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Kinetic Resolution of *rac*-Phenylalanine by Stereoselective Complexation to a Chiral Cobalt Complex through π–π Stacking Interaction

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A cobalt(III) complex with chiral ligand, H2cpel (*N*-carboxymethyl-*N*-pyridylethyl-L-leucine), was prepared for chiral recognition of amino acids. Through the competitive coordination of racemic phenylalanine to the chiral cobalt complex, $[Co(cpel)(CO_3)]^-$ (**1**), enantioselective recognition was achieved on the ternary complex, which was determined on the basis of HPLC analysis with a chiral column. The formation rate for the [Co(cpel)(L-phe)] complex (**2**) was 6-times superior to that of [Co(cpel)(D-phe)] (**3**). The preferential formation of **2** might be illustrated by the interligand π–π stacking interaction. Crystal structural analysis for **2** and **3** revealed that aromatic rings, pyridine ring of CPEL and phenylalanine sidechain, in **2** were very close each other but those in **3** were far apart. Such interligand aromatic interaction in **2** was also examined by the use of ^{1}H NMR spectra.

Biologically specific and highly efficient reactions are demonstrated at or near the active site of enzyme−substrate complex through a combination of some weak noncovalent interactions, such as hydrogen bonding, steric repulsion, aromatic ring stacking, electrostatic interaction, hydrophobic interaction, etc.[1] The folded conformation of proteins is also regulated by these weak interactions.[2] In protein−DNA[3] and −RNA complexes reported recently,[4] phenylalanine plays an important function in recognition of the hydrophobic moiety through the aromatic stacking interaction. Taking into account the biological significance of natural amino acids, investigation of the amino acid side chain in the molecular recognition process is very important in relation to the appearance of substrate selectivity and specificity.[5]

For the molecular recognition model on amino acids, several studies have been carried out using transition metal complexes.[6,7] Yamauchi et al. emphasized the importance of aromatic ring interaction in molecular recognition using the ternary transition metal complexes with aromatic diamines and aromatic amino acids.[8] The studies that demonstrate that hydrophobic interactions, induced by aromatic ligands, regulate the coordination structure, substrate selectivity, and stability of the ternary metal complexes have also been reported.[7,9] Chin et al. reported a unique cobalt(III) complex with chiral tetradentate ligand, demonstrating the regiospecific and stereospecific recognition of natural amino acids.[10] We have previously constructed some ternary cobalt(III) complexes as a molecular recognition model for an enzyme−substrate complex, where the complex containing an asymmetric $(N)(O)_3$-type tripodal tetradentate ligand, bis-*N*,*N*-carboxymethyl-L-phenylalanine (H_3bcmpa), as a host site-specifically bound with a bidentate amino acid (Haa) as a guest.[11,12] In this host−guest complex, the Co(bcmpa) complex preferentially bound the amino acid in the manner of the *trans*-N configuration of $[Co(bcmpa)(aa)]^-$ complex

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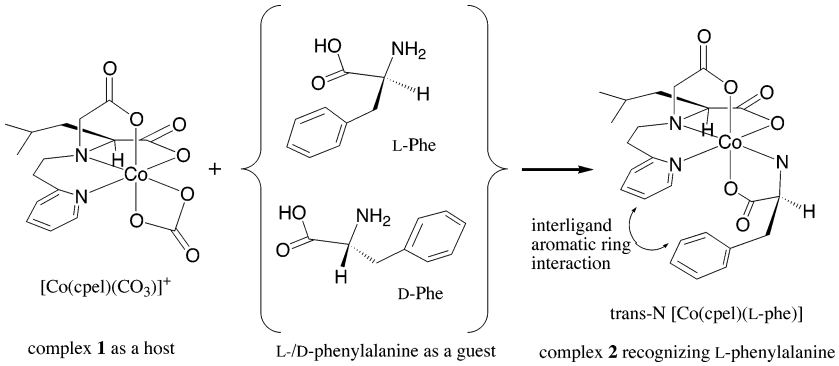
Chart 1



