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[CONTRIBUTION FROM THE DEPARTMENT OF INORGANIC CHEMISTRY, JOHN CURTIN SCHOOL OF MEDICAL RESEARCH, AUSTRALIAN NATIONAL UNIVERSITY]

The Preparation of 1,2-Propylenediaminetetraacetic Acid and its Resolution through the Cobalt(III) Complex

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Racemic propylenediaminetetraacetic acid and the optically active forms have been prepared in good yield by the condensation of the *dl* and active bases with sodium chloroacetate at 20°. The optical isomers gave $[\alpha]_D$ ±47° for the monohydrate. The pure optical forms were also obtained from the Co(III) complex which had been resolved through the active *cis*-dinitrobis-(ethylenediamine)-cobalt(III) salt.

Introduction

The only references in the literature to 1,2-propylenediaminetetraacetic acid, (H_4PDTA), are to patents[2–9] in which the preparation of the acid and some of the esters and sodium salts are quoted in relation to a number of general preparative reactions for aminopolycarboxylic acids and esters. No metal complexes have been isolated.

The preparation of the racemic acid, and its resolution, have been undertaken in order to carry out ligand exchange studies with metal complexes, in which the ligand is labeled by its optical activity, and to investigate the principle of stereospecific limitation in complexes containing a single optically active organic molecule. This work will be described later.

The detailed method of preparation[10] of ethylenediaminetetraacetic acid when applied to H_4-PDTA gave only a viscous sirup which could not be induced to crystallize.[11]

The difficulty of crystallization, and the low yields of aminopolycarboxylic acids after acidification of the reaction mixture, have been ascribed to enhanced solubility due to dissolved inorganic and organic compounds and reaction by-products.[3]

It has been found that *dl*-propylenediamine condenses readily at room temperature with sodium chloroacetate in strongly alkaline solution, but low yields result when the reaction mixture is heated.[11] Slow crystallization of the amino acid ensues on acidification, but ultimately a good yield results. Unlike the racemic compound, the optical forms are quite soluble in water and do not crystallize when the reaction mixture is acidified. Great difficulty was found in separating the active acid from the extraneous sodium salts. After addition of hydrochloric acid to *p*H 3.5, the solution was evaporated to one-third volume and sodium chloride and a sodium salt of the acid precipitated by a large volume of ethanol. The latter salt was dissolved in glacial acetic acid, in which sodium chloride is insoluble and precipitated with benzene. Finally it was converted to the optically active acid itself by the use of the hydrogen form of a strong cation exchange resin. Some retention on the resin lowered the yield.[12] The exchange column was heated to prevent crystallization. Strong cation exchange resins of the sulfonic acid type adsorb Fe^{+3} very strongly, and as supplied usually contain this ion. In order to avoid contamination of the acid, the iron was removed from the column by prolonged washing with hot hydrochloric acid[13] rather than with the more efficient disodium salt of ethylenediaminetetraacetic acid.[14] After passage through the column the active acids crystallized as the monohydrates, ($[\alpha]_D$ ±47°), from a small volume of water.

The specific rotation decreases with increasing deprotonation. The respective values of $[\alpha]_D$ in 0.5% solution in the presence of 1,2,3 and 4 equivalents of potassium hydroxide were ±39, ±37, ±30 and ±22°. The rotation rose to ±42° in the presence of 15 equivalents of alkali.

The infrared spectra of the *dl* and active acids in Nujol show differences in the 1500 to 1800 cm.$^{-1}$ region, the former having bands at 1700 cm.$^{-1}$ (strong) and 1620 cm.$^{-1}$ (weak). The 1700 cm.$^{-1}$ band is due to carboxyl groups. Evidently hydrogen bonding has decreased the frequency as double bond character is lost for the COOH group. The optically active acids (monohydrates) show bands at 1727 cm.$^{-1}$ (strong), 1630 cm.$^{-1}$ (weak) and 1570 cm.$^{-1}$(strong). The carboxyl groups show the normal frequency, revealing less effective hydrogen bonding. The band at 1570 cm.$^{-1}$ can be assigned to OH bending from the water of crystallization. The OH stretching frequency is also shown by a strong 3470 cm.$^{-1}$ band. The

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(1) Rev. Brother F. L. Garvan, F.S.C.H., General Motors-Holden's Ltd. post-graduate research fellow.

