Syntheses of Silver(I) Complexes with *N,N'*-Ethylene-Bridged-(*S*)-Histidyl-(*S*)-Histidine and -(*S*)-Methionyl-(*S*)-Methionine Derivatives

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Silver(I) complexes of *N,N'*-ethylene-bridged-(*S*)-histidyl-(*S*)-histidine and -(*S*)-methionyl-(*S*)-methionine derivatives have been synthesized and characterized as monomeric complex ions coordinated only by two functional groups on the side chains of each ligand.

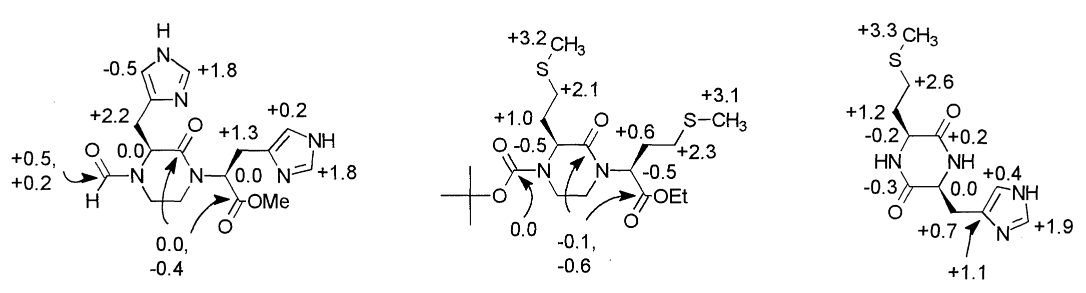
Transition metal complexes with the cyclic dipeptides cyclo((*S*)-histidyl-(*S*)-histidyl) (cHH)[1] and cyclo((*S*)-methionyl-(*S*)-methionyl) (cMM)[2] were synthesized earlier as simple model compounds of nonheme type metallo-proteins or -enzymes, in which only the functional groups on the side chains of the peptides coordinate to metal ions. Two side chains of a chiral cyclic dipeptide locate on the same site of the piperazin-2,5-dione ring and chelate to a copper(II) ion.[1a,1b] However, it has already been shown that cHH[1c] or cMM[2] bridges between two silver(I) ions, that is, their complexes select polymeric structures. Recently, various *N,N'*-ethylene-bridged-dipeptides (eXX: X = α-(*S*)-amino acid residue) constraining their peptide conformations[3] have been simply synthesized by a convenient method[4] and two side chains of eXX locate on the same site of the piperazin-2-one ring similarly to the side chains of chiral cyclic dipeptide.[5]

In this paper, we report the syntheses and characterizations of silver(I) complexes with *N,N'*-ethylene-bridged-(*S*)-histidyl-(*S*)-histidine and -(*S*)-methionyl-(*S*)-methionine derivatives for the first time. Methyl *N,N'*-ethylene-bridged-(*S*)-histidyl-(*S*)-histidinate (eHH-OMe), its *N*-formyl derivative (HCO-eHH-OMe)[6] and ethyl *N, N'* -ethylene -bridged -(*S*) -methionyl -(*S*) -methioninate (eMM-OEt)[4] were synthesized earlier. Boc-eMM-OEt was prepared from $(Boc)_2O$ and eMM-OEt by the usual liquid phase method and purified by silica gel column chromatography.[7] Two silver(I) complexes [Ag(HCO-eHH-OMe)](ClO_4) **1** and [Ag(Boc-eMM-OEt)](ClO_4) **2** were synthesized by the mixing of the equimoles of each ligand and silver(I) perchlorate salt in MeOH at room temperature, and recrystallized from MeOH and AcOEt/CH_3CN, respectively.[8]

The experimental value (305) of the molecular weight determined for **1** in water is identical with the theoretical value (568/2 = 284) given in the complete dissociation of this complex to a monomeric complex cation {$[Ag(HCO\text{-}eHH\text{-}OMe)]^+$} and a perchlorate anion (ClO_4^-), but the value for **2** was not measured in water because of low solubility.[9] On the other hand, the values (380 and 455 for **1** and **2**, respectively) of the molecular weight obtained in MeOH are identical with the theoretical values (568 × 2/3 = 379 and 642 × 2/3 = 428 for **1** and **2**) given in about 50% dissociation of these complexes to a monomeric complex cation and a perchlorate anion {$[Ag(HCO\text{-}eHH\text{-}OMe)](ClO_4) \rightleftharpoons [Ag(HCO\text{-}eHH\text{-}OMe)]^+ + ClO_4^-$ and $[Ag(Boc\text{-}eMM\text{-}OEt)](ClO_4) \rightleftharpoons [Ag(Boc\text{-}eMM\text{-}OEt)]^+ + ClO_4^-$} or in the complete dissociation of these complexes to a dimeric complex cation {$[Ag_2(HCO\text{-}eHH\text{-}OMe)_2]^{2+}$ and $[Ag_2(Boc\text{-}eMM\text{-}OEt)_2]^{2+}$} and two perchlorate anions ($2ClO_4^-$).[10] We believe that both silver(I) complexes **1** and **2** have a monomeric structure in MeOH referring to the result of **1** in water. FAB MS spectra also showed the formation of monomeric Ag(I) complexe cations $[Ag(HCO\text{-}eHH\text{-}OMe)]^+$ and $[Ag(Boc\text{-}eMM\text{-}OEt)]^+$.[8]

