Preparations and Strucutures of Silver(I) Complexes with *cyclo*(Glcyl-L-histidyl), *cyclo*(L-Methionyl-L-histidyl), and *cyclo*(L-Histidyl-L-histidyl)

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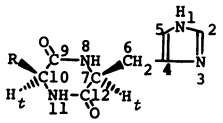
(Received March 14, 1983)

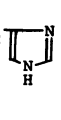
Synopsis. The structures of silver(I) complexes with *cyclo*(glycyl-L-histidyl), *cyclo*(L-methionyl-L-histidyl), and *cyclo*-(L-histidyl-L-histidyl) were examined using ^1H and ^{13}C NMR. The NMR measurements suggest that the silver(I) ion links to the sulfur atom of thioether and the nitrogen atom of imidazole group of the above cyclic peptides, but not to their amide groups.

The present authors have used a copper(II) complex with *cyclo*(L-histidyl-L-histidyl) (**3**) and a silver(I) complex with *cyclo*(L-methionyl-L-methionyl) (**4**) as simple model compounds[1] for studying metalloproteins and metalloenzymes, in which the ligating groups for metal ions are the functional groups of the side chains of peptides, but not the amide groups. In our previous papers,[1] the coordinations of the imidazole (Im) group of histidyl residue to the copper(II) ion and of the thiother group of the methionyl residue to the silver(I) ion were confirmed using ^1H NMR and X-ray crystal analysis. Other workers[2] have investigated the conformations of cyclic dipeptides using NMR and X-ray measurements, and have found that the cyclic dipeptides containing histidine, phenylalanine, and tyrosine prefer a folded form, in which the aromatic ring of the side chain of the peptide lies over 2,5-piperazinedione. This paper will report the preparations and characteristics of silver(I) complexes with cyclic dipeptides containing Im and thioether groups. *cyclo*(Glycyl-L-histidyl) (**1**), *cyclo*-(L-methionyl-L-histidyl) (**2**), and **3** were used as ligands in this experiment.



1: R=H$_c$

2: R=CH$_2$CH$_2$SCH$_3$ (13 14 15)



Experimental

Materials. **1**,[3] **2**,[4] and **3**[1a] were prepared according to the methods reported earlier. *cyclo*(Glycyl-glycyl) (**5**) and silver(I) salts(perchlorate, nitrate, and hexafluorophosphate) obtained commercially were used without further purification.

Preparations of Silver(I) Complexes. A mixture of **1** (0.50 mmol) and silver(I) perchlorate (0.53 mmol) was completely dissolved in hot water (50 cm^3) with stirring. After standing at room temperature for a few days, the precipitate was filtered off and recrystallized from water. Other complexes were similarly obtained by the procedure described above. Table 1 shows the values of the elemental analyses and melting points of silver(I) complexes with **1**, **2**, and **3**.

Measurements. The ^1H and ^{13}C NMR data of silver(I) complexes and their corresponding ligands were obtained in D_2O at 27, 40, and 50 °C, using sodium 3-trimethylsilyl-1-propanesulfonate as the internal reference. The molecular weights of silver(I) complexes with **1** and **2** were measured in H_2O at 56 °C, using urea as the standard material. JEOL FX-100 and FX-90Q (for ^1H and ^{13}C NMR spectra) apparatuses and a Knauer Vapor-pressure Osmometer (for molecular weight) were used for the measurements of the samples.

