One hundred grams of Erdmann's salt in 2,000 ml. of water was converted to the acid, and to this solution there was added a solution of 26.6 g. of carbonatopentamminecobalt(III) nitrate,[2] always keeping the acid in excess. Effervescence was observed almost immediately as the carbonate group of the cation was replaced, and an orange, crystalline precipitate of aquopentamminecobalt(III) tris-(tetranitrodiammine)-cobaltate(III) separated quickly in almost quantitative yield.

Anal. Calcd. for $[Co(H_2O)(NH_3)_5][Co(NO_2)_4(NH_3)_2]_3$: Co, 23.74; N, 32.44. Found: Co, 23.74; N, 32.37.

The solubility was 0.12 g. per 100 g. water at 20°. The derivatives of the other complex acids with the aquopentammine cation were obtained by the same method.

Aquopentamminecobalt(III) trioxalatocobaltate(III), small, dark green crystals, insoluble in water.

Anal. Calcd. for $[Co(H_2O)(NH_3)_5][Co(C_2O_4)_3]$: Co, 24.27; N, 14.43. Found: Co, 24.22; N, 14.33.

Aquopentamminecobalt(III) trioxalatochromate(III), fine brown needles, insoluble in water.

Anal. Calcd. for $[Co(H_2O)(NH_3)_5][Cr(C_2O_4)_3]$: Co, 12.32; Cr, 10.87; N, 14.65. Found: Co, 12.30; Cr, 10.88; N, 14.62.

Aquopentamminecobalt(III) tris-(tetrathiocyanatodiamminechromate)(III), fine red crystals; solubility 0.039 g. in 100 ml. water at 20°. *Anal.* Calcd. for $[Co(H_2O)(NH_3)_5][Cr(SCN)_4(NH_3)_2]_3$: Co, 5.27; Cr, 13.96; N, 28.84. Found: Co, 5.23; Cr, 13.87; N, 28.74.

Cobalt was determined as sulfate in the first two compounds, electrolytically in the others. Chromium was oxidized to the dichromate ion, and determined volumetrically, and nitrogen was determined by the semi-micro Kjeldahl method.

Aquopentamminecobalt(III) trioxalatocobaltate(III) was reported by Sörensen,[3] and the aquopentamminecobalt(III) derivative of Reinecke's salt was used by Brönsted[4] in studies on the solubilities of strong electrolytes.

The Green Carbonatocobalt(III) Anion.—The intensely green solution resulting from the Field–Durant reaction[5] (oxidation of a cobalt(II) salt in the presence of an excess of an alkali bicarbonate) has been the subject of numerous investigations resulting in differing opinions about the composition and structure of the complex. An excellent account of earlier work has been given by Duval.[6] The complex has been used recently in a volumetric method for the determination of cobalt.[7] As stated above, the free acid cannot be obtained by the ion-exchange method.

We have found that the green anion may be prepared readily from a cobalt(III) compound, and it has been converted to a stable derivative with the hexamminecobalt(III) cation,[6] according to the following procedure: a solution containing 2.2 g. of carbonatotetramminecobalt(III) sulfate dissolved in 90 ml. of water at 60° was added to a hot (90°) solution containing 28 g. of potassium bicarbonate and 1.5 g. of potassium persulfate in 80 ml. of water. The mixture was heated on the steam-bath until the red color changed to dark green (about 25 min.), to which was then added 4 g. of hexamminecobalt(III) nitrate dissolved in 100 ml. of water. One-half of the resulting solution was added gradually to another solution of hexamminecobalt(III) nitrate containing 2 g. of the complex in 50 ml. of water, which had been heated just to the boiling point on the hot-plate. The addition was made at such a rate as to maintain the temperature as close to the boiling point as possible without allowing intervals of boiling.

A finely crystalline, grayish-green precipitate of hexamminecobalt(III) tricarbonatocobaltate(III) separated during the process, which was filtered on a sintered glass filter (contact with filter paper caused partial reduction), washed with cold water, and air-dried. The second half of the solution was treated in the same manner. The total yield was 70%. After thorough drying in a dust-free atmosphere, there has been no evidence of decomposition after six months.

