Amino Acid Exchange Reaction of Bis(pyridoxylidene-amino acidato)cobalt(III) Complex Promoted by the α-Hydroxylation

Koichiro Jitsukawa,* Tetsuya Yamamoto, Hiroshi Takahashi, Hideki Masuda,* and Hisahiko Einaga
Department of Applied Chemistry, Nagoya Institute of Technology, Showa-ku, Nagoya 466

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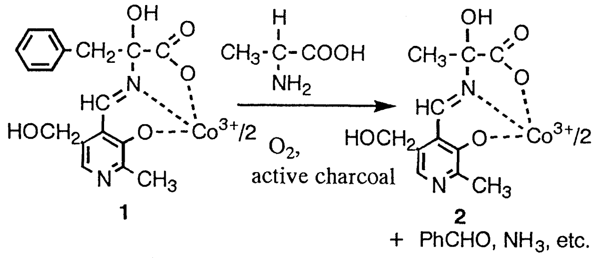
A new type of amino acid exchange reaction that is promoted by the α-hydroxylation was found to proceed on the bis(pyridoxylidene-α-hydroxyamino acidato)cobalt(III) complexes under aerobic conditions.

Amino acid transformation catalyzed by pyridoxal coenzyme is an attractive subject for our investigation of the enzyme model reactions.[1-3] In the biomimetic transformation of amino acid, the Schiff base compound formed by the condensation of pyridoxal coenzyme and amino acid derivative has been inferred to be a key intermediate.[4] Bioinorganic approach is expected to powerfully contribute for such a study, because the model reaction for the vitamin B_6 enzyme by using the metal ion as a mediator can clarify the nature of the intermediate in the transformation.[5-7] In the course of our studies on the amino acid transformation using substitutionally inert Co(III) complexes with Schiff base ligands, a novel hydroxylation at the α-position of amino acid has previously been discovered.[1] For the purpose of throwing more light on the transformation, we have investigated the interesting amino acid exchange reaction mediated on the cobalt(III) complex with pyridoxylidene-α-hydroxyamino acid ligand under aerobic conditions (Scheme 1), which is a vitamin B_6 reaction model, to find that a new type of reaction proceeds.[8,9]



Scheme 1.

Ligand exchange reaction of the Co(III) binary complex containing pyridoxylidene-α-hydroxyphenylalanine ligand, $[Co(phfs)_2]^-$ **1**, was carried out in an aqueous solution at 50°C in the presence of active charcoal and 10-fold excess amount of L-alanine under an aerobic condition. From the reaction mixture ammonia gas gradually generated, which was checked by the Nessler's reagent. After 8 h, 43% yield of benzaldehyde based on **1** was detected in the reaction solution by GLPC analysis. The reaction mixture was filtered to remove the active charcoal, and passed through an anion exchange QAE Sephadex column (Cl^- form). After eluting neutral and cationic compounds with water, four adsorbed bands were fractionated with a 1 M NaCl solution to successively give three anionic complexes, **2a**, **2b**, and **2c** (total yield 36%), and unreacted starting complex **1**.

All the ^1H-NMR spectra of **2a-c** in D_2O revealed that phenyl protons of phenylalanine residue derived from the starting complex were not observed in their spectra but singlet peaks assignable to methyl group of alanine were detected at 1.89~2.02 ppm. Although other peaks characteristic of pyridoxal moieties were observed at the same regions as those in **1**, any peaks assignable to α-proton of alanine moieties were not observed in each diastereoisomer of **2a-c**. In order to elucidate the structures of **2a-c**, crystallization of the each eluate from the QAE Sephadex column was performed. Fortunately, the standing of the first eluate for several weeks gave single crystals, **2a**, suitable for X-ray structure analysis.[10]

The crystal structure of **2a** established, as shown in Figure 1, demonstrates that the two Schiff base ligands coordinate to the Co(III) ion with mer-trans(N)-