more than the *cis*-N one, and furthermore, the cis-N complex isomerized to the *trans*-N form in the presence of a catalytic amount of active charcoal.[11,12] Thermal stability of the ternary complexes containing various noncovalent interligand interactions between the host and guest ligands might accelerate these reactions. It is very interesting that such a simple metal complex with a multidentate ligand demonstrates selective recognition for amino acids. On the basis of the hydrophobic aromatic ring interaction and specific trans-N coordination as mentioned, we designed and synthesized a unique cobalt(III) complex with chiral $(N)_2(O)_2$-type tetradentate ligand, *N*-carboxymethyl-*N*-pyridylethyl-L-leucine (H_2cpel), and succeeded in an enantioselective coordination of racemic phenylalanine. Here, we describe the preparation and characterization of the ternary cobalt(III) complexes with CPEL and phenylalanine through the enantioselective coordination of the L-isomer, which is accelerated by the $\pi-\pi$ stacking interaction as shown in Chart 1.

Reaction of Na[Co(cpel)(CO_3)] (**1**) with L- or D-phenylalanine gave the cobalt(III) complex with *trans*-N configuration[13] as a main product, *trans*-N [Co(cpel)(L-phe)] (**2**) or *trans*-N [Co(cpel)(D-phe)] (**3**), respectively, whose structures were determined on the basis of the characteristic absorption band that appeared near 500 nm ($\epsilon = 100$ M^{-1} cm^{-1}) with shoulder peak at 580 nm ($\epsilon = 26$ M^{-1} cm^{-1}), respectively.[14] The ratio of *trans*-N isomer[13] to the *cis*-N one[13] in the [Co(cpel)(L- or D-phe)] complex was estimated to be over 40. These experimental findings agree well with the previous reports that the complexation of amino acid to cobalt(III) complex with the $(N)(O)_3$ type ligand preferentially gave the *trans*-N form as a more thermodynamically stable product.[11,12,15]

The interligand aromatic interactions upon the ternary cobalt(III) complexes in solution phase were examined by the use of ^{1}H NMR spectra. The aromatic ring stacking interaction will be enhanced by the shielding effect in an aqueous solution, but reduced in DMSO.[16] The pyridine ring protons of **2** in D_2O were observed at 7.15 (Py-H5), 7.43 (Py-H3), 7.85 (Py-H4), and 7.98 ppm (Py-H6), respectively, which showed downfield shift in DMSO-d_6 at 7.38 (Py-H5), 7.54 (Py-H3), 7.95 (Py-H4), and 8.36 ppm (Py-H6), respectively. Benzene ring protons of the phenylalanine residue in complex **2** observed at 7.02−7.19 ppm in D_2O also exhibited downfield shift in DMSO-d_6 at 7.08−7.23 ppm. In addition, the pyridine-H6 proton observed at 7.98 ppm in D_2O shifted to 8.13 ppm in the less-polar D_2O/dioxane-d_8 (3:7) solution. These findings apparently indicate the aromatic stacking interaction between pyridine and benzene rings in **2**. On the other hand, complex **3** in DMSO-d_6 gave the ^{1}H NMR peaks at 7.52 (Py-H5), 7.61 (Py-H3), 8.03 (Py-H4), and 8.85 ppm (Py-H6), respectively, for the pyridine ring and at 7.14−7.46 ppm for the benzene ring. As complex **3** was insoluble in water, the spectral pattern for pyridine ring protons of the CPEL ligand of **3** in D_2O was not obtained. That in DMSO-d_6 (7.51 (Py-H3), 7.54 (Py-H5), 7.99 (Py-H4), and 8.55 ppm (Py-H6), respectively) was very similar to that of starting complex **1** without the phenylalanine moiety. Accordingly, we conclude that the benzene ring of D-phe and the pyridine ring of cpel in **3** are far apart from each other in the solution phase.

