Partial Resolution of Diamines, Amino Acids and Dicarboxylic Acids Through Coördination with Optically Active Complexes

By B. Das Sarma and John C. Bailar, Jr.

When a 100% excess of a racemic mixture of propylenediamine, alanine or tartaric acid reacts with an optically active complex of copper(II), nickel(II) or cobalt(III), there is a partial resolution of the racemic ligand, probably due to preferential coördination of one of the active forms. The resolution achieved was low, not over 5% in the case of Cu^{+2} and Ni^{+2} complexes and somewhat higher (6–20%) with Co^{+3} complexes. There seems to be some correlation between the structure of the complexes, their configurations, and the configuration of the ligand preferentially coördinated.

Since the work of Smirnoff[1] showed that the resolution of $[Pt^{IV}pn_3]^{+4}$ into D- and L-forms gave isomers which are identical with those obtained by coördination of pure l- and d-propylenediamine with platinum(IV), Bailar and co-workers[2] have been investigating the possibility of the partial resolution of racemic mixtures of organic ligands through coördination with the asymmetric metal ion in a complex. The present investigation is a critical study of such a method and its applicability as regards different metal complexes and various organic addenda.

It has been found that the method is quite general in its application, the amount of resolution effected being dependent on the stabilities of the complex species involved and the rate and mechanism of coördination of the added ligand to the asymmetric metal ion. This latter factor is subject to the mode of operation as regards solvent, temperature and pH of the solution.

Of the eight possible isomers of $[Pt\ pn_3]^{+4}$ or $[Co\ pn_3]^{+3}$, only two are known. The configurations of these can be represented as $[D(lll)]$ and $[L(ddd)]$, where D and L represent the direction of rotation of the complex and d and l, that of propylenediamine. There is, seemingly, a good deal of difference between the stabilities of these isomers and the rest of eight possible ones. This has been advantageously used in the resolution of *racemic*-tartaric, α-chloropropionic and lactic acids,[2] where $[Co(l\text{-pn})_2CO_3]^+$ was employed for the resolution. A similar compound recently has been used for the successful resolution of *trans*-1,2 cyclohexanediamine.[3]

Our aim was to investigate this method, starting with inexpensive active complexes, which are also easier to prepare than $[Co(l\text{-pn})_2CO_3]^+$. d-Tartaric, l-glutamic and d-gluconic acids were chosen as the optically active coördinating agents. The complexes can be made easily by mixing the metal salt solution with the requisite amount (or more) of the chelating agent at the proper acidity. It is not even always necessary to isolate the complexes in their pure condition. The only difficult part is the separation of the resulting mixtures of the complex and active ligands from the solution without racemization. Separations were achieved by taking advantage of differences in solubility between components or their derivatives, differences in volatility, and differences in adsorption on ion-exchange

resins. The following scheme represents the general type of reaction

$$[M^*A_n] + 2m(dl)B \longrightarrow [M^*A_{n-m}(d\ or\ l)B_m] + mA + (l\ or\ d)mB$$
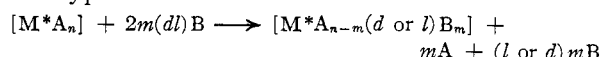
where M is Cu^{+2}, Ni^{+2} or Co^{+3}; A is d-tartaric acid, l-glutamic acid or d-gluconic acid and B is propylenediamine, α-alanine or tartaric acid. In some cases an optically active complex like L-[Co trien $Cl_2]^+$ has also been used with success. It is evident, therefore, that it does not matter whether the asymmetry is introduced by an optically active ligand, or otherwise.

Experimental

1. Resolutions through Cobalt(III) d-Gluconate.—A solution of cobalt nitrate 6-hydrate (4.2 g.) and 4 g. of d-gluconic acid in 25 cc. of water was added to 25 cc. of an 18% solution of sodium hydroxide. Aerial oxidation yielded a green solution. Traube and Kuhbier[4] obtained $Ba[Co^{III}(C_6H_7O_7)]\cdot H_2O$ and $K[Co^{III}(C_6H_8O_7)]\cdot H_2O$ from this by the addition of barium and potassium salts, respectively.