Anal. Calcd. for $[Co(NH_3)_6][Co(CO_3)_3]$: Co, 29.46; N, 21.01. Found: Co, 29.44; N, 21.02.

The solubility was 0.038 g. per 100 g. of water at 20°.

Acknowledgment.—We are indebted to Mr. Inman H. Moon, of this Laboratory, for his work on the Field–Durant reaction.

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[2] Arthur B. Lamb and Karol J. Mysels, *ibid.*, **67**, 468 (1945).

[3] S. P. L. Sörensen, Diss. 87, Copenhagen, 1899.

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[5] F. Field, *Quart. J. Chem. Soc.*, **14**, 51 (1862); R. G. Durant, *ibid.*, **87**, 1782 (1905).

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[7] H. A. Laitinen and L. W. Burdett, *Anal. Chem.*, **23**, 1268 (1951).

PHILADELPHIA, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF ILLINOIS INSTITUTE OF TECHNOLOGY]

The Dissociation Constants of Acids in Salt Solutions. V. Monohydroxycyclohexanecarboxylic Acids

BY MARTIN KILPATRICK AND JEROME G. MORSE[1]

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The *cis*- and *trans*-hydroxy-substituted cyclohexanecarboxylic acids have been synthesized and their dissociation constants measured. An attempt has been made to correlate the structures of these acids with their dissociation constants. The calculated values of the relative acid strengths using electrostatic theory are in poor agreement with the observed values.

The purpose of this work was to study the dissociation constants of the monohydroxycyclohexanecarboxylic acids and if possible to relate the structure to the relative acid strengths in the solvents water, methyl and ethyl alcohol, and ethylene glycol.

The experimental method was the same as given in papers I[2] and II.[3] In all cases the reference acid was cyclohexanecarboxylic acid and the equilibrium measured was

$$A_x + B_0 \rightleftarrows A_0 + B_x \qquad (1)$$

where A_x is the hydroxy substituted acid and B_x the conjugate base. The equilibrium constant of the reaction is the ratio of the dissociation constant of the substituted acid to the parent acid.

A limiting factor in the present investigation which precluded a more extensive comparison with aromatic systems previously examined was the inherent difficulty encountered in the synthesis of these stereoisomeric acids. The hydroxy-substi-

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[1] This paper was abstracted from the dissertation presented by Jerome Gilbert Morse to the Graduate School of Illinois Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1952.

[2] M. Kilpatrick, THIS JOURNAL, **75**, 584 (1953).

[3] M. Kilpatrick and R. D. Eanes, *ibid.*, **75**, 586 (1953).

tuted cyclohexanecarboxylic acids were selected as the starting point, as they offered the possibility of separation and proof of structure by chemical methods, and they also appeared to be convenient starting materials for synthesis of other substituted cyclohexanecarboxylic acids.

Preparation of the Compounds

A. *cis*- **and** *trans*-**2-Hydroxycyclohexanecarboxylic Acids.**—Although the higher melting isomer of 2-hydroxycyclohexanecarboxylic acid was synthesized in 1894,[4,5] the lower melting form remained unknown until 1929, at which time Balaš and Šrol[6] isolated two geometric isomers from the reduction of salicylic acid. The configurations of the two isomers resulting from the reduction of 2-carbethoxycyclohexanone over platinum were established by Pascual and co-workers.[7] By using the von Auwers and Skita rule and a comparison of the relative viscosities of the ethyl esters of the two isomers, they showed that the higher melting isomer has the *trans* configuration and the lower the *cis*.

In this work, methyl salicylate was reduced as described by Connor and Adkins,[8] and the isomeric acids were isolated as described by Pascual and co-workers.[7]

Methyl Hexahydrosalicylate.—Methyl salicylate was prepared for hydrogenation by refluxing 150 g. of the compound over Raney nickel (10 g.) for two hours, followed by a fractional distillation of the ester under reduced pressure. The material boiling at 62° at 1 mm. of mercury was collected and stored in a Pyrex glass-stoppered bottle.