Fortunately, complexes **2** and **3** were obtained as single crystals suitable for X-ray diffraction measurements. The crystal structures of **2** (Figure 1)[17] and **3** (Figure 2)[18] revealed that the ternary cobalt(III) complexes with CPEL and L-/D-phenylalanine ligands were both an octahedral $(N)_3(O)_3$ geometry with *trans*-N configuration.[13] Notably, the aromatic ring interaction indicated in solution is also found in the crystal structure of **2**. The distance (3.55 Å) between the two aromatic rings in **2**, which is comparable to the cases of [Cu(L-trp)(bpy)]$^+$ (trp = tryptophanate) and [Cu(L-trp)-

(13) According to the IUPAC Red Book, *Nomenclature of Inorganic Chemistry, Recommendations 1990*, the configuration around the cobalt ion of the *trans*-N complex (**2**) is described as OC-6-35, and that of *cis*-N one is OC-6-45.

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(17) Elemental analysis of **2**. Anal. Calcd for [Co(cpel)(L-phe)]·1.5H_2O ($C_{24}H_{33}CoN_3O_{7.5}$): C, 53.13; H, 6.13; N, 7.75. Found: C, 53.02; H, 6.17; N, 7.73. Crystallographic data for [Co(cpel)(L-phe)]·2H_2O complex (**2**): orthorhombic, space group $P2_12_12_1$, $a = 10.687(2)$ Å, $b = 28.08(1)$ Å, $c = 8.550(1)$ Å, $V = 2565(1)$ Å^3, $Z = 4$, $D_{calcd} = 1.428$ g cm^{-1}, no. reflns obsd. 2468, no. valuables used 2214, $R = 0.048$, $R_w = 0.136$.

(18) Elemental analysis of **3**. Anal. Calcd for [Co(cpel)(D-phe)]·H_2O ($C_{24}H_{32}CoN_3O_7$): C, 54.03; H, 6.05; N, 7.88. Found: C, 53.80; H, 6.00; N, 7.79. Crystallographic data for [Co(cpel)(D-phe)]·H_2O complex (**3**): orthorhombic, space group $P2_12_12_1$, $a = 15.993(3)$ Å, $b = 20.975(9)$ Å, $c = 7.447(1)$ Å, $V = 2498.1$ Å^3, $Z = 4$, $D_{calcd} = 1.418$ g cm^{-1}, no. reflns obsd. 4140, no. valuables used 2806, $R = 0.058$, $R_w = 0.178$.

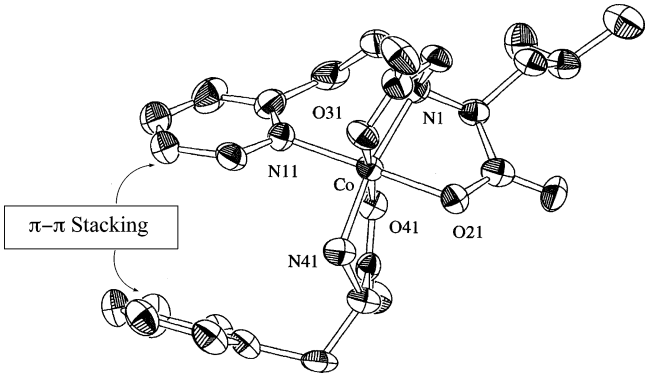

Figure 1. Molecular structure of [Co(cpel)(L-phe)] (**2**). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Co−O(21) 1.881(4); Co−O(31) 1.900(5); Co−O(41) 1.901(4); Co−N(1) 1.979(6); Co−N(11) 1.975(5); Co−N(41) 1.946(5); O(21)−Co−N(11) 177.4(2); N(1)−Co−N(11) 96.8(2); N(1)−Co−N(41) 169.3(2); O(41)−Co−N(41) 85.1(2).