(2) U. S. Patent 2,384,816 (1945).

(3) U. S. Patent 2,387,735 (1945).

(4) U. S. Patent 2,407,645 (1946).

(5) U. S. Patent 2,428,353 (1947).

(6) British Patent 601,816 (1948).

(7) British Patent 601,817 (1948).

(8) U. S. Patent 2,461,519 (1949).

(9) British Patent 710,705 (1954).

(10) R. Smith, J. L. Bullock, F. C. Bersworth and A. E. Martell, *J. Org. Chem.*, **14**, 355 (1949).

(11) A. M. Sargeson, private communication.

(12) Rohm and Haas Co., "Amberlite IRC 50," Technical Bulletin, 1954, p. 8.

(13) "Permutit Ion Exchange Resins in the Laboratory," The Permutit Co., Pty Ltd., London, 1955, p. 8.

(14) R. A. Edge, *Chemist Analyst*, **47**, 72 (1958).

differences in hydrogen bonding are possibly due to different crystal lattices in the *dl* and active acids.

The Co(III) complex of the *dl*-acid was best prepared by oxidation of the Co(II) complexes in alkaline solution in the presence of charcoal and hydrogen peroxide in a stream of air. Reduced yields due to decomposition resulted when the method described[15] for the Co(III) complex of ethylenediaminetetraacetic acid was used. Resolution was effected as the salt of the active *cis*-dinitrobis-(ethylenediamine)-cobalt(III) cation. Recovery of the optically active acid was carried out by conversion of the [Co PDTA]$^-$ anion to the [Co $(CN)_6$]$^{3-}$ anion and removal of the latter as the copper(II) salt. Excess copper ion was bound in the anion [Cu PDTA]$^{2-}$. Extraneous cations were exchanged for hydrogen ions with a cation-exchange resin, and the acid H_2[Cu PDTA] isolated by evaporation of the solution. After removal of the copper as the sulfide, the pure acids were crystallized by evaporation and gave $[\alpha]_D$ ±47°.

The resolution of *trans*-1,2-cyclohexanediaminetetraacetic acid through the Co(III) complex will be described in a later paper.

Experimental

All rotations were measured in a 2 dm. polarimeter tube at 20° unless otherwise stated. The melting points recorded are uncorrected.

***dl*-Propylenediaminetetraacetic Acid.**—Monochloroacetic acid (280 g., 3 moles) in water (150 ml.) was cooled to 10° and a cold solution of sodium hydroxide (240 g., 6 moles) in water (500 ml.) added slowly from a dropping funnel with good stirring, so that the temperature did not exceed 20°. *dl*-Propylenediamine (37 g., 0.5 mole) was then added and the mixture allowed to stand for six days at 20°. After filtration, the cooled, well stirred mixture was treated with concentrated sulfuric acid (65 ml.) added dropwise. The sides of the vessel were scratched with a rod and the mixture allowed to crystallize for 16 hr. at 8 to 10°. The fine crystalline powder, sometimes contaminated with sodium sulfate, was washed by stirring with cold water (500 ml.), and after filtration washed with water, ethanol and ether and dried at 100°; yield 100 g. The mother liquor, treated with concentrated hydrochloric acid (30 ml.) and allowed to crystallize overnight in the refrigerator gave a further 30 g. The crude material in water (450 ml.) was treated, with stirring, with solid sodium hydroxide (34.7 g.), and the clear solution of the sodium salt acidified with sulfuric acid (9 *N*, 92 ml.). The acid crystallized slowly on cooling, and after washing with water, aqueous ethanol and acetone, was dried at 100°; m.p. 236°, yield 126 g., 82%.

Anal. Calcd. for $C_{11}H_{18}N_2O_8$: C, 43.13; H, 5.92; N, 9.15. Found: C, 43.16; H, 6.06; N, 9.16.

