_1	6.25	2.55	3.48	2.25
	K_2		1.85	3.34	1.59
Pyridine[b)]	K_1	5.21	1.78	2.41	0.88
	K_2		1.22	1.88	0.47
	K_3		0.3	1.14	0.15
	K_4		−0.3	0.60	−0.2

a) The average values of this report (see Table 1), except b). b) The values of Ref.4).

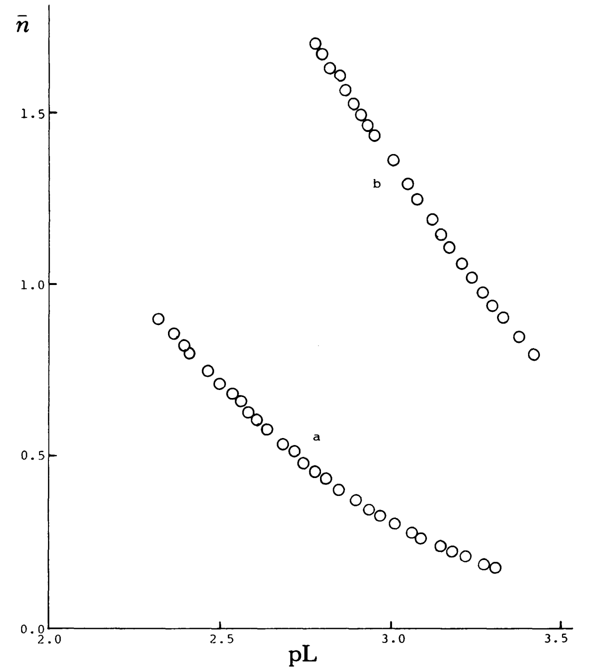


Fig. 3. Formation curves. a, Ni:CGH=1:3.0; b, Cu: CMH=1:3.6.

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