A. Resolution of Propylenediamine.—A solution of 1.54 g. (0.005 mole) of $K[Co\ gluc]\cdot H_2O$ in the least possible quantity of water was vigorously shaken with 2.2 g. of propylenediamine (0.03 mole). The color changed to red-violet very quickly. After an hour, a mixture of 100 cc. of acetone and 100 cc. of ethanol was added and the solution was cooled in ice. The clear, colorless liquid was separated from the precipitated solid by decantation and was acidified with hydrochloric acid. White crystals of propylenediamine dihydrochloride separated and were filtered and washed with acetone. This propylenediamine hydrochloride was mixed with sodium hydroxide solution and distilled at low pressure ($t = 50$–$60°$). The distillate gave a rotation[5] of $-0.023 \pm 0.001°$. The solution was found to be 0.88 N with respect to propylenediamine; $[\alpha]D$ $-0.7°$.

The residue after decantation was red-violet in color. This was mixed with a concentrated solution of caustic soda and distilled similarly. The observed rotation was $+0.026 \pm 0.001°$ and the concentration of the distilled propylenediamine solution was 0.38 N, $[\alpha]D$ $+1.85°$. The resolution of dl-propylenediamine was 6.4% assuming $+29°$ as the specific rotation of d-propylenediamine.

The reaction mechanism is not clear, nor is the structure of the cobalt(III) gluconate or that of the red-violet residue. It may, however, be outlined tentatively as

$$[Co^{III}(d\text{-gluc})]^- + 6dl\text{-pn} \longrightarrow [Co^{III}{}^{d\text{-gluc H}}_{d\text{-pn}_2}] + 2l\text{-pn} + 4dl\text{-pn}$$

This scheme is supported by the approximately threefold resolution of propylenediamine inside the complex as compared to that of the free amine left over. The color change from green to red-violet suggests that some Co^{III}–O bonds have been replaced by Co^{III}–N bonds.

B. Resolution of Alanine.—An excess of dl-alanine was added to a solution of potassium cobalt(III) gluconate in water. The solution slowly turned violet, and violet crystals, insoluble in water, separated. These were filtered, washed with water and dried. The specific rotation in 50%

(1) A. P. Smirnoff, *Helv. Chim. Acta*, **3**, 177 (1920).

(2) A. D. Gott and John C. Bailar, Jr., THIS JOURNAL, **74**, 4820 (1952); S. Kirschner, Ph.D. Thesis, University of Illinois, 1954.

(3) Mary J. Sirotek, Thesis, University of Illinois, 1956.

(4) W. Traube and F. Kuhbier, *Ber.*, **69**, 2655 (1936).

(5) Optical rotations recorded in this article were taken at room temperature (30–31°) in a 1-decimeter tube at the D-line of sodium.

sulfuric acid was −12.0°, indicating that one form of alanine had coördinated preferentially with the cobalt.

2. Resolution through Levorotatory [Co^III trien CO₃]₂-CO₃·CH₃OH. A. Resolution of Tartaric Acid.—Levocarbonato-triethylenetetramine cobalt(III) carbonate (0.65 g.), obtained by asymmetric synthesis,[6] was dissolved in 50 cc. of water and 0.67 g. of *dl*-tartaric acid monohydrate in finely powdered form was added to it. The mixture was slowly evaporated to dryness on the steam-bath. A little water was added to dissolve the residue and the solution was once more evaporated to dryness. The residue was then powdered and taken up with 50-cc. portions of warm ethanol. This ethanol solution containing uncoördinated tartaric acid was evaporated to dryness. The residue, which had a light red color due to adsorbed complex, was again taken up with boiling ethanol, filtered and cooled. To this alcoholic solution was added 4 cc. of *N* sodium hydroxide. The precipitated disodium tartrate was collected by filtration and dried in air. The optical rotation of 0.2 g. of this tartrate in 20 cc. of 0.5 *N* sodium hydroxide solution was +0.040 ± 0.002°. A similar solution of pure disodium *d*-tartrate in 0.5 *N* sodium hydroxide gives [α]D +25.52°. The resolution of the *racemic*-tartaric acid by preferential coördination was therefore about 16%.

The red residue of the tartrato complex left over after extraction with alcohol was acidified with acetic acid, warmed and a solution of saturated barium chloride was added. When it was heated on the steam-bath, barium tartrate slowly separated from it. This was filtered, washed with dilute acetic acid and dried. The barium tartrate was treated with an equivalent quantity of dilute sulfuric acid and the liberated tartaric acid was extracted with ethanol and filtered. Disodium tartrate was obtained from this filtrate as before. A 0.25% solution in 0.5 *N* sodium hydroxide gave a rotation of −0.013 ± 0.002°; [α]D −5.2°. The tartaric acid coördinated was thus about 20% resolved.