Results and Discussion

Table 2 shows the chemical shifts of the protons of ligands and their corresponding silver(I) complex ions. As is shown in Table 2, 10-H$_c$ (δ=3.13) and 10-H$_t$ (δ=3.72) of **1** absorb at a higher field than the methylene proton (δ=4.00) of **5** because of the magnetic shielding effect[2a] of the Im ring, showing that **1** exists as a folded form. The chemical shifts (δ=3.13 and 3.77) of 10-H$_c$ and 10-H$_t$ of [Ag(**1**)$_2$]$^+$(**A-1**) are almost the same as those of **1**, so a preferred form for **A-1** is a folded one. Table 2 also describes how the 13-H (δ=1.05—1.43 and 1.46—1.90) of **2** absorbs at a higher field than the β-methylene (δ=2.10—3.00) of **4**[1b] because of the magnetic anisotropy of the Im ring, indicating that **2** prefers a folded form. Though the peaks of 13-H of **2** are complicated and unresolved, the values of the chemical shifts are used for elucidating the conformation of [Ag(**2**)]$^+$ (**A-2**). The possibility that **A-2** favors a folded form is suggested by the small difference between the chemical shifts of 13-H of **2** and those (δ=1.49—1.97) of **A-2**. The downfield shift ($\Delta\delta$=0.32) of the 14-H and 15-H of **A-2** from **2** supports the coordination of the S atom to the silver(I) ion.[1b] The differences ($\Delta\delta$=0.86 and 0.46) in the chemical shifts of 6-H between **3** and

TABLE 1. ANALYTICAL DATA AND MELTING POINTS FOR SILVER(I) COMPLEXES

Complex	Found (%)			Calcd (%)			Mp (decomp) θ_m/°C
	C	H	N	C	H	N	
[Ag(**1**)$_2$]NO$_3$·H$_2$O	33.5	3.7	21.6	33.4	3.9	21.9	183—205
[Ag(**1**)$_2$]ClO$_4$·1/4 H$_2$O	32.0	3.4	18.7	32.0	3.4	18.7	244—259
{[Ag(**2**)](ClO$_4$)}$_2$	28.1	3.4	11.8	27.8	3.4	11.8	195—208
{[Ag(**3**)](ClO$_4$)}$_n$	29.9	3.0	17.8	29.9	2.9	17.5	281—286
{[Ag(**3**)](PF$_6$)}$_n$	27.2	2.8	15.8	27.3	2.7	15.9	230—251

Table 2. ^{1}H NMR data of cyclic dipeptides and their silver(I) complexes in D_2O at 50 °C

Compound	Chemical shifts, δ ($\Delta\delta$[a])									
	2-H	5-H	6-H		7-H$_t$	10-H$_t$	10-H$_c$	13-H	14-H	15-H
1[b]	7.70	6.97	3.21	3.06	4.32	3.72	3.13	—	—	—
A-1[b]	7.98	7.16	3.36	3.19	4.41	3.77	3.13	—	—	—
	(0.28)	(0.19)	(0.15)	(0.13)	(0.09)	(0.05)	(0.00)			
2	7.69	6.96	3.26	3.01	d)	4.08	—	1.05—1.43[c] 1.46—1.90	2.16	2.04
A-2	7.99	7.17	3.38	3.14	d)	4.15	—	1.49—1.97[c]	2.48	2.36
	(0.30)	(0.21)	(0.12)	(0.13)		(0.07)			(0.32)	(0.32)
3	7.71	6.88	2.86	2.39	4.24	4.24	—	—	—	—
A-3	7.86	7.17	3.32	3.25	4.20	4.20	—	—	—	—
	(0.15)	(0.33)	(0.46)	(0.86)	(−0.04)	(−0.04)				

a) $\Delta\delta=\delta$(Ag(I) complex) − δ(free ligand). b) Measured at 27 °C. c) Complicated and unresolved signals were given for 13-H at this region. d) These peaks could not be observed because of the overlapping of the signal of D_2O.

Table 3. ^{13}C NMR data of cyclic dipeptides and their silver(I) complex ions

Compound	Chemical shifts, δ ($\Delta\delta$[a])										
	2-C	4-C	5-C	6-C	7-C	9-C	10-C	12-C	13-C	14-C	15-C
1[b]	138.8	134.1	120.7	33.8	57.5	171.2	46.0	172.3	—	—	—
A-1[b]	140.9	134.9	120.5	35.0	57.3	171.1	45.9	171.9	—	—	—
	(2.1)	(0.8)	(−0.2)	(1.2)	(−0.2)	(−0.1)	(−0.1)	(−0.4)			
2[b]	138.5	133.8	121.2	33.1	57.6	171.4	56.1	171.9	35.3	30.4	16.7
A-2[b]	140.4	134.9	121.6	33.8	57.6	171.6	55.9	171.6	36.5	33.0	20.0
	(1.9)	(1.1)	(0.4)	(0.7)	(0.0)	(0.2)	(−0.2)	(−0.3)	(1.2)	(2.6)	(3.3)

a) $\Delta\delta = \delta$(Ag(I) complex) − δ(free ligand). b) **1** and **A-1** were measured at 27 °C, while **2** and **A-2** were done at 40 °C.