***l*-Propylenediaminetetraacetic Acid 1-Hydrate.**—The initial part of the procedure was as above. The *l*-propylenediamine, ($[\alpha]_D$ in benzene, −34.1°) was prepared as described previously.[16] The reaction mixture, after 6 days, was brought to *p*H 3.5 by the addition of concentrated hydrochloric acid (160 ml.) and the solution evaporated on the steam-bath in a current of air to a volume of 600 ml. After removal of the solid sodium chloride, the filtrate was poured into vigorously stirred ethanol (2 l.). The gum which deposited initially, crystallized overnight and was filtered off and washed with ethanol (200 ml.), ether (100 ml.) and air-dried. It was suspended in glacial acetic acid (600 ml.) at 40° and shaken to dissolve out the sodium salt of the active acid. The undissolved sodium chloride was removed and washed with a further (30 ml.) portion of glacial acetic acid. The filtrate and washings added to benzene (2 l.) deposited a viscous gum which became crystalline by pouring off the benzene and adding acetone (2 l.). The acetone was poured off, the solid ground up to a fine powder and a fresh portion of acetone (2 l.) added and allowed to stand overnight to dissolve out traces of acetic acid. The solid was filtered off, sucked dry, dissolved in water (1500 ml.) and evaporated to one liter. In this way the last traces of acetone and much of the acetic acid were removed. The pale yellow solution (*p*H 4.6) was passed through the hydrogen form of a strong cation exchange resin of the sulfonic acid type (Zeo Karb 225 or Amberlite IR 120. 1.6 l., bed volume). The resin (Na form) was first washed with hydrochloric acid (3 *N*, 8 l.) at 70° in the column to remove Fe^{+3} ion, at an elution rate of 4 l./hr., and the excess acid then removed with water (6 l.) in 1.5 hr. The solution of the sodium salt of the active propylenediaminetetraacetic acid was followed by cold water at the rate of 50 ml./min. The first 2 liters of effluent were pale yellow and contained traces of acetic acid but only negligible amounts of optically active material. This fraction was rejected. The column was then heated to 70° with heating tapes or infrared lamps and the eluting water was added at 95° at the rate of 80 ml./min. About 15 liters of water were required to remove the acid from the column. This was determined by periodic measurement of the rotation of the effluent. The volume of water was reduced to 900 ml. by evaporation under reduced pressure. The sides of the flask were scratched and the solution was cooled in ice and allowed to crystallize at 8° overnight. The first fraction (70 g.) was washed with ice-water (150 ml.) and then ethanol and acetone and air-dried. The aqueous washings and the filtrate were evaporated to 120 ml. and yielded a further 10 g. of material. A third crop (5 g.) was obtained on evaporation to 20 ml. (total yield 85 g., 52%). Some of the acid appeared to be retained by the resin. All fractions gave $[\alpha]_D$ −47° in 0.5% aqueous solution. The anhydrous acid, ($[\alpha]_D$ −50°), was obtained by heating at 130° for 5 hr. The m.p. (194°) was raised to 198° after recrystallization from water by evaporation to a small volume.

Anal. Calcd. for $C_{11}H_{20}N_2O_9$: C, 40.74; H, 6.22; N, 8.64; H_2O, 5.56. Found: C, 40.94; H, 6.22; N, 8.40; H_2O, 5.53.

***d*-Propylenediaminetetraacetic Acid 1-Hydrate.**—This was prepared in the same way as the *levo*-acid; the *d*-propylenediamine[16] used had $[\alpha]_D$ +33° in benzene. A small amount of inactive material, which separated when the final solution was evaporated to 900 ml. and cooled to room temperature, was removed before cooling in ice overnight. The monohydrate gave $[\alpha]_D$ +47° for a 0.5% aqueous solution, and the anhydrous acid had $[\alpha]_D$ +50°.

Anal. Found: C, 40.56; H, 6.11; N, 8.38; H_2O, 5.57.