The pretreated ester (29.5 g., 0.194 mole) was diluted with 25 ml. of absolute ethanol and hydrogenated in a glass-lined high pressure apparatus containing W-6 Raney nickel (4 g.).[9] With an initial pressure of 170 atmospheres of hydrogen, the calculated amount of hydrogen was absorbed in two hours, at 200°. The catalyst was removed by filtration and washed with 10 to 15 ml. of ethanol. The combined washings and filtrate were concentrated on a steam-bath and the remaining solution was fractionated under reduced pressure. The material boiling at 109–110° at a pressure of 10 mm. was collected (27 g., 88% of calculated yield). The reported boiling point of methyl hexahydrosalicylate is 117–118° at 17 mm.[8]

Hydrolysis of Methyl Hexahydrosalicylate.—The reduced ester was transferred to a 500-ml. flask fitted with a Hershberg stirrer, and 200 ml. of a 25% aqueous sodium hydroxide solution was added. The system was stirred while it was heated to boiling and the heat was removed when the mixture became homogeneous. Stirring was continued for one hour. On cooling, a massive white precipitate formed, corresponding to that described by Pascual as the sodium salt of the *cis*-acid.

cis-**2-Hydroxycyclohexanecarboxylic Acid.**—The solid was filtered with suction, washed with 40 ml. of 95% ethanol and transferred to a flask immersed in an ice-bath. The salt was decomposed with 20% aqueous hydrochloric acid, which was added slowly to the vigorously stirred solution until it was acidic to litmus. The solution was then saturated with ammonium sulfate and extracted with ether for 24 hours in a continuous extractor. The ether extract was dried for one hour over anhydrous magnesium sulfate, the salt removed by filtration and the ether evaporated on a steam-bath. The final traces of the solvent were removed in a vacuum desiccator, and a solid (5.3 g., m.p. 77°) remained. Two recrystallizations of this solid from ethyl acetate raised its melting point to 80.0°, which is the value reported for the *cis*-acid.[7] The calculated equivalent weight was 144.2 and that observed was 144.6.

trans-**2-Hydroxycyclohexanecarboxylic Acid.**—The combined filtrate and washings of the sodium salt of the *cis* isomer were heated under reflux for 40 hours with 200 ml. of a 7.5 *N* aqueous potassium hydroxide solution. The solution, cooled in an ice-bath, was slowly neutralized with concentrated hydrochloric acid until it was acidic to congo red. After saturating the solution with ammonium sulfate, it was extracted continuously with ether, and was treated as described above. A yellow oil (18 g.), which crystallized overnight, remained after the evaporation of the dried ether extract. Two recrystallizations of this solid from ethyl acetate raised its melting point from 95–106° to 110.5–111.0°, which is the reported melting point of the *trans* isomer. The equivalent weight was calculated as 144.2 and found to be 144.1.

B. *cis*- **and** *trans*-**3-Hydroxycyclohexanecarboxylic Acids.**—The earlier workers[10,11] found that the sodium reduction in ethyl alcohol of *m*-hydroxybenzoic acid produced two isomers which were separated, in small yields, by recrystallization. It was later shown by Boorman and Linstead[12] that only the *cis* modification can form a lactone, thus affording a convenient means of separation of the two isomers.

The method of synthesis employed in this study involved the high pressure hydrogenation of methyl *m*-hydroxybenzoate, followed by hydrolysis of the ester and isolation of the mixture of isomeric acids. The mixture was then treated according to the procedure of Boorman and Linstead in order to separate the isomers.