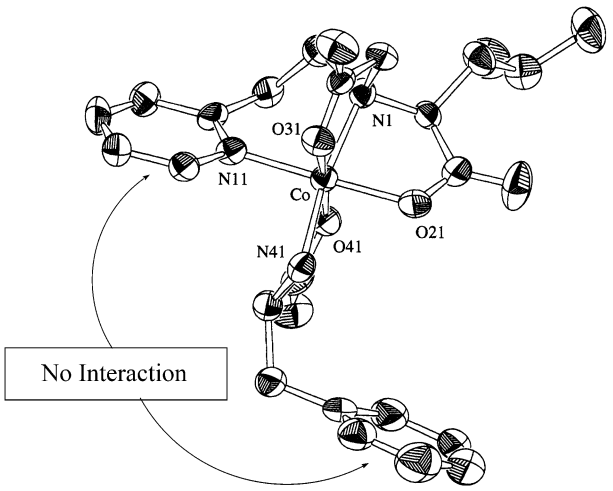

Figure 2. Molecular structure of [Co(cpel)(D-phe)] (**3**). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Co−O(21) 1.888(4); Co−O(31) 1.879(5); Co−O(41) 1.901(5); Co−N(1) 1.982(6); Co−N(11) 1.941(5); Co−N(41) 1.938(5); O(21)−Co−N(11) 178.6(2); N(1)−Co−N(11) 94.7(2); N(1)−Co−N(41) 170.6(2); O(41)−Co−N(41) 82.5(2).

(phen)]$^+$ complexes (3.67 and 3.51 Å, respectively),[19] strongly suggests the attractive $\pi-\pi$ interaction. The crystal structure of **2** reveals that the stacked conformation between the aromatic rings is favored rather than the edge-to-face one, which is also supported by the molecular dynamics simulations for aromatic ring interaction in aromatic amino acid.[20] In complex **3**, however, such an interaction is not observed, and both aromatic rings are far apart from each other in the crystal as well as in solution phase. The benzene ring of the D-phenylalanine ligand in **3** has difficulty approaching the pyridine ring of CPEL under consideration from a CPK model study.

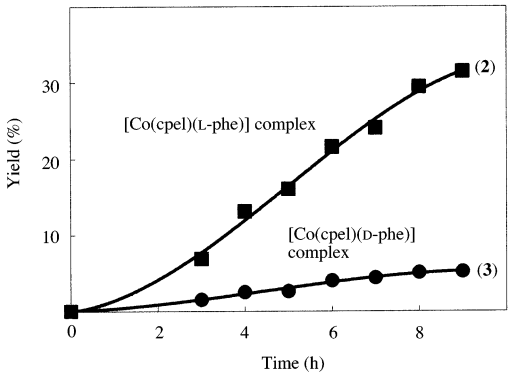

Figure 3. Time course of the yields of [Co(cpel)(L-phe)] (**2**) and [Co(cpel)(D-phe)] (**3**) obtained in competitive reaction of $[Co(cpel)(CO_3)]^-$ (**1**) and racemic L-/D-phenylalanine.

The dynamics for coordination selectivity were examined by means of the competitive coordination of racemic phenylalanine to **1** at pH 5 in aqueous solution. The formation rates of the complexes were measured by a chiral HPLC column. As shown in Figure 3, the ratio for the formation rate of the L-complex (**2**) to the D-complex (**3**) was about 6. Since the ratio was constant during the reaction, transformation from **3** to **2** might not occur. Obviously, chiral recognition of L-phenylalanine was achieved by using chiral tetradentate ligand, CPEL. The preferential formation of the *trans*-N [Co(cpel)(L-phe)] complex (**2**) might be interpreted by the thermal stability of the product complex, which is caused by the interligand interactions.[11,12] In the case in which racemic leucine was used instead of racemic phenylalanine, the selectivity for the ternary complex [Co(cpel)(L-leu)] to [Co(cpel)(D-leu)] was 1.1:1. Notably, the selectivity for chiral recognition is reduced in a system without $\pi-\pi$ stacking. It is clear that the interligand $\pi-\pi$ interaction mediated upon the ternary cobalt(III) complex leads to preferential formation of **2**.

In conclusion, we found that complex **2**, a model for an enzyme−substrate complex, demonstrated higher enantioselectivity for recognition of an L-aromatic amino acid rather than a D-aromatic amino acid, which was achieved through the interligand $\pi-\pi$ stacking interaction between the aromatic rings of L-phenylalanine and CPEL.

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Supporting Information Available: Experimental procedures for synthesis and characterization of complexes **1**−**3** and X-ray analysis data for **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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