***dl*-Potassium (Propylenediaminetetraacetato)-cobaltate-(III) 1-Hydrate.**—*dl*-Propylenediaminetetraacetic acid (31 g.) was dissolved by shaking in water (600 ml.) containing potassium acetate (50 g.) and cobalt(II) acetate 4-hydrate (25 g.) in water (200 ml.) added. After addition of activated charcoal (10 g.) and hydrogen peroxide (30%, 25 ml.) a stream of air was drawn through the mixture for 42 hr. After removal of the charcoal, which was washed with water (250 ml.), the filtrate and washings were evaporated on a steam-bath in a current of air to a volume of 95 ml. The purple crystalline solid that deposited on cooling in the refrigerator was collected and washed with 90% ethanol (300 ml.) and then acetone (yield 31.2 g.). A further 7.3 g. was obtained by the addition of absolute ethanol to the filtrate and aqueous ethanolic washings; total yield 38.5 g., 92%. The substance was recrystallized from water by the addition of ethanol and air-dried.

Anal. Calcd. for $K[Co(C_{11}H_{14}N_2O_8)]\cdot H_2O$: C, 31.58; H, 3.85; N, 6.70. Found: C, 31.45; H, 3.77; N, 6.68.

***dl*-Silver (Propylenediaminetetraacetato)-cobaltate(III) 1-Hydrate.**—Cobalt(II) hydroxide from cobalt(II) sulfate 7-hydrate (5.6 g.) was boiled with the *dl*-acid (6 g.) in water (50 ml.) for a few minutes and then hydrogen peroxide (3%, 20 ml.) added and the heating continued on a steam-bath until all the solid dissolved. Freshly precipitated moist silver oxide (12 g.) was added and the mixture shaken at 60 to 70° for 0.25 hr. After removal of the excess silver oxide, the purple silver salt was made to crystallize by the addition of ten volumes of ethanol and cooling in ice. The deliquescent salt was recrystallized from water by the addition of ethanol.

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[15] F. P. Dwyer, E. C. Gyarfas and D. P. Mellor, *J. Phys. Chem.*, **59**, 296 (1955).

[16] F. P. Dwyer, F. L. Garvan and A. Shulman, THIS JOURNAL, **81**, 290 (1959).

Anal. Calcd. for $Ag[Co(C_{11}H_{14}N_2O_8)]\cdot H_2O$: C, 27.12; H, 3.31; N, 5.76. Found: C, 27.02; H, 3.88; N, 5.99.

***dl*-Barium (Propylenediaminetetraacetato)-cobaltate-(III) 8-Hydrate.**—Barium hydroxide 8-hydrate (94.8 g., 0.3 mole) was stirred into a suspension of the *dl*-acid (61.2 g., 0.2 mole) in water (1 l.) and the mixture then heated until the base had dissolved and a white crystalline material formed. A solution of cobalt(II) sulfate 7-hydrate (56.2 g., 0.2 mole) in water (200 ml.) was added and the whole digested on the steam-bath for 1 hr. The mixture, after cooling to room temperature, was treated with activated charcoal (30 g.) and hydrogen peroxide (30%, 50 ml.) and a vigorous stream of air drawn through for 20 hr. A slight odor of formaldehyde was observed during the oxidation. The mixed barium sulfate–charcoal precipitate was removed and washed with cold water (1 l.). The filtrate and washings were evaporated to 200 ml. on the steam-bath with an air-stream. On cooling to room temperature crystals began to separate slowly. After 3 hr. ethanol (300 ml.) was added over a period of 2 hr. The substance was allowed to crystallize in the refrigerator overnight; yield 82.5 g., 82%.

Anal. Calcd. for $Ba[Co(C_{11}H_{14}N_2O_8)]_2\cdot 8H_2O$: C, 26.32; H, 4.42; N, 5.58. Found: C, 26.29; H, 4.02; N, 5.75.