Methyl *m*-**Hydroxybenzoate.**—One-half mole (69.1 g., m.p. 199–200°) of *m*-hydroxybenzoic acid (Eastman Kodak Co.) was added to a 500-ml. flask containing 1.5 moles of anhydrous methanol, 150 ml. of ethylene chloride and 8 ml. of concentrated sulfuric acid, and was heated under reflux for 22 hours. The brown mixture was cooled to room temperature and then successively washed with 200 ml. of water, 250 ml. of a saturated sodium carbonate solution and finally with 300 ml. of water. The now milky ethylene chloride solution was dried over anhydrous magnesium sulfate and filtered. A large portion of the solvent was removed by evaporation on a steam-bath, but the final traces were removed in a vacuum desiccator. The solid product weighed 75 g. (98% of the theoretical yield) and melted between 59–62°. After the product was recrystallized from benzene, its melting point was raised to 68°. The literature value is 70°.

Methyl 3-Hydroxycyclohexanecarboxylate.—The ester (51 g., 0.33 mole) was added to the liner of the hydrogenation bomb with 25 ml. of dry ethanol and 3 to 5 g. of W-6 Raney nickel, and reduced at an initial pressure of hydrogen of 170 atmospheres. The temperature of the reaction was 160–200° and the calculated amount of hydrogen was absorbed in two hours.

After the mixture was filtered to remove the catalyst, the solvent was evaporated on a steam-bath and the product was distilled under reduced pressure. The material distilling between 143–146° at 23 mm. was collected (35 g., 69% of the calculated yield).

Hydrolysis of Methyl 3-Hydroxycyclohexanecarboxylate.—The resulting ester (35 g.) was refluxed on a steam-bath with 18 g. of potassium hydroxide in 75 ml. of methanol for 1.8 hours. After cooling the solution to room temperature, it was diluted with 25 ml. of water, chilled in an ice-bath, acidified with concentrated hydrochloric acid and steam distilled until approximately 250 ml. of distillate was collected. This precautionary measure was undertaken to remove any cyclohexanecarboxylic acid formed through the hydrogenolysis of the hydroxyl group during the reduction.

The residue of the steam distillation was saturated with ammonium sulfate and continuously extracted with ether for 24 hours. After treating the ether extract as described previously, the evaporation of the solvent and drying the residue in a vacuum desiccator overnight resulted in 31 g. of a white solid, melting at 70–94°.

Separation of the Isomers.—A portion of this solid (19 g.) was distilled through a short path still and two fractions were collected. The first (4.8 g.) distilled between 100–105° at 10 mm. and was a water-white oil that solidified completely (m.p. 70°). The second fraction, 1.8 g. of a slowly crystallizing viscous yellow oil, was collected between 135–150° at 10 mm. The tarry residue weighed 3.7 g.

trans-**3-Hydroxycyclohexanecarboxylic Acid.**—The second fraction of the distillation (m.p. 102–110°) was very soluble in water but insoluble in benzene and hexane. After recrystallization from ethyl acetate, this solid melted at 119–120°, and two further recrystallizations from the same solvent raised the melting point to 120.0°, the reported

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(5) A. Einhorn and J. Meyerberg, *ibid.*, **27**, 2472 (1894).

(6) F. Balaš and L. Šrol, *Coll. trav. chim. Czech.*, **1**, 658 (1929).

(7) J. Pascual, J. Sistare and A. Regas, *J. Chem. Soc.*, 1943 (1949).

(8) R. Connor and H. Adkins, This Journal, **54**, 4678 (1932).

(9) H. Adkins and H. R. Billica, *ibid.*, **70**, 695 (1948).

(10) A. Einhorn, *Ann.*, **291**, 301 (1896).

(11) W. H. Perkin and G. Tattersall, *J. Chem. Soc.*, **91**, 486 (1907).

(12) E. J. Boorman and R. P. Linstead, *ibid.*, 258 (1935).

value for the *trans* isomer.[11] Titration of a weighed sample of this solid with carefully standardized aqueous sodium hydroxide solution showed its equivalent weight to be 144.1 (calculated weight 144.2).

