

The First Complete Optical Resolution Based on Chiral Discrimination
between Ions of the Same Sign, u-fac-[Co(ida)₂]⁻ and [Sb₂(d-tart)₂]²⁻

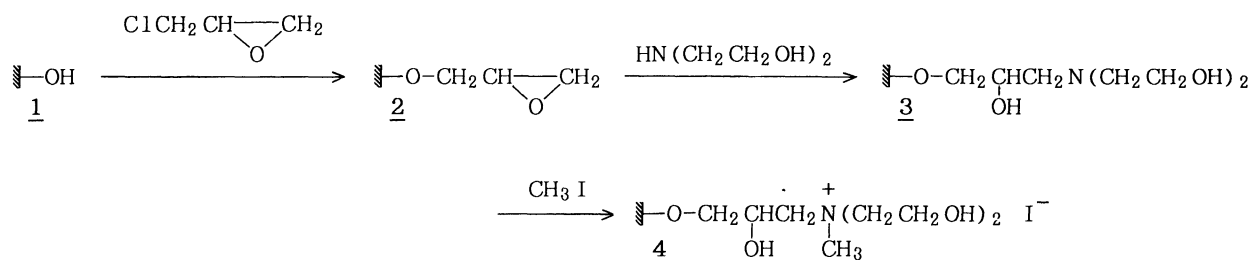
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The complete optical resolution of the anionic complex, u-fac-[Co(ida)₂]⁻, was achieved chromatographically by use of the anionic resolving agent, [Sb₂(d-tart)₂]²⁻, on a strong anion-exchanger derived from Toyopearl (Fractogel TSK) gel. The chiral discrimination mechanism without direct contact of the racemate and resolving agent is suggested.

Column chromatography is one of the most useful techniques for the optical resolution of cationic and neutral metal complexes.^{1,2)} For anionic complexes, there has been no effective method in the preparative resolution, although the complete resolution has been achieved by use of various cationic chiral selectors (resolving agents).²⁻⁷⁾ The selectors used to resolve anionic complexes have been limited to chiral cations and neutral adsorbents. As the only exception, Yoshikawa and Yamasaki used anionic selectors for the resolution of anionic complexes, but they obtained unseparated elution curves.⁸⁾ This technique is employed for the present resolution. On the other hand, the preparative complete resolution of metal complexes has been achieved almost exclusively by use of Sephadex ion-exchangers.¹⁻³⁾ A new strong anion-exchanger, which was derived from Toyopearl HW50S (Tosoh Co., Ltd.) in this laboratory, was successfully applied to the resolution of cationic and neutral complexes.⁹⁾ The preparation method of the new exchanger is described here. The exchanger of [Sb₂(d-tart)₂]²⁻ (tart = tartrate) form is applied to the optical resolution of u-fac-[Co(ida)₂]⁻ (ida = iminodiacetate), which has the chiral disposition of chelate rings around the cobalt atom.

Toyopearl HW50S gel, a support for gel-filtration (20-40 μm on the swelling in water), is a synthetic polymer with hydroxyl groups. The anion-exchanger was prepared from the gel as follows. The epoxy-activation of Toyopearl was carried



out by a modification of the method of Matsumoto et al.¹⁰⁾ To 72 g of suction-dried Toyopearl HW50S 1 were added 140 cm³ of 1-chloro-2,3-epoxypropane and 55 cm³ of 15 mol dm⁻³ sodium hydroxide. The suspension was shaken at 30 °C for 4 h. The gel was filtered and washed with methanol, water and again with methanol, and dried under vacuum. The epoxy-activated Toyopearl 2 (24 g) was suspended in 190 cm³ of 50% (v/v) methanol containing 20 g of bis(2-hydroxyethyl)-amine. After refluxing for 2 h, the gel was filtered and washed with methanol and dried under vacuum. The 3-[bis(2-hydroxyethyl)aminio]-2-hydroxypropyl Toyopearl 3 (28.5 g) was suspended in 110 cm³ of methanol containing 28 cm³ of methyl iodide. After refluxing for 2 h, the gel was filtered and washed with methanol and water, yielding the quarternary ammonium type of exchanger, 3-[bis(2-hydroxyethyl)-methylamino]-2-hydroxypropyl Toyopearl of iodide form 4. The ion-exchange capacity of the exchanger of chloride form was 0.47 mmol cm⁻³ for the [Co(edta)]⁻ (edta = ethylenediaminetetraacetate) ion. For the present optical resolution, the exchanger of [Sb₂(d-tart)₂]²⁻ form was used.

The exchanger was packed in a column (1.0 ϕ x 70 cm) and 50 mg of racemic u-fac-K[Co(ida)₂] \cdot 2.5H₂O was loaded on the top of the column. The adsorbed band was eluted with 0.06 mol dm⁻³ of an aqueous solution of K₂[Sb₂(d-tart)₂] \cdot H₂O at an elution rate of 0.25 cm³ min⁻¹. The absorbance for each 0.7 cm³ fraction was determined at the first absorption maximum. Figure 1 shows the elution curve; the enantiomers were eluted in the order of $\Delta\Delta\Delta$ and $\Lambda\Lambda\Lambda$. Fifty milligrams of the ida complex was completely resolved in a short time (10.2 h) and with a small elution volume (120 cm³), indicating practical use for the preparative resolution.