$[Ag(\mathbf{3})]^+$ (**A-3**) are considerably larger than those ($\Delta\delta$= 0.12—0.15) between **1** and **A-1** or **2** and **A-2**. This distinct downfield shift of **A-3** from **3** suggests that there is no magnetic shielding effect of the Im group, so that **A-3** prefers an unfolded form in which the Im group lies away from the 2,5-piperazinedione. Table 2 suggests that each 1- or 3-N atom of the Im groups of **1**, **2**, and **3** coordinates to the silver(I) ion because the downfield shifts ($\Delta\delta$=0.19, 0.21, and 0.33) of 5-H of **A-1**, **A-2**, and **A-3** from **1**, **2**, and **3**, and those ($\Delta\delta$=0.28, 0.30, and 0.15) of 2-H are observed, respectively.

The ^{13}C NMR data of **1**, **2**, **A-1**, and **A-2** are given in Table 3; those of **3** and **A-3** could not be obtained because of their low solubilities. Table 3 suggests that the 1- or 3-N atom of each Im group of **1** and **2** coordinates to the silver(I) ion, because the downfield shifts ($\Delta\delta$=0.8 or 1.1) of the 4-C of **A-1** or **A-2** from **1** or **2** and those ($\Delta\delta$=2.1 or 1.9) of 2-C are observed. The coordination of the S atom of **2** to the silver(I) ion is also confirmed by the marked downfield shifts ($\Delta\delta$=2.6 and 3.3) of the 14-C and 15-C of **A-2** from **2**. Table 3 indicates that no O atoms of the 2,5-piperazinedione of **1** and **2** coordinates to the silver(I) ion, for no distinct shifts of the 7-C, 9-C, 10-C, and 12-C of **A-1** or **A-2** from **1** or **2** are observed. As is shown in Table 2, this suggestion is also supported by the small shift ($\Delta\delta$=0.09 or −0.04) of the 7-H$_t$ of **A-1** or **A-3** from **1** or **3** and that ($\Delta\delta$=0.05 or 0.07) of the 10-H$_t$ of **A-1** or **A-2** from **1** or **2**.

The molecular weights (300 and 331) for **A-1** and **A-2** show **A-1** as a monomeric form, $[Ag(\mathbf{1})_2]^+ + NO_3^-$ (596/2=298), and **A-2** as a dimeric one, $\{[Ag(\mathbf{2})]_2\}^{2+} + 2ClO_4^-$ (951/3=317). The molecular weight of **A-3** could not be measured because of its extremely low solubility, suggesting that **A-3** prefers a polymeric form.

The results obtained in this paper suggest that the 1- or 3-N atom of the Im group and the S atom of thioether in **2** coordinate linearly to the silver(I) ion. In the cases of **1** and **3**, each silver atom is coordinated linearly to each 1- or 3-N atom of two Im groups.

The authors wish to thank Mr. Junichi Gohda for elemental analyses.

References

1) a) Y. Kojima, *Chem. Lett.*, **1981**, 61; b) Y. Kojima, T. Yamashita, Y. Ishino, T. Hirashima, and K. Hirotsu, *ibid.*, **1983**, 453.

2) a) K. D. Kopple and M. Ohnishi, *J. Am. Chem. Soc.*, **91**, 962 (1969); b) R. Ramani, K. Venkatesan, and R. E. Marsh, *ibid.*, **100**, 949 (1978).

3) K. D. Kopple and H. G. Ghazarian, *J. Org. Chem.*, **33**, 862 (1968).

4) D. E. Nietecki, B. Halpern, and J. W. Westly, *J. Org. Chem.*, **33**, 864 (1968).