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PARTIAL ASYMMETRIC TRANSFORMATION OF RACEMIC AMINO ACIDS USING COBALT(III) SCHIFF BASE COMPLEX OF ℓ-MENTHYL β-(2-HYDROXYBENZOYL)PROPIONATE[1)]

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Cobalt(III) complexes, $[Co(\ell\text{-mop=aa})_2]^-$, where $H_2(\ell\text{-mop=aa})$ denotes Schiff bases obtained from ℓ-menthyl β-(2-hydroxybenzoyl)-propionate and an amino acid (aa=gly, ala, val, leu), were prepared in solution and examined with absorption and circular dichroism spectra. It was shown that an asymmetry around the cobalt(III) was induced by the vicinal effect of ℓ-menthyl group and that racemic amino acids were partially transformed to an optical isomer.

It is well known[2-5)] that the metal complex formation of Schiff base of an amino acid labilizes the hydrogen attached to the α-carbon in the condensed amino acid, thereby an optically active amino acid being isomerized. This phenomenon is considered as a racemase model in biological system. On the other hand, transformation of racemic amino acids to an optically active form might be brought about, if a chiral group is introduced into the ligand moiety. This type of the reaction may occur in biological transamination with pyridoxal,[6)] which is bonded to chiral peptide via $-CH_2-O-PO_3^{2-}$ group adjacent to the formyl group. However, asymmetric transformation of racemic amino acids by use of Schiff base metal complexes have not yet been reported. Thus, it was aimed in this study to transform racemic amino acids to optically active amino acids using cobalt(III) complexes with Schiff bases of ℓ-menthyl β-(2-hydroxybenzoyl)propionate (abbreviated as ℓ-mop).

Preparation of ℓ-mop. To a solution of β-(2-hydroxybenzoyl)propionic acid[7)] (10 g) and ℓ-menthol (15 g) in benzene (120 ml) was added a few drops of concd. sulfuric acid, and the mixture was refluxed on a water-bath for 48 hours. In the course of this reaction, water formed by esterification was eliminated as benzene azeotrope. When the reaction mixture was concentrated to 30 ml and allowed to stand overnight, pale yellow prisms separated. They were collected and recrystallized twice from ethanol to give colorless needles melting at 79-80°C.

Found: C, 72.44; H, 8.51%. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49%.

Procedure. Racemic amino acid (5×10^{-4}mole), ℓ-mop (166 mg, 5×10^{-4}mole), cobalt(II) acetate tetrahydrate (62 mg, 5×10^{-4}mole) and triethylamine (0.4 ml) were placed in a 50 ml volumetric flask and the volume was adjusted with methanol or ethanol. After two days, clear red solutions were obtained. Electronic absorption

spectra and circular dichroism spectra of the solutions were measured by a Shimazu Multipurpose Spectrophotometer Model MSP-5000 and a JASCO ORD/SP Optical Dispersion Recorder.

Recovery of Amino Acids. The ethanol solution prepared according to the above prescription was allowed to stand at ambient temperature for 10 days. To this solution was introduced hydrogen chloride. The reaction mixture assumed green color. Then the solvent was evaporated to dryness to give an oily substance, which was washed several times with hot chloroform by decantation. When acetone was added to the residue, white prisms separated. They were collected and recrystallized from an ethanol-acetone mixture. The product was identified to be the amino acid hydrochloride by comparing the IR spectrum with that of the authentic sample. Specific rotations of the amino acid hydrochlorides were determined in 5M-hydrochloric acid with a Union Giken High Sensitive Polarimeter Model PM-71.

Electronic spectra of the solutions showed absorption bands at 530 and 400 nm, whos extinction coefficients gradually increased and converged after 120 hours to ca. 200 and 1600, respectively. Electronic spectra indicated that cobalt(II) ion was oxidized by molecular oxygen to give a cobalt(III) complex in solution. Although we were unsuccessful in isolating the complexes, it is assumed that $[Co(\ell\text{-mop=aa})_2]^-$ (aa=gly, ala, val, leu) is formed in the solution (Fig. 1), where $H_2(\ell\text{-mop=aa})$ denotes the Schiff bases obtained from ℓ-mop and an amino acid. It is likely that $\ell\text{-mop=aa}^{2-}$ facially coordinates to the cobalt(III) ion, since, as was pointed out by Burrows and Bailar, Jr.,[8] the fac-form is more stable than the mer-form for cobalt(III) complexes with N-salicylideneamino acids.