Resolution of the (Propylenediaminetetraacetato)-cobaltate (III) Anion.—This can be done using either the silver salt or the barium salt, but the latter is the easier to prepare. *d-cis*-Dinitrobis-(ethylenediamine)-cobalt(III) sulfate from the *dextro*-bromide[17] (21.1 g.) and silver sulfate (9.4 g.) in water (800 ml.)[18] at 60° was treated with the barium salt (30.1 g.) in water (200 ml.) and shaken vigorously for ten min. The volume was then reduced to 500 ml. by evaporation on the steam-bath with a stream of air so that the temperature did not exceed 55°. After removal of the barium sulfate–silver bromide precipitate the deep maroon filtrate was further evaporated to 200 ml. The diastereoisomer, [*d*-Co(en)$_2$(NO$_2$) *d*-Co(PDTA)]·2H$_2$O (15 g.) crystallized on standing at 5°, for three hours, and was washed with 70% acetone (60 ml.) and acetone and air-dried. The aqueous acetone washings were added to the filtrate containing the *levo* form. A 0.01% aqueous solution of the diastereoisomer gave $[\alpha]_{5461}$ +700°, and the rotation was unchanged after recrystallization.

Anal. Calcd. for $[Co(C_2H_8N_2)_2(NO_2)_2\text{-}Co(C_{11}H_{14}N_2O_8)]\cdot 2H_2O$: C, 26.97; H, 5.13; N, 16.77. Found: C, 26.80; H, 5.19; N, 16.92.

***d*-Barium and Potassium (Propylenediaminetetraacetato)-cobaltate(III).**—The diastereoisomer (15.6 g.) was ground in a mortar with barium iodide 2-hydrate (15 g.) in water (40 ml.) and the mixture cooled to 4° for 0.75 hr. to allow crystallization of the resolving agent as the iodide.

The latter, after filtration was washed with ice-cold 10% barium iodide (20 ml.). The filtrate and washings at 45° were treated with ethanol (110 ml.) whereupon a purple oil separated that crystallized on scratching the sides of the vessel with a glass rod. After crystallization had proceeded at 20° for 0.75 hr., the solution was heated to 50° and a further 320 ml. of ethanol added slowly over an hour while stirring rapidly. The solution was kept around 45° during this addition of ethanol. The solution was then allowed to crystallize for 3 hr. The granular crystalline material was washed with ethanol and acetone and air-dried; yield 10.7 g. A 0.01% solution gave $[\alpha]_{5461}$ +800° in a one dm. tube. The rotation was unchanged after recrystallization from water by the addition of ethanol. *Anal.* Calcd. for $Ba[Co(C_{11}H_{14}N_2O_8)]_2\cdot 8H_2O$: C, 26.32; H, 4.42; N, 5.58. Found: C, 26.29; H, 4.44; N, 5.49.

The potassium salt cannot be easily freed from potassium iodide when prepared as the barium salt above. It is best made from the barium salt (1.0 g.) by double decomposition with potassium sulfate (0.175 g.) and then precipitated from the concentrated aqueous solution (5 ml.) by the addition of methanol (20 ml.). The very soluble salt had $[\alpha]_{5461}$ +1000° for a 0.01% aqueous solution in a one dm. tube.

Anal. Calcd. for $K[Co(C_{11}H_{14}N_2O_8)]\cdot 3H_2O$: C, 29.07; H, 4.44; N, 6.17. Found: C, 29.5; H, 4.54; N, 6.21.

***l*-Barium and Potassium (Propylenediaminetetraacetato)-cobaltate(III).**—The filtrate and washings from the resolution above, after evaporation to 60 ml. volume, were shaken up with barium iodide 2-hydrate (20 g.) and cooled to 4° for 0.75 hr. The *d*-[Co (en)$_2$(NO$_2$)$_2$]I was removed, washed with cold 10% barium iodide solution (15 ml.), and ethanol (120 ml.) added to the filtrate and washings. The oil that separated became solid on the addition of ethanol (400 ml.). The crude barium salt (17.7 g.) after recrystallization from water (80 ml., 50°) by the addition of ethanol (250 ml.) and allowing to crystallize overnight, gave $[\alpha]_{5461}$ −600°; yield 15 g. It was transformed to the *levo*-diastereoisomer, as above, using proportionate amounts of solvent, Ag_2SO_4 (4.7 g.) and *l*-[Co (en)$_2$ (NO$_2$)$_2$]Br (10.5 g.). The diastereoisomer (13.1 g.), [*l*-Co (en)$_2$ (NO$_2$)$_2$ *l*-Co(PDTA)]·2H$_2$O had $[\alpha]_{5461}$ −700°.