Lactone of 3-Hydroxycyclohexanecarboxylic Acid.—The first fraction of the distillation was soluble in benzene and hexane, but insoluble in water. Recrystallization of this solid from hexane raised its melting point to 119–120°, which is the reported value for this lactone.[12] Titration of a weighed sample of this sample in water at 5°, with standardized aqueous sodium hydroxide solution, indicated the absence of acidity. A mixture of the recrystallized solids from the first and second fractions of the distillation melted between 84–104°.

***cis*-3-Hydroxycyclohexanecarboxylic Acid.**—Solution was effected slowly with the generation of heat, when 3 g. of the lactone was mixed with 20 ml. of a 10% aqueous solution of potassium hydroxide. After one hour the clear solution was chilled in an ice-bath, acidified with concentrated hydrochloric acid, saturated with ammonium sulfate and extracted with ether. Evaporation of the dried ether extract yielded 2.5 g. of a white solid (m.p. 118–125°). Two recrystallizations from ethyl acetate raised the melting point to 131.5–132.0°, the reported value for the *cis*-acid. Its equivalent weight was calculated as 144.2 and found to be 143.9.

C. *cis*- and *trans*-4-Hydroxycyclohexanecarboxylic Acids.—Balaš and Šrol[6] reduced *p*-hydroxybenzoic acid over platinum oxide in ethyl alcohol and isolated two substances in addition to the hydrogenolysis product. The two acidic substances (m.p. 152° and 120°) were considered to be the *cis* and *trans* isomers, respectively, of 4-hydroxycyclohexanecarboxylic acid. Recently[13] it has been shown that the lower melting modification is actually a mixture of isomers. This observation results from the study by Hardegger, Plattner and Blank[14] which maintains that the *cis* isomeride will lactonize in the presence of acetic anhydride. Campbell and Hunt[13] treated the lower melting modification with acetic anhydride and, after distillation of the mixture, isolated two products, the lactone of the 4-hydroxy acid and an acetoxy acid. Hydrolysis of the lactone yielded the *cis* isomer, and hydrolysis of the acetylated derivative gave a new compound (m.p. 148°) which was considered to be the *trans* isomer.

Preparation of the Isomeric Mixture.—The reduction of ethyl *p*-hydroxybenzoate (232 g.) was performed, as previously described,[8] in the presence of W-6 Raney nickel. The calculated amount of hydrogen was absorbed in 1.5 hours at a temperature of 150–170°. The product was distilled and the material which boiled between 118–126° at 3 mm. was collected ($n^{23}D$ 1.4556, 229 g., 93%). The ester was saponified as described previously and the resulting mixture was acidified and steam distilled to remove any cyclohexanecarboxylic acid formed during the reduction. To mitigate the obnoxious odor of the latter, due to its presence in this impure state, the steam distillate was collected in dilute ammonia. The mixture remaining in the boiler was evaporated to dryness, or near dryness, on a steam-bath and the solid residue was dried further by azeotropic distillation of the water with benzene, conveniently performed with a Dean–Stark separator. A white crystalline solid was obtained subsequent to the removal of benzene. Analysis of the solid for acidity indicated the presence of 51.2% of the hydroxycyclohexanecarboxylic acids. From a 10-g. portion of this mixture, 5.2 g. of a solid was readily extracted by means of acetone (m.p. 116–117°). The equivalent weight calculated for $C_7H_{12}O_8$ was 144.1 and found for the extract was 146.7. The extraction was apparently complete.

***cis*-4-Hydroxycyclohexanecarboxylic Acid.**—The crude mixture of isomeric acids (14.4 g.) was heated under reflux with acetic anhydride (110 ml.). The excess acetic anhydride and acetic acid were removed *in vacuo* and the product was distilled through a short path still at 3 mm. and a bath temperature of 230–250°. The temperature of the vapor was not determined since it was expedient to heat the side arm of the flask to maintain the distillate in the liquid phase. The first portion collected (5.8 g.) solidified in the receiver, while the latter portion (6.9 g.) solidified much more slowly.