The silver(I) induced the ^{13}C NMR chemical shift changes of *N,N'*-ethylene-bridged dipeptide derivatives HCO-eHH-OMe and Boc-eMM-OEt, and cyclo((*S*)-histidyl-(*S*)-methionyl) (cHM)[1c] (Figure 1). It has previously been shown that cHM coordinates to silver(I) ion only by imidazole nitrogen and sulfur atoms on the side chains of cHM.[1c] Both imidazole groups of HCO-eHH-OMe coordinate to a silver(I) ion, because the downfield shift values {Δδ (δ[Ag(I) complex] - δ(free ligand)) = 1.8 ppm} of the two ε-carbons[11] of HCO-eHH-OMe are comparable to the downfield shifts (Δδ = 1.9 ppm) of histidine ε-carbon of cHM. The coordination of sulfur atoms of Boc-eMM-OEt to a silver(I) ion is similarly confirmed by the marked downfield shifts (Δδ = 2.1~ 3.2 ppm) of the two kinds of γ- and ε-carbons[11] of Boc-eMM-OEt. Furthermore, Figure 1 indicates that no oxygen atoms of amide or ester groups of HCO-eHH-OMe or Boc-eMM-OEt coordinate to silver(I) ions, because no distinct shifts ($-0.6 \leqq \Delta\delta \leqq 0.5$) of the carbonyl and α-carbon of HCO-eHH-OMe and Boc-eMM-OEt are observed.

The results found here suggest that only the S (or imidazole nitrogen) atoms on the side chains in Boc-eMM-OEt (or HCO-eHH-OMe) coordinate to a silver(I) ion. While silver(I) complexes of cHH and cMM have polymeric structures, those of



(A) (B) (C)

Figure 1. The Δδ {δ[Ag(I) complex] - δ(free ligands); ppm} values of ^{13}C NMR spectra of (A) HCO-eHH-OMe in D_2O at 50 °C, (B) Boc-eMM-OEt in CD_3OD at 30 °C and (C) cHM in D_2O at 40 °C.

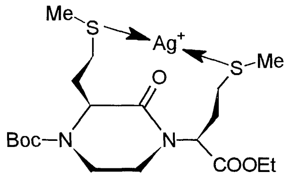


Figure 2. The proposed structure of [Ag(Boc-eMM-OEt)]$^+$.

eHH and eMM derivatives are monomeric. A proposed structure of **2** is shown in Figure 2 on the basis of the Corey-Pauling-Koltun model.[12] A side chain outside the piperazinone ring of *N,N'*-ethylene-bridged dipeptide coordinates to a silver(I) ion more flexibly than do the side chains of cyclic dipeptide. Since eXX has N- and C-terminals, its peptide chain has been freely extended.[3,13,14] The development of eXX derivatives having the functional groups such as imidazole, thioether, carboxylate and thiolate on the side chains is expected to offer various bi- and tridentate ligands and to produce model complexes of the active sites of metalloproteins.

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7 Characterization of Boc-eMM-OEt: Yield: 96%. Anal. Found: C, 50.84; H, 7.70; N, 5.87%. Calcd for $C_{19}H_{34}N_2O_5S_2 \cdot H_2O$: C, 50.42; H, 8.02; N, 6.19%. mp: 36-39 °C. $[\alpha]_D$: +13.1 deg dm^{-1} g^{-1} cm^3 (MeOH). MS m/z 434(M$^+$). IR($CHCl_3$): 1650, 1690, 1740 cm^{-1}. ^{1}H NMR(400 MHz, CD_3CN, 1.93 ppm): δ 4.90(1H, dd, *J* = 10.1, 5.3 Hz), 4.52(1H, t, *J* = 7.0 Hz), 4.11(2H, m), 3.93(1H, bd), 3.23-3.39(3H, m), 2.38-2.55(4H, m), 2.09(1H, m), 2.06(6H, s), 1.95-2.09(3H, m), 1.44(9H, s), 1.20(3H, t, *J* = 7.0 Hz). ^{13}C NMR (CD_3CN, 118.2 ppm): δ 171.2, 169.6, 154.9, 81.0, 62.0, 57.2, 44.7, 33.0, 31.2, 31.1, 28.5, 28.3, 15.4, 15.3, 14.4.

8 Characterization of **1**: Yield: 77%. Anal. Found: C, 33.88; H, 3.78; N, 14.82%. Calcd for $[Ag(C_{16}H_{20}N_6O_4)](ClO_4)$ (MW; 567.7): C, 33.85; H, 3.55; N, 14.80%. mp: 195-202 °C. $[\alpha]_D$: -18.6 deg dm^{-1} g^{-1} cm^3(H_2O). FAB MS: m/z 467, 469(M$^+$). Characterization of **2**: Yield 67%. Anal. Found: C, 35.30; H, 5.26; N, 4.36%. Calcd for $[Ag(C_{19}H_{34}N_2O_5S_2)]$ (ClO_4) (MW; 641.9): C, 35.55; H, 5.34; N, 4.36%. mp: 78-84 °C. $[\alpha]_D$: +18.6 deg dm^{-1} g^{-1} cm^3 (MeOH). FAB MS: m/z 541, 543(M$^+$).

9 A Knauer vapor pressure osmometer was used to measure molecular weights. The molecular weight of **1** was measured in H_2O at 90 °C, using urea as standard material.

10 The molecular weights of **1** and **2** were measured in methanol at 58 °C, using benzil as a standard material.

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