Chirality

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A Multinuclear Coordination System of L-Cysteine and L-Penicillamine That Induce Opposite Chiralities at Metal Centers

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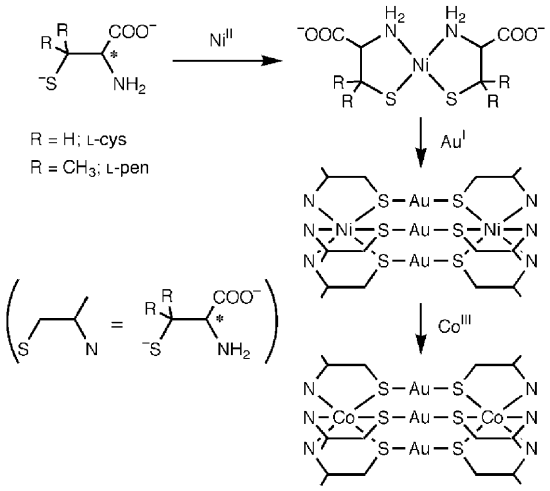
Long-standing interest in the chemistry of sulfur-containing amino acids stems from their importance in living and physiological systems.[1–3] Among sulfur-containing amino acids, cysteine and penicillamine bearing a thiol group are of particular interest and have been dealt with in numerous reports over the past decades.[4–8] Despite the structural similarity between cysteine and penicillamine other than the absence or presence of two methyl groups on the β-carbon atom, their stereochemical configurations in nature are opposite to each other; the natural cysteine is in the L form as are other protein-forming amino acids, whereas the natural penicillamine exists in the D form. In parallel with this fact, D-penicillamine has been used as a drug for the treatment of metal metabolism,[8–10] although its L form is highly toxic, even in a small quantity.[10,11] In addition, it has been shown that the mutagenic potency of D-penicillamine is almost the same as that of L-cysteine.[12] Thus, it appears that the biological nature of penicillamine corresponds to L-cysteine when it possesses a D configuration. However, the exact reason why D-penicillamine behaves like L-cysteine in biological systems still remains unknown.

In metal coordination systems, cysteine and penicillamine have been recognized as a multifunctional organic ligand that can bind to a variety of metal ions through amine, carboxylate, and thiolate groups to form chiral mononuclear and multinuclear complexes.[13–26] Although a difference in coordination behavior between cysteine and penicillamine toward a given metal ion has been observed in some cases,[18,19] D-penicillamine commonly induces a chiral effect at a metal center opposite to that induced by L-cysteine,[20–26] which is consistent with their opposite D and L configurations. A clear example is the selective formation of the Λ configurational isomer for $[Co(D\text{-penicillaminato-}N,S)_3]^{3-}$,[26b] while the analogous $[Co(L\text{-cysteinato-}N,S)_3]^{3-}$ produces the Δ isomer under the same conditions.[26a] Herein we report a remarkable $Au^I_3Ni^{II}_2$ coordination system constructed from cysteine/penicillamine in combination with Ni^{II} and Au^I ions (Scheme 1). In this system, the chiral behavior of the $Au^I_3Ni^{II}_2$ complex with L-cysteinate was found to be opposite to that with L-penicillaminate. This was also the case for analogous



Scheme 1. Synthetic routes of mononuclear Ni^{II}, pentanuclear $Au^I_3Ni^{II}_2$ ($\mathbf{1}^{5-}$ for L-cys, $\mathbf{2}^{5-}$ for L-pen), and pentanuclear $Au^I_3Co^{III}_2$ ($\mathbf{3}^{3-}$ for L-cys, $\mathbf{4}^{3-}$ for L-pen) complexes.