3. Resolutions through *d*-Tartratocopper(II) Complexes. A. Resolution of Alanine.—Copper carbonate (1.24 g.) was suspended in 25 cc. of water and 3.0 g. of *d*-tartaric acid was added to it. The mixture was heated on the steam-bath for half an hour and then boiled for a few minutes to ensure complete expulsion of carbon dioxide. The mixture was cooled in ice and a cold solution of 4.5 g. of potassium hydroxide in water was slowly added to it with frequent shaking. The precipitated copper tartrate dissolved, forming a deep blue solution, to which 3.6 g. of *dl*-α-alanine was added. The solution was stirred and filtered. On keeping, the filtrate deposited glistening blue-violet crystals of copper bis-alaninate. These (A) were separated by filtration and washed with cold water. When the filtrate was concentrated at room temperature, more copper bis-alaninate came out. The filtrate from this was treated with a solution of 1.7 g. of copper chloride dihydrate in 25 cc. of water. The mixture was shaken well and allowed to stand. The copper bis-alaninate which separated (B) was filtered and washed with cold water.

The two fractions (A and B) of copper bis-alaninate were purified by recrystallization from warm water. The copper percentages in the dry samples were 23.58 and 23.63 in (A) and (B), respectively, while a sample made from copper salts and alanine directly gave 23.54% copper. Calcd. for [Cu(C₆H₁₂N₂O₄)]1.5·H₂O: Cu, 23.84.

One-gram portions of (A) and (B) were each dissolved in 25 cc. of water containing 2 cc. of concentrated hydrochloric acid and the copper was separated as the sulfide. The filtrates were evaporated almost to dryness at room temperature. The alanine from these was precipitated by the addition of 50 cc. of acetone, and was purified by dissolving in a minimum quantity of water and reprecipitating with acetone. It was finally washed with ethanol and acetone and dried *in vacuo*.

One-half gram of alanine from (A) in 28 cc. of *N* HCl gave α = −0.010 ± 0.002°, [α]D −0.56°; percentage resolution = 3.8%. One-half gram of alanine from (B) in 25 cc. of *N* HCl gave α = +0.011 ± 0.002°, [α]D +0.55°. Resolution is 3.74%.

B. Resolution of Propylenediamine.—Copper carbonate (1.24 g.) was made to react as before with 1.5 g. of *d*-tartaric acid and 3.0 g. of *dl*-propylenediamine and 25 cc. of water were added to the mixture, which was then distilled at a re-

duced pressure at a temperature of 50–55°. The first fraction of the distillate was found to be inactive and contained very little propylenediamine. The rotation of the rest of the distillate was −0.012°. The concentration of the solution was 0.3 *N* with respect to propylenediamine. The specific rotation is therefore −1.0°, representing about 3.33% resolution.

After the whole of the liquid was distilled over, a solution of 1 g. of potassium hydroxide in 50 cc. of water was added and the mixture was distilled as before. The distillate gave a rotation of +0.013° and the concentration was found to be 0.31 *N*. This gives [α]D +1.01°, which represents approximately 3.4% resolution.

Similar experiments using nickel carbonate in place of copper carbonate gave 2–3% resolution.

4. Resolutions through Copper *l*-Glutamate. A. Resolution of Alanine.—To a solution of 2.4 g. of sodium hydroxide and 3.0 g. of *l*-glutamic acid in 50 cc. of cold water was added a solution of 1.6 g. of copper chloride 2-hydrate in 25 cc. of water. To the resulting deep blue solution was added 3.6 g. of *dl*-α-alanine. The solution was filtered immediately and the filtrate was allowed to crystallize slowly at room temperature. The copper bis-alaninate separated was filtered and recrystallized from warm water. Calcd. for [Cu(C₆H₁₂N₂O₄)]·1.5 H₂O: Cu, 23.84. Found: Cu, 23.77.

This was dissolved in dilute hydrochloric acid and the solution was saturated with hydrogen sulfide. The precipitated copper sulfide was filtered off and the filtrate was evaporated almost to dryness at room temperature. The addition of acetone precipitated the alanine, which was filtered, washed with acetone, and purified by again dissolving in water and reprecipitating with acetone.