Although several attempts to resolve anionic complexes have been made by using chiral cations or adsorbents as selectors,^{1-7,11)} only a few examples of successful resolution have been published. Tatehata et al. first succeeded in the complete resolution of anionic cobalt(III) complexes on a weak anion-exchanger using Λ -[Co(en)₃]³⁺ (en = ethylenediamine) as a selector.³⁾ Yoneda et al., completely resolved anionic cobalt(III) complexes by two methods: on a stationary phase with octadecyl groups using alkaloid cations as selectors,⁴⁾ and on strong anion-exchangers using chiral cationic cobalt(III) complexes⁷⁾ or alkaloid cations^{5, 6)} as selectors. Thus, high efficiency in the resolution of anionic complexes has been attained only by using cationic selectors.

The extent of separation of enantiomers is expressed by means of the separation factor (α), which is the ratio of the retention volumes for the enantiomers, more fundamentally, the ratio of equilibrium distribution coefficient. The separation factor is approximately regarded as the difference in free energies of distribution for the enantiomers which results from the diastereomeric interactions of enantiomers with a selector in the ion-exchange

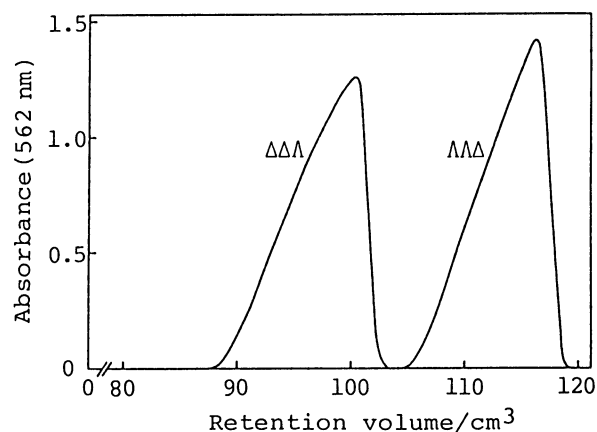


Fig. 1. Elution curve of u-fac-[Co(ida)₂]⁻.

process: $\Delta(\Delta G^\circ) = -RT \ln \alpha$.¹²⁾ The α value of the present resolution is estimated to be 1.18 from the elution curve, but the true value is larger (1.23 in a preliminary experiment), because the void volumes are contained in the retention volumes used in the estimation. This value is comparable to those obtained by the use of cationic selectors, which are less than 1.28³⁻⁷⁾ except for 1.72 and 1.82 (calculated from the data of the elution distance of bands) in two special cases,⁵⁾ in a large number of resolutions.

The mechanism of chiral discrimination between ions of the same sign has been experimentally examined in the systems exhibiting the Pfeiffer effect (the displacement of enantiomer equilibrium of a labile racemic compound caused by an optically active "environment substance").^{5, 13, 14)} In such systems, one or both of the racemic (e.g., $[\text{Zn}(\text{phen})_3]^{2+}$ (1,10-phenanthroline)) and environment (d-cinchoninium) ions contain aromatic moieties. It has been proposed that the hydrophobic bonding^{5, 13)} or hydrogen bonding¹⁴⁾ interaction involving aromatic moiety(s) leads to association between ions of the same sign against their mutual electrostatic repulsion inevitably expected, and that this direct contact provides a main driving force for the chiral discrimination in the Pfeiffer-active systems.

The present resolution system is related to the interaction between the two anions, $[\text{Co}(\text{ida})_2]^-$ and $[\text{Sb}_2(\text{d-tart})_2]^{2-}$. A remarkable difference of this system from the above Pfeiffer systems is that both of the interacting species are hydrophilic. It may be probable between the two anions that an attractive force leading their direct contact is provided by hydrogen bonding between imino hydrogen atoms in $[\text{Co}(\text{ida})_2]^-$ and carboxylic or alcoholic oxygen atoms in $[\text{Sb}_2(\text{d-tart})_2]^{2-}$. However, a similar hydrophilic anion, $[\text{Co}(\text{edta})]^-$, which is unlikely to form a hydrogen bond with $[\text{Sb}_2(\text{d-tart})_2]^{2-}$, could be also completely resolved in the same way, although its separation factor (1.12) is smaller than that for $[\text{Co}(\text{ida})_2]^-$.¹⁵⁾ In these resolution systems, therefore, electrostatic repulsion is a dominant interaction between the two anions, so that each ion must essentially exist as species solvated with water, forming a so-called ionic atmosphere.¹⁶⁾ Thus, our results indicate that a significant chiral discrimination can be induced without direct contact of the racemate and selector in water, and probably by chiral perturbation of water lattice structure intervening between the two species. Such a mechanism has been speculated in discussions on the Pfeiffer effect by Bosnich and Watts¹⁷⁾ and Schipper.¹⁸⁾ It should be noted that the free energy difference for the chiral discrimination in the present resolution system, as described above, is comparable to those in the resolution systems consisting of the ions of opposite sign; the associative mechanism has been proposed for the latter systems.³⁻⁷⁾ The present finding seems to provide a new subject in a field of the solution chemistry of electrolytes.

For the resolution of charged enantiomers, including cationic ones, there has been no report that the ionic selector of the same sign as the enantiomers was used, except by Yoshikawa.⁸⁾ This situation is probably due to a preconception that the interaction between ions of the same sign would be too weak to distinguish between enantiomers. The present complete resolution based on the chiral discrimination between ions of the same sign is the first case not only for

metal complexes but for any charged molecules, including the organic species.

The enantiomer resolution factor (R_s)^{1,2)} in the present resolution is much larger than those seen in the conventional preparative optical resolution.¹⁻³⁾ This may mainly attributed to the use of the exchanger with advantageous physical properties for chromatographic use: smaller and more uniform particle size. Including the results of our preceding work,⁹⁾ all types of cobalt(III) complex, anionic, neutral, and cationic, could be completely resolved by using the present exchanger of $[\text{Sb}_2(\text{d-tart})_2]^{2-}$ form.

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