$Au^I_3Co^{III}_2$ complexes with L-cysteinate/L-penicillaminate, which were derived from the $Au^I_3Ni^{II}_2$ complexes by metal replacement reactions. As far as we know, such a coordination system that shows the opposite chiral effect due to L-cysteine and L-penicillamine has never been reported.[27]

Treatment of $Ni(NO_3)_2$ with excess L-cysteine (L-H_2cys) neutralized by Na_2CO_3 in water quickly produced a dark brown solution. The electronic absorption and circular dichroism (CD) spectral measurements indicated the formation of a mononuclear nickel(II) complex with N,S-chelating L-cysteinate ($[Ni(L\text{-cys-}N,S)_2]^{2-}$; Figure 1).[20a,b] When this reaction mixture was treated with $[AuCl\{S(CH_2CH_2OH)_2\}]$, the color of the solution gradually changed to blue within 2 days. Anion-exchange column chromatography (QAE Sephadex A-25) of the resulting blue solution eluting with 0.2 M aqueous $NaClO_4$ gave a single blue band, from which blue plate crystals of $Na_5[Au_3\{Ni(L\text{-cys-}N,S)_3\}_2]$ (Na_5-**1**) were isolated. X-ray fluorescence spectrometry suggested that Na_5-**1** contains Au and Ni atoms in a 3:2 ratio, and its elemental analytical data were in agreement with the formula for a compound containing Au, Ni, and L-cys in a 3:2:6 ratio. The appearance of an intense ν_{CO} band at 1586 cm^{-1} in the IR spectrum of Na_5-**1** is indicative of the presence of deprotonated COO^- groups.[28,29] Octahedral geometry of Ni^{II} ions in Na_5-**1** was assumed from its electronic absorption spectrum, which exhibits a near-infrared band at 901 nm with a shoulder at longer wavelength assignable to $^3T_{2g} \leftarrow {}^3A_{2g}$, as well as a visible band at 600 nm assignable to $^3T_{1g} \leftarrow {}^3A_{2g}$ (Fig-

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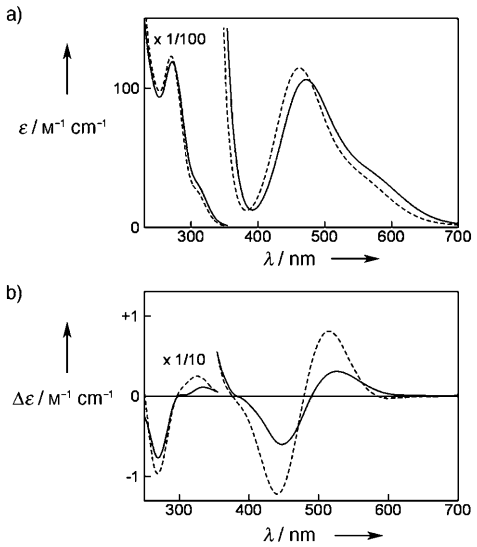

Figure 1. a) Absorption and b) CD spectra of the aqueous reaction solutions containing $[Ni(L\text{-}cys)_2]^{2-}$ (——) and $[Ni(L\text{-}pen)_2]^{2-}$ (-----).

ure 2a).[30,31] Magnetic measurements indicated that Na_5-**1** is paramagnetic,[28] which is consistent with the octahedral geometry of Ni^{II} in Na_5-**1**.

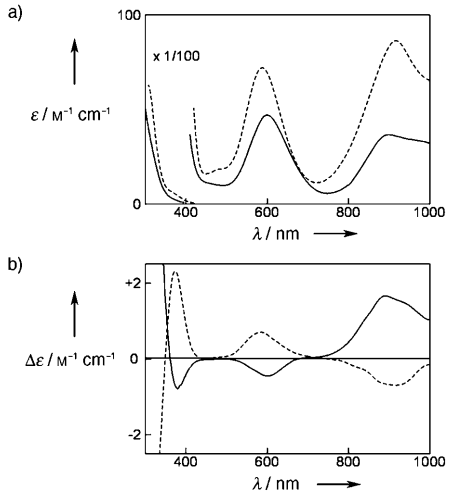

Figure 2. a) Absorption and b) CD spectra of $\mathbf{1}^{5-}$ ($(\Lambda)_2$-$[Au_3\{Ni(L\text{-}cys)_3\}_2]^{5-}$, ——) and $\mathbf{2}^{5-}$ ($(\Delta)_2$-$[Au_3\{Ni(L\text{-}pen)_3\}_2]^{5-}$, -----) in water.