A 5% solution of this alanine in *N* HCl gave a rotation of +0.024 ± 0.002, whence [α]D +0.48°. This represents a 3.3% resolution.

B.—**Resolution of Tartaric Acid.**—A solution of 1.5 g. of *dl*-propylenediamine in 25 cc. of ethanol was shaken with a suspension of 2.2 g. of finely powdered copper monoglutamate.[7]

The deep blue solution which resulted was stirred with 250 cc. of acetone, whereupon a light blue solid separated. This was collected by filtration and washed with acetone. The filtrate was acidified with 4 cc. of concentrated hydrochloric acid and evaporated to dryness at room temperature. The residue was mainly propylenediamine dihydrochloride mixed with a little copper salt. This residue was decomposed with aqueous sodium hydroxide and the propylenediamine recovered by distillation at low pressure. The distillate (concentration, 1%) had a rotation of +0.012°. This represents a specific rotation of +1.2° and a resolution of about 4%.

In some cases ion-exchange resins were used to separate the different components, and different conditions as regards the solvent, temperature of reaction, and precipitation of the complexes with solvents like acetone or ether were attempted. The resolution in no case could be improved over 4% while using a copper or nickel complex. In some cases smaller or even no resolutions were observed. This is seemingly due to exchange of ligands inside and outside the coördination sphere, which can be demonstrated by distillation of a mixture of [Cu(or Ni)pn₂]^++ and *l*- or *d*-pn at a reduced pressure. The propylenediamine that distils over is optically active, but has a lower specific rotation than the active propylenediamine added.

There seems to be some correlation between the forms of the ligand coördinated preferentially and the configuration of the optically active complex that effects this partial resolution as shown in Table I.

TABLE I

Resolving agent	*dl*-mixtures	Form preferentially coördinated	Resolution, %
(+) Co(III) *d*-gluconate	pn	(+) *d*-pn	6.4
(−) [Co^III trienCO₃]⁻· CH₃OH	H₂tart	(−) *l*-H₂tart.	20.0
(+) [Cu(*d*-tart)ₙ]²⁻²ⁿ	alan	(−) *d*-alan	3.8
{Cu(Ni)-[*d*-tart]}²⁻²ⁿ	pn	(+) *d*-pn	2–3.4
(+) [Cu(*l*-glutamate)₂]⁻²	alan	(+) *l*-alan	3.3
[Cu₂·(*l*-glutamate)₂·H₂O]	pn	(−) l-pn	4.0

The result supports the view of Bailar and Gott[2] that the structure of a ligand can be ascertained by comparison of

(6) B. Das Sarma and J. C. Bailar, Jr., This Journal, **77**, 5480 (1955).

(7) B. Das Sarma, *ibid.*, **78**, 892 (1956).

the reactions of an optically active complex with ligands of known configuration and those of doubtful configuration. On the other hand, in the communication by Bailar and Gott, the complex $[Co(l\text{-pn})_2CO_3]^+$ containing two molecules of l-propylenediamine was found to coördinate preferentially with the d-forms of tartaric, lactic and α-chloropropionic acid. In the present investigation a copper complex containing d-tartaric acid seems to favor the formation of complexes with d-pn. It may be, however, that the configurations of complexes of different metals with the same optically active ligand may differ, or may form complexes with either configuration.[8] The configuration of the same

(8) F. M. Jaeger and H. B. Blumendal, Z. anorg. allgem. Chem., 175, 161 (1928); J. Lifschitz, Z. physik. Chem., 114, 485 (1925).

compound may vary at different[9] temperature or pH, so it seems necessary to run the same reactions under widely different experimental conditions. The reaction mechanism in these cases, when studied, will probably throw more light on the matter.

(9) Sister Mary Martinette and J. C. Bailar, Jr., THIS JOURNAL, 74, 1054 (1952).