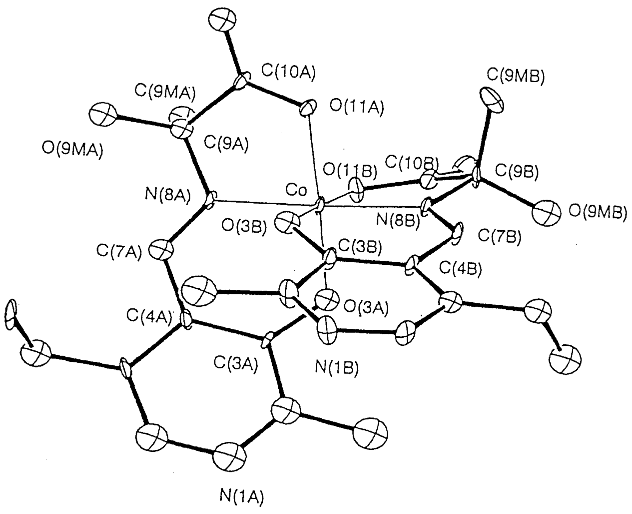


Figure 1. Molecular structure of one of the enantiomeric isomers, $\Lambda(S,S)$-$[Co(phas)_2]^-$, **2a**. Important interatomic distances (Å) and angles (°) are as follows:
Co-O(3A) 1.862(3), Co-O(3B) 1.871(2), Co-N(8A) 1.883(3), Co-N(8B) 1.877(3), Co-O(11A) 1.912(3), Co-O(11B) 1.911(2), C(7A)-N(8A) 1.273(5), C(7B)-N(8B) 1.283(5), N(8A)-C(9A) 1.485(6), N(8B)-C(9B) 1.477(4), C(9A)-O(9MA) 1.402(5), C(9B)-O(9MB) 1.396(5) C(9A)-C(9MA) 1.503(5), C(9B)-C(9MB) 1.524(6);
O(3A)-Co-N(8A) 94.1(1), O(3B)-Co-N(8B) 93.1(1), N(8A)-Co-O(11A) 84.0(1), N(8B)-Co-O(11B) 85.1(1), O(3A)-Co-O(11A) 178.0(1), N(8A)-Co-N(8B) 177.6 (1), C(4A)-C(7A)-N(8A) 124.0(4), C(4B)-C(7B)-N(8B) 123.8(4), C(7A)-N(8A)-C(9A) 120.9(4), C(7B)-N(8B)-C(9B) 119.9(3), Co-N(8A)-C(7A) 125.0(3), Co-N(8B)-C(7B) 126.8(2).

configuration. Judging from the bond lengths of C(7A)-N(8A) (1.273(5) Å) and C(7B)-N(8B) (1.283(5) Å), the double bond character of the azomethine bond is retained in the product complex. Pyridoxylidene-α-hydroxyphenylalanine ligand of the starting Co(III) complex **1** has been replaced to pyridoxylidene-α-hydroxyalanine, as expected from the ^{1}H-NMR spectrum. The hydroxyl groups attached to the α-carbon were assigned on the basis of the electron density of the positions located from the Fourier map and the bond lengths; the two bond lengths between α-carbon and the oxygen atom in **2a** were 1.402(5) and 1.396(5) Å. These results clearly indicate that an amino acid exchange reaction has occurred on the Co(III) complex containing pyridoxylidene Schiff base under aerobic conditions, accompanying the α-hydroxylation of amino acid.

An alternative exchange reaction of the isolated $[Co(phas)_2]^-$ with an excess of L-phenylalanine afforded bis(pyridoxylidene-α-hydroxyphenylalaninato)-cobalt(III) complex, $[Co(phfs)_2]^-$, (23% yield). The addition of excess β-alanine in place of α-alanine, however, caused no amino acid exchange reaction and the starting Co(III) complex **1** was recovered. In the absence of active charcoal, these exchange reaction did not proceed at all. Since an obvious oxygen absorption was observed during the reaction with α-amino acid but not with β-alanine, the α-hydroxyl oxygen atoms of **2a-c** seem to originate from molecular oxygen.[1]

On the basis of the above results, this amino acid exchange reaction is considered to proceed as follows. The hydroxyl group at the α-position withdraws electron on the azomethine bond to weaken the coordinate bond of nitrogen atom to the central metal atom, which is presumed from the fact that the Co-N(8) bonds in **1** previously reported (1.888(1), 1.897(2), 1.884(5), and 1.879(5) Å) are somewhat longer in comparison with those in bis(pyridoxylidene-phenylalaninato)cobalt(III) complex (1.875 (9) and 1.857(9) Å).[1] This weakened coordinate bond of the Schiff base nitrogen to the central metal atom causes an easy attack by external amino acid and promotes the exchange reaction on the surface of an active charcoal catalyst. In addition, we have recently observed another type of amino acid exchange reaction; the Co(III) binary complex containing pyridoxylidene-β-alanine with a weakened Co-N bond causes an amino acid exchange reaction from β-alanine to α-amino acid in the presence of active charcoal, in which the Co-N bond lengths were elongated to 1.902(6) and 1.919(6) Å.

The α-amino acid derivative once replaced on the complex is oxidized at the α-position of the amino acid moiety through the aldimine-ketimine equilibrium in Schiff base and then the α-hydroxyamino acid complexes **2a-c** are formed.[1] α-Hydroxyphenylalanine dissociated from the starting complex **1** by the exchange reaction decomposes to generate benzaldehyde and ammonia via phenylpyruvic acid as an intermediate.[11] Further detailed comprehension of the amino acid exchange reaction on the Co(III) complex promoted by the α-hydroxylation will be reported elsewhere.

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10 Crystal data for **2a**: $C_{22}H_{24}CoN_4NaO_{10}\cdot 5H_2O$, M = 676.45, triclinic, $P\bar{1}$, a = 9.973(3), b = 10.464(5), c = 14.801(9) Å, α = 83.67(4), β = 74.86(4), γ = 71.67(3)°, Z = 2, V = 1414.6 Å^3, Dc = 1.59 g cm^{-3}, Mo-Kα (λ = 0.71073 Å), μ = 6.70 cm^{-1}, $3 < 2\theta < 55°$. A total of 8512 unique reflections were collected on an Enraf-Nonius CAD4-EXPRESS four-circle diffractometer. A total number of 6310 reflections having $I > 3\sigma(I_0)$ were used in the structure analysis and refinement using the SDP-MolEN program system. Absorption correction was applied by DIFABS. The structure was solved by the heavy-atom method and refined anisotropically. The hydrogen atoms, except those of hydroxy and a part of water molecules, were located on Fourier difference maps, which were not refined, but included in the calculation. Final R and R_w factors were 0.075 and 0.094, respectively. The unit cell contains two enantioisomers (Λ(S,S) and Δ(R,R)) of the Co(III) binary complexes with pyridoxylidene-α-hydroxyalanine ligands, $[Co(phas)_2]^-$.

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