The crystal structure of Na_5-**1** was established by single-crystal X-ray analysis. As shown in Figure 3a, $\mathbf{1}^{5-}$ has an S-bridged $Au^{I}_3Ni^{II}_2$ pentanuclear structure in $[Au_3\{Ni(L\text{-}cys\text{-}N,S)_3\}_2]^{5-}$, in which two $\{Ni(L\text{-}cys\text{-}N,S)_3\}^{4-}$ units are linked by three Au^{I} atoms through S atoms in a linear arrangement.[32] Each Ni^{II} atom is in a *fac*-N_3S_3 octahedral environment and is coordinated by three bidentate *N*,*S*-L-cys ligands. Considering two kinds of stereochemical configurations of the central unit—Δ/Λ for the two octahedral $\{Ni(L\text{-}cys\text{-}N,S)_3\}^{4-}$ units and *R*/*S* for the six bridging S atoms—a total of 21 stereoisomers are possible. Both the $\{Ni(L\text{-}cys\text{-}N,S)_3\}^{4-}$ units in $\mathbf{1}^{5-}$ adopt the

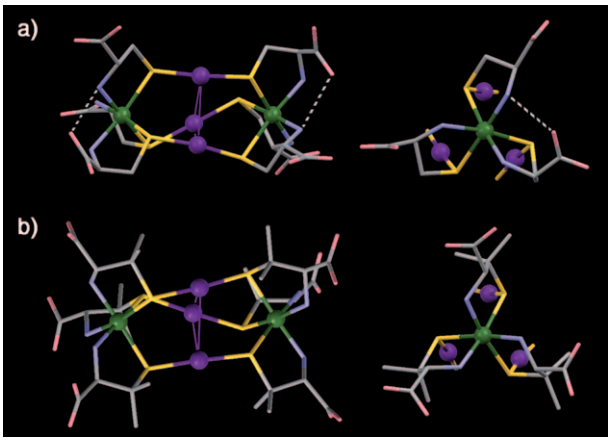

Figure 3. Perspective views of a) $\mathbf{1}^{5-}$ and its $[Au_3\{Ni(L\text{-}cys)_3\}]$ moiety, and b) $\mathbf{2}^{5-}$ and its $[Au_3\{Ni(L\text{-}pen)_3\}]$ moiety. Au purple, Ni green, S yellow, O red, N blue, C gray. Hydrogen atoms are omitted for clarity. Dotted line represents the intramolecular hydrogen bonds between carboxylate and amine groups.

Λ configuration, and all the six bridging S atoms have *R* configurations, thus giving only the $(\Lambda)_2(R)_6$ isomer.

A similar reaction of $Ni(NO_3)_2$ with L-penicillamine (L-H_2pen) neutralized by K_2CO_3 also produced a dark brown solution. As compared in Figure 1, the absorption and CD spectra of this solution are nearly the same as those of a brown solution obtained from $Ni(NO_3)_2$ and L-cys, indicating that L-cys and L-pen form the same chiral structure at this stage. Subsequent treatment of the brown solution with $[AuCl\{S(CH_2CH_2OH)_2\}]$ gave a blue solution, from which purple-blue crystals of $K_5[Au_3\{Ni(L\text{-}pen\text{-}N,S)_3\}_2]$ (K_5-**2**) were isolated. X-ray fluorescence and elemental analytical data implied that K_5-**2** also contains Au, Ni, and L-pen in a 3:2:6 ratio. The presence of deprotonated COO^- groups in K_5-**2** was confirmed by its IR spectrum, which shows an intense ν_{CO} band at 1591 cm^{-1}. Moreover, the absorption spectral features of K_5-**2** are very similar to those of Na_5-**1**, namely a near-infrared band at 917 nm and a visible band at 588 nm (Figure 2a).[31] From these results, $\mathbf{2}^{5-}$ is assigned as an S-bridged $Au^{I}_3Ni^{II}_2$ pentanuclear complex with L-penicillaminate ($[Au_3\{Ni(L\text{-}pen\text{-}N,S)_3\}_3]^{5-}$), the structure of which is analogous to that in $\mathbf{1}^{5-}$. The CD spectrum of K_5-**2**, however, exhibits a CD curve roughly enantiomeric to that of $\mathbf{1}^{5-}$ (Figure 2b). This observation strongly suggests that $\mathbf{2}^{5-}$ has $\{Ni(L\text{-}cys\text{-}N,S)_3\}^{4-}$ units with Δ configuration.