URBANA, ILLINOIS

The Uranyl Cupferrates

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It is shown that the complex formed between uranyl ion and cupferron (ammonium nitrosophenylhydroxylamine) crystallizes in the cubic system with $a_0 = 13.3$ Å. and space group $T^4\text{-}P2_13$. Because of the space group symmetry the UO_2 group is linear and the three cupferron residues must be equivalent. Therefore the compound may be called ammonium uranyl cupferrate, $NH_4[UO_2(C_6H_5N_2O_2)_3]$. The symmetry of the space group also requires that the arrangement of the oxygen atoms with respect to the central uranium atom be a trigonal bipyramid in case the coördination number is five, and either a cube or dodecahedron for coördination number eight. The information presently available cannot distinguish these. The uranyl cupferrate group is sufficiently stable to form compounds also with sodium, potassium, rubidium and cesium in the place of the ammonium ion. On the other hand, the hydrogen compound decomposes slowly on standing. A lithium compound has not been successfully separated. Methods for preparing these compounds are given. The aqueous solubilities appear to be moderately small.

Introduction

Since Baudisch[2] introduced cupferron (ammonium nitrosophenylhydroxylamine), it has been used for a variety of analytical separations. Uranium is an interesting example since in strongly acid solution U(VI) (as UO_2^{++}) does not precipitate but U(IV) does. The fact that uranyl ion does form a complex with cupferron was discovered quite early[3] but went more or less unnoticed until recently when it was found to be the source of minute traces of uranium extracted from an acid solution by an organic solution of cupferron.[4] It is also interesting that, like 8-quinolinol, cupferron provides three groups to the complex although the uranyl ion is divalent.

The direct preparation of this complex was found to be relatively simple and to lead to crystals of the cubic system. In view of the stability of the compound to 200°, which greatly contrasts with other cupferrates, a crystallographic and chemical investigation was undertaken to learn more of its nature. As will be seen, this led to the discovery of a group of compounds which may be called "uranyl cupferrates" somewhat analogous to the uranyl acetates and uranyl nitrates.

Crystallography of Ammonium Uranyl Cupferrate.[5]—By mixing a methanol (or ethanol) solution

(1) The Knolls Atomic Power Laboratory is operated by the General Electric Company for the Atomic Energy Commission. The work reported here was carried out under Contract No. W-31-109 Eng-52.

(2) E. Bamberger and O. Baudisch, Chem. Z., 33, 1298 (1909).

(3) O. Baudisch and R. Furst, Ber., 50, 324 (1917).

(4) (a) N. H. Furman and D. R. Norton, MDDC 1623, April, 1947; (b) N. H. Furman, W. B. Mason and J. S. Poklea, Anal. Chem., 21, 1325 (1949).

(5) The assistance of C. W. Tucker, Jr., and P. Senio, Fuels Research Unit of this Laboratory with this phase of the investigation is gratefully acknowledged.

of uranyl nitrate hexahydrate with a solution of cupferron in 50% aqueous methanol, an orange yellow precipitate is obtained in good yield. The dried crystals occasionally appear as tiny cubes when viewed under the microscope. They are isotropic to polarized light, and have a refractive index of about 1.53. Hull–Debye–Scherrer X-ray diffraction patterns, taken with filtered copper radiation in a 114.59 mm. camera, gave the d-spacings listed in Table I, where they may be compared with those calculated for a cell edge of 13.28 Å. These spacings verify the cubic nature of the unit cell, and since only the 100 reflection was absent the cell is primitive. An experimental specific gravity, determined by flotation to be 2.02, agrees with that calculated for four molecules per cell— 1.98.

Easily prepared (although of poor shape) single crystals were obtained by slow evaporation of a saturated methanol solution. One was mounted in a Weissenberg camera and eventually oriented to rotate about a 100 axis. The zero-level Weissenberg photograph, when indexed, showed systematic absences for $h00$ reflections with h odd. Therefore the crystallographic space group is either T^4-$P2_13$ or O^2-$P4_23$. These space groups may be distinguished by locating the four uranium atoms in the unit cell since these are necessarily at the fourfold positions: $x, x, x;$ $^1/_2 - x, \bar{x}, ^1/_2 + x;$ $\bar{x}, ^1/_2 + x, ^1/_2 - x;$ $^1/_2 + x, ^1/_2 - x, \bar{x}$ for $T^4 - P2_13$ and $^1/_4, ^1/_4, ^1/_4;$ $^1/_4, ^3/_4, ^3/_4;$ $^3/_4, ^3/_4, ^1/_4;$ $^3/_4: ^1/_4, ^3/_4$ for $O^2 - P4_23$. A Patterson $hk0$ projection was calculated using zero-level Weissenberg intensities determined visually with the multiple-film technique. The results are shown in Fig. 1, where the units shown on the contours are arbitrary. The peak at