From the first fraction, the lactone was isolated by recrystallization from a mixture of hexane and benzene. It was identified by its melting point, 126° (lit. 128°), solubility (soluble in alcohol, benzene and hexane, but difficultly soluble in water), saponification equivalent weight (calculated for $C_7H_{10}O_2$, 126.6; found, 130.6), and conversion by hydrolysis with cold 10% aqueous potassium hydroxide to the *cis*-acid, m.p. 152.5°. The equivalent weight calculated for the *cis*-acid was 144.2 and that found was 144.6.

***trans*-4-Hydroxycyclohexanecarboxylic Acid.**—From the second fraction of the distillation, a further quantity (1.4 g.) of the lactone was isolated by fractional crystallization with a mixture of benzene and hexane. In addition, an acidic compound (4.1 g., m.p. 135–137°) was isolated. The compound (1 g.) was saponified with 20 ml. of 20% aqueous potassium hydroxide solution at room temperature. The solution was chilled, acidified with concentrated hydrochloric acid and extracted continuously with ether. From the extract, an acid was isolated (0.8 g., m.p. 139–146°). Recrystallization of this acid from ethyl acetate raised its melting point to 148.0°. This acid is *trans*-4-hydroxycyclohexanecarboxylic acid (m.p. 148°, equivalent weight calculated, 144.1; found, 144.2). A mixture of the *cis* (m.p. 152°) and the *trans* isomeric acids melted at 116–126°, identifying the product isolated with the lactone in the second fraction of the distillation as the *trans*-4-acetoxycyclohexanecarboxylic acid (m.p. 139°). Calcd. for $C_9H_{14}O_4$: C, 58.06; N, 7.53; equiv. wt., 186.2. Found: C, 58.50; N, 7.73; equiv. wt., 184.0.

Purity of the Acids.—The above acids were finally dried in an Abderhalden drier over phosphorus pentoxide and stored in desiccators over calcium sulfate. Their purity was determined by titration with carefully standardized carbonate-free sodium hydroxide solution.

TABLE I

PURITY OF THE CYCLOHEXANOIC ACIDS

Acid	Melting point, °C. Obsd.	Lit.	Ref.	Titration, %
(Benzoic)[a]	122.0	121.7	15	99.9
Cyclohexanecarboxylic[b]	31.1	29–31	16	99.9
cis 2-OH	80.0	80	7	100.2
trans 2-OH	110.5–111.0	111	7	99.9
cis 3-OH	131.5–132.0	132.0	11	99.8
trans 3-OH	120.0	120	11	99.6
cis 4-OH	152.5	152	17	100.1
trans 4-OH	148.0	148–149	13	100.0

[a] Kahlbaum. [b] Eastman Kodak Company, redistilled at reduced pressure.

The solvents were purified by the methods used by Elliott and Kilpatrick[18] and the water content of the alcohols determined by use of the Karl Fischer reagent. Solutions were made up and stored in a dry-box so that the water content was usually below 0.03% by weight.

The effect of ionic strength on the ratio of the dissociation constants ($K_{A_xB_0}$) was again studied and the data for aqueous solution are given in Table II.

TABLE II

RELATIVE ACID STRENGTH AND DISSOCIATION CONSTANTS OF *cis*-2-HYDROXYCYCLOHEXANECARBOXYLIC ACID IN WATER

μ[a]	$K_{A_xB_0}$	$K_c \times 10^5$	K_c/K_a
0.108	1.27	2.51	1.57
.206	1.27	2.76	1.72
.304	1.27	2.89	1.81
.402	1.25	2.90	1.81
.500	1.25	2.94	1.84

[a] Mainly NaCl.

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[13] N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1379 (1950).

[14] E. Hardegger, P. A. Plattner and F. Blank, *Helv. Chim. Acta*, **27**, 793 (1944).

[15] J. F. J. Dippy and F. R. Williams, *J. Chem. Soc.*, 1888 (1934).

[16] J. S. Lumsden, *ibid.*, **87**, 90 (1905).

[17] L. Owen and P. Robins, *ibid.*, 326 (1949).