The direct structural information of this compound was gained by single-crystal X-ray analysis of Cs_2Na_3-**2**, which was isolated by using Cs_2CO_3 instead of K_2CO_3. As shown in Figure 3b, $\mathbf{2}^{5-}$ has an S-bridged $Au^{I}_3Ni^{II}_2$ structure in $[Au_3\{Ni(L\text{-}pen\text{-}N,S)_3\}_2]^{5-}$ consisting of two octahedral $\{Ni(L\text{-}pen\text{-}N,S)_3\}^{4-}$ units linked by three Au^{I} atoms in a linear arrangement. Although this S-bridged structure in $\mathbf{2}^{5-}$ resembles that in $\mathbf{1}^{5-}$, the two octahedral Ni^{II} units have Δ configuration and six bridging S atoms are fixed to the *S* configuration, thus giving only the $(\Delta)_2(S)_6$ isomer. Thus, the stereochemical configurations about the Ni^{II} units and the S atoms in $\mathbf{2}^{5-}$ are all opposite to those in $\mathbf{1}^{5-}$. As expected, the use of D-penicillamine instead of L-penicillamine selectively

afforded $(\Lambda)_2$-$[Au_3\{Ni(D\text{-pen})_3\}_2]^{5-}$, which shows a CD spectrum entirely enantiomeric to that of $\mathbf{2}^{5-}$.[33,34]

To elucidate the steric factors that govern the selective formation of the $(\Lambda)_2$ isomer for $\mathbf{1}^{5-}$ versus the $(\Delta)_2$ isomer for $\mathbf{2}^{5-}$, their molecular structures were compared in detail. In $\mathbf{2}^{5-}$, having Δ configurational Ni^{II} centers, all the L-pen N,S-chelate rings adopt a *lel* (λ for Δ) conformation with free COO^- groups pointing to an equatorial orientation (Figure 3b). In general, a five-membered chelate ring prefers to have a *lel* conformation (λ for Δ, δ for Λ) rather than *ob* conformation (δ for Δ, λ for Λ), and a free COO^- group favors an equatorial orientation rather than an axial orientation, which are explained by the thermodynamic aspect.[35–37] Thus, the Δ configurational selectivity found in $\mathbf{2}^{5-}$ originates from the preference of the equatorial orientation of the COO^- groups, together with the preference of the *lel* conformation of the N,S-chelate rings. In contrast, in $\mathbf{1}^{5-}$, having Λ configurational Ni^{II} centers, four of six L-cys N,S-chelate rings adopt an *ob* (λ for Λ) conformation with free COO^- groups pointing to an equatorial orientation, while the remaining two N,S-chelate rings have a *lel* (δ for Λ) conformation with COO^- groups pointing to an axial orientation (Figure 3a). A notable structural feature of $\mathbf{1}^{5-}$ is the formation of an intramolecular hydrogen bond between an axially oriented COO^- group and an adjacent NH_2 group (N···O 2.883(16) Å). A similar hydrogen bonding interaction has been found in an S-bridged tricobalt(III) complex with L-cysteinate ($(\Lambda)_2$-$[Co\{Co(L\text{-cys})_3\}_2]^{3-}$), and the existence of this interaction has been ascribed to the selective formation of the $(\Lambda)_2$ isomer for this complex.[26a] Thus, it is most likely that the stabilization resulting from the hydrogen bonding, together with that from the *lel* conformation, leads to the selective formation of the $(\Lambda)_2$ isomer for $\mathbf{1}^{5-}$. Molecular modeling examinations revealed that in the corresponding L-pen complex with the Λ configuration, the axial orientation of COO^- group, which is required for the formation of an intramolecular hydrogen bond, is unfavorable owing to the steric repulsion between L-pen methyl groups and Au^I linkers, thus forming the opposite Δ configuration with *lel* conformational N,S-chelate rings and equatorial COO^- groups.