Anal. Found: C, 26.5; H, 5.15; N, 16.82.

The pure diastereoisomer was transformed to the barium salt ($[\alpha]_{5461}$ −800°, yield 9.1 g.) as before.

Anal. Found: C, 26.86; H, 4.37; N, 5.53.

The potassium salt prepared from the barium salt in the usual way gave $[\alpha]_{5461}$ −1000°.

Anal. Found: C, 29.31; H, 4.45; N, 6.17.

Recovery of *d*- and *l*-Propylenediaminetetraacetic Acid from the Active Barium Salts. *d*-Propylenediaminetetraacetic Acid. 1-Hydrate.—The *levo* barium salt (7.33 g.) in water (150 ml.) was treated with potassium sulfate (1.27 g.) and the barium sulfate precipitate removed after digestion on the steam-bath. Potassium cyanide (7.0 g.) was added to the cooled filtrate and the mixture gently boiled for five minutes, during which time the color changed to pale yellow. Complete oxidation of any Co(II)-cyano complex to Co(III) was effected by cooling to 65° and adding hydrogen peroxide (3%, 5 ml.). Glacial acetic acid (5 ml.) was added, the hydrogen cyanide boiled off in the hood and the volume reduced to 100 ml. Cooper(II) acetate 1-hydrate (9.0 g.) in water (200 ml.) was added at 65° whereupon the insoluble pale green copper(II) hexacyanocobaltate(III) precipitated. After cooling in ice and centrifuging off the precipitate, the deep blue centrifugate and water washings (100 ml.) of the copper(II) complex were evaporated to 200 ml. and shaken with two separate amounts (100 ml.) of the hydrogen form of the cation-exchange resin Zeo Karb 225 (20 NC). This resin was used as it has a smaller tendency to adsorb amino acids than the normal Zeo Karb 225. The hot water washings (400 ml.) of the resin and the exchanged solution were evaporated to a small volume and the crystallization of the acid $H_2[Cu(C_{11}H_{14}N_2O_8)]$ completed by the addition of ethanol (60 ml.). The copper complex (3.6 g.) was decomposed by the passage of hydrogen sulfide in hot aqueous solution in the usual way. The filtrate, after removal of the copper(II) sulfide, was concentrated to 10 ml. and allowed to crystallize at 4° overnight. The white crystals were washed with ice-water (10 ml.), ethanol (30 ml.) and acetone (20 ml.) and air-dried; yield 1.9 g. A second fraction (0.7 g.) was obtained by concentration of the filtrate and aqueous washings to 5 ml. and adding absolute ethanol (5 ml.). After recrystallization from water by evaporation to 10 ml. the substance gave $[\alpha]_D$ +47°, for a 0.5% aqueous solution.

Anal. Calcd. for $C_{11}H_{20}N_2O_9$: C, 40.74; H, 6.22; N, 8.64. Found: C, 40.76; H, 6.16; N, 8.58.

***l*-Propylenediaminetetraacetic Acid 1-Hydrate.**—The optically pure *levo* isomer (3.0 g.) was isolated in the same manner from the *d*-barium salt of the cobalt(III) complex (7.33 g.). A 0.5% aqueous solution gave $[\alpha]_D$ +47°.

Anal. Found: C, 40.58; H, 6.21; N, 8.44.

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[17] F. P. Dwyer and F. L. Garvan, "Inorganic Syntheses," Vol. VI, E. G. Rochow (Ed.), in publication.

[18] The large volume of water is necessary to ensure that the Ag_2SO_4 is completely dissolved in order to obtain a pure diastereoisomer.