[18] J. H. Elliott and M. Kilpatrick, *J. Phys. Chem.*, **45**, 454, 466, 472 (1941).

The ratio of the activity coefficients is essentially constant up to 0.5 molar and experiments in the alcoholic solvents with lithium chloride also show that the ratio of the dissociation constants at 25° is independent of the lithium chloride concentration. This justifies the assumption that the value found is also the ratio of the thermodynamic dissociation constants.

Table III gives the relative acid strengths and dissociation constants in water.

TABLE III

RELATIVE ACID STRENGTHS AND DISSOCIATION CONSTANTS IN WATER AT 25°

Acid	$K_{A_xB_0}{}^a$	$K_c \times 10^{5a}$	$K_a \times 10^5$
HCy	1.00	1.96[b]	1.25
HB	5.05	10.1[b]	6.32[c]
cis 2-OH	1.28	2.51	1.60
trans 2-OH	1.66	3.25	2.08
cis 3-OH	2.00	3.92	2.50
trans 3-OH	1.22	2.39	1.53
cis 4-OH	1.17	2.29	1.46
trans 4-OH	1.68	3.29	2.10

[a] Total ionic strength is 0.10 M, mainly NaCl. [b] Measured against HCl at 0.10 M, mainly NaCl. [c] F. G. Brockman and M. Kilpatrick.[19]

Tables IV, V and VI summarize the results in the solvents ethylene glycol, methyl and ethyl alcohol.

TABLE IV

RELATIVE ACID STRENGTHS AND DISSOCIATION CONSTANTS IN ETHYLENE GLYCOL AT 25°

Acid	$K_{A_xB_0}{}^a$	$K_c \times 10^{9a}$
HCy	1.00	9.50[b]
HB	4.69	44.6[b]
cis 2-OH	3.22	30.6
trans 2-OH	2.21	21.0
cis 3-OH	1.92	18.2
trans 3-OH	0.952	9.06
cis 4-OH	0.908	8.62
trans 4-OH	1.56	14.8

[a] Total ionic strength is 0.10 M, mainly LiCl. [b] Measured against HCl at 0.10 M, mainly LiCl.

TABLE V

RELATIVE ACID STRENGTHS AND DISSOCIATION CONSTANTS IN METHANOL AT 25°

Acid	$K_{A_xB_0}{}^a$	$K_c \times 10^{10a}$	$K_a \times 10^{10}$
HCy	1.00	8.32[b]	0.923
HB	4.55	37.8[b]	4.20
cis 2-OH	4.80	39.9	4.42
trans 2-OH	2.52	21.0	2.33
cis 3-OH	1.84	15.3	1.70
trans 3-OH	0.885	7.36	0.817
cis 4-OH	0.825	6.87	0.761
trans 4-OH	1.63	13.5	1.50

[a] Total ionic strength is 0.10 M, mainly LiCl. [b] Measured against HCl at 0.10 M, mainly LiCl.

TABLE VI

RELATIVE ACID STRENGTHS AND DISSOCIATION CONSTANTS IN ETHANOL AT 25°

Acid	$K_{A_xB_0}{}^a$	$K_c \times 10^{10a}$	$K_a \times 10^{11}$
HCy	1.00	7.61[b]	1.70
HB	5.12	39.0[b]	8.69
cis 2-OH	10.0	76.2	17.0
trans 2-OH	4.58	34.9	7.79
cis 3-OH	1.82	13.9	3.09
trans 3-OH	0.917	6.97	1.56
cis 4-OH	0.869	6.61	1.48
trans 4-OH	1.44	11.0	2.45

[a] Total ionic strength is 0.10 M, mainly LiCl. [b] Measured against HCl at 0.10 M, mainly LiCl.

It is to be noted that all of the substituted acids are stronger than the parent acid in water and according to the observations of Wooten and Hammett[20] this should mean an increase in relative strength on decreasing the dielectric constant of the solvent. Figure 1 shows that this is not the case as both increases and decreases in $K_{A_xB_0}$ with decreasing dielectric constant are observed.