With the aim of checking the generality of the selective formation of the $(\Lambda)_2$ isomer for this class of L-cys complexes, Na_5-**1** was treated with $K_3[Co(CO_3)_3]$ in water to synthesize an analogous $Au^I_3Co^{III}_2$ pentanuclear complex by the replacement of Ni^{II} by Co^{III}. When the resulting dark red reaction solution was chromatographed on an anion-exchange column (QAE Sephadex A-25), a main purple-brown band of $[Au_3\{Co(L\text{-cys-}N,S)_3\}_2]^{3-}$ ($\mathbf{3}^{3-}$) was eluted with 0.2 M aqueous NaCl.[38] The absorption spectral features of $\mathbf{3}^{3-}$ are reminiscent of those of $(\Delta)_2$-$[Ag_3\{Co(L\text{-cys-}N,S)_3\}_2]^{3-}$, which was prepared by the reaction of Δ-$[Co(L\text{-cys-}N,S)_3]^{3-}$ with a silver(I) salt.[28,39] The CD spectrum of $\mathbf{3}^{3-}$ exhibits a positive and a negative CD bands from longer wavelength in the d–d absorption band region.[28] This CD pattern is opposite to that of $(\Delta)_2$-$[Ag_3\{Co(L\text{-cys-}N,S)_3\}_2]^{3-}$, indicating that $\mathbf{3}^{3-}$ is the $(\Lambda)_2$ isomer like the parent $\mathbf{1}^{5-}$. A similar reaction of K_5-**2** with $K_3[Co(CO_3)_3]$ also gave a dark red solution. Anion exchange column chromatography of this reaction solution gave a main red-purple band ($[Au_3\{Co(L\text{-pen-}N,S)_3\}_2]^{3-}$; $\mathbf{4}^{3-}$) that was also eluted with 0.2 M aqueous NaCl.[38] The absorption spectrum of $\mathbf{4}^{3-}$ is very similar to that of $\mathbf{3}^{3-}$, while its CD spectrum is nearly enantiomeric to that of $\mathbf{3}^{3-}$.[28] These spectral features clearly indicate that $\mathbf{4}^{3-}$ has an S-bridged $Au^I_3Co^{III}_2$ structure in $(\Delta)_2$-$[Au_3\{Co(L\text{-pen})_3\}_2]^{3-}$, in which the stereochemical configurations about the two Co^{III} centers are opposite to those in $\mathbf{3}^{3-}$.[40] Thus, it can be concluded that L-cys and L-pen form the S-bridged $Au^I_3M_2$ ($M = Ni^{II}$, Co^{III}) pentanuclear structures with the opposite $(\Lambda)_2$ and $(\Delta)_2$ configurations, respectively.

In summary, we showed that L-cysteine and L-penicillamine both organize into S-bridged $Au^I_3Ni^{II}_2$ pentanuclear structures in combination with Ni^{II} and Au^I, by way of the Ni^{II} mononuclear structures. Although the precursory Ni^{II} complex with L-cysteinate gives the same chiral structure as that with L-penicillaminate, the $Au^I_3Ni^{II}_2$ complexes with L-cysteinate and L-penicillaminate were found to selectively afford the $(\Lambda)_2$ and $(\Delta)_2$ isomers, respectively, which are converted to the corresponding $Au^I_3Co^{III}_2$ complexes with $(\Lambda)_2$ and $(\Delta)_2$ configurations. These results imply that the higher organization of the mononuclear structure into the pentanuclear structure leads to the dramatic change in chiral effects due to L-cysteinate and L-penicillaminate. The formation of a favorable amine–carboxylate hydrogen bond and the existence of an unfavorable steric interaction appears to be responsible for this remarkable result.

Experimental Section

Experimental details, together with spectroscopic data, are given in the Supporting Information.

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[38] Solid samples of Na_3-**3** and Na_3-**4** were isolated from the eluates. Compounds Na_3-**3** and Na_3-**4** were assigned to have S-bridged $Au^{I}_3Co^{III}_2$ structures in $[Au_3\{Co(L\text{-cys-}N,S)_3\}_2]^{3-}$ and $[Au_3\{Co(L\text{-pen-}N,S)_3\}_2]^{3-}$, respectively, by X-ray fluorescence and elemental analyses, IR spectroscopy, and NMR spectroscopy.[28]

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