Circular dichroism spectra of the complexes were measured in the range 650-450 nm and exemplified by $[Co(\ell\text{-mop=ala})_2]^-$ (Fig. 2). As is seen in Fig. 2, a positive CD peak appeared at 520 nm, whose intensity increased gradually and converged after 240 hours. Similar CD spectra were observed for the complexes with gly, DL-val and DL-leu. Optical activity is undoubtedly associated with an asymmetry around the cobalt(III), since $[Co(\ell\text{-mop=gly})_2]^-$, which has no asymmetric carbon atom in amino acid moiety, displayed a Cotton effect. Six geometric isomers are considered for fac-$[Co(\ell\text{-mop=aa})_2]^-$ and five of them are optically active. Thus, we may assume that equilibria are established between the optical isomers (diastereoisomers to be exact) in some of the geometric forms of fac-$[Co(\ell\text{-mop=aa})_2]^-$ and an optical isomer displaying a positive CD peak at 520 nm predominates by an effect of the ℓ-menthyl group.

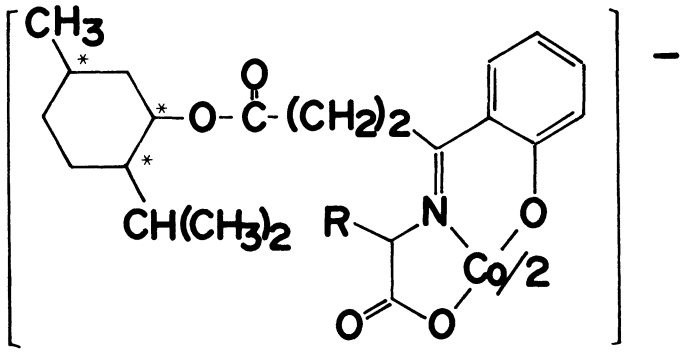

Fig. 1.

In order to examine whether ℓ-menthyl group can exert any Pfeiffer effect[9]

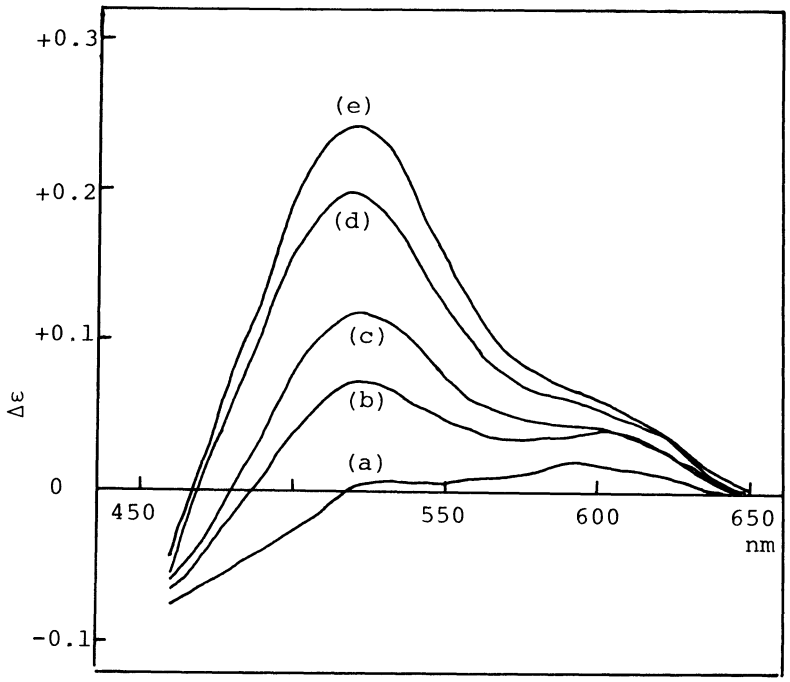

Fig. 2. Induced CD spectra of $[Co(\ell\text{-mop=ala})_2]^-$ at various reaction times: (a) 20, (b) 43, (c) 63, (d) 113, and (e) 230 hours.

upon the Schiff base complexes when detached from the ligand, the complexes were prepared by dissolving 2-hydroxypropiophenone, ℓ-menthol, a racemic amino acid and cobalt(II) acetate tetrahydrate (2:2:2:1) in methanol. After being allowed to stand for 10 days, the solutions showed no Cotton effect, although electronic spectra of these solutions were almost the same as those of $[Co(\ell\text{-mop=aa})_2]^-$. No CD peak was induced even when complexes were prepared in the presence of a large excess of ℓ-menthol (Co:ℓ-menthol=1:250). Accordingly, ℓ-menthyl group can effect the asymmetric induction only when it is connected to the ligand. It is likely that some interaction between ℓ-menthyl group and the aromatic nucleus in the ligand plays an important role in determining the configuration and the conformation of the complexes.

In Fig. 3 the time dependence of the CD intensity at 520 nm of $[Co(\ell\text{-mop=aa})_2]^-$ is shown. It is seen that the equilibrium of the optical isomers for $[Co(\ell\text{-mop=gly})_2]^-$ was reached within 120 hours. On the other hand, the equilibria for $[Co(\ell\text{-mop=ala})_2]^-$, $[Co(\ell\text{-mop=val})_2]^-$ and $[Co(\ell\text{-mop=leu})_2]^-$ were reached after the solutions were allowed to stand for 240 hours, while absorption spectra of these complexes did not change any more after 120 hours. Furthermore, it is to be noted that $\Delta\varepsilon$ values observed for $[Co(\ell\text{-mop=ala})_2]^-$, $[Co(\ell\text{-mop=val})_2]^-$ and $[Co(\ell\text{-mop=leu})_2]^-$ are larger than that for $[Co(\ell\text{-mop=gly})_2]^-$. These facts imply that asymmetric induction around the cobalt by ℓ-menthyl group is followed by a slow asymmetric transformation of racemic amino acid. In order to confirm this, the complexes prepared in ethanol and allowed to stand for 10 days were decomposed with hydrogen chloride, and the amino acid hydrochlorides were recovered. Specific rotations of ala·HCl, val·HCl and leu·HCl were -3.20, +3.57 and +1.83°, respectively, in 5M-hydrochloric acid. Thus, racemic amino acids were partially transformed into an optical isomer. Optical purities of the amino acids determined on the basis of the specific rotations of authentic L-amino acid hydrochlorides were 22.0 for D-alanine, 12.6 for L-valine and 11.4%.e.e.

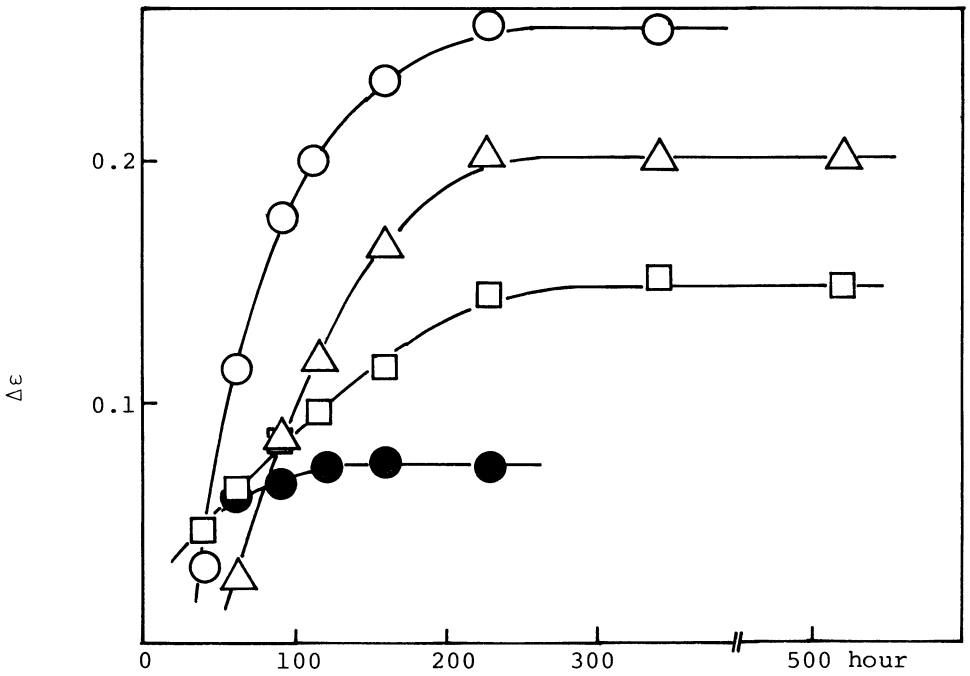

Fig. 3. CD intensity (at 520 nm) of complex solutions at different reaction times: (●)[Co(ℓ-mop=gly)$_2$]$^-$, (○)[Co(ℓ-mop=ala)$_2$]$^-$, (□)[Co(ℓ-mop=val)$_2$]$^-$ and (△)[Co(ℓ-mop=leu)$_2$]$^-$.

(% enantiomer excess) for L-leucine. It is to be noted that DL-alanine was transformed into D-form, while DL-valine and DL-leucine were transformed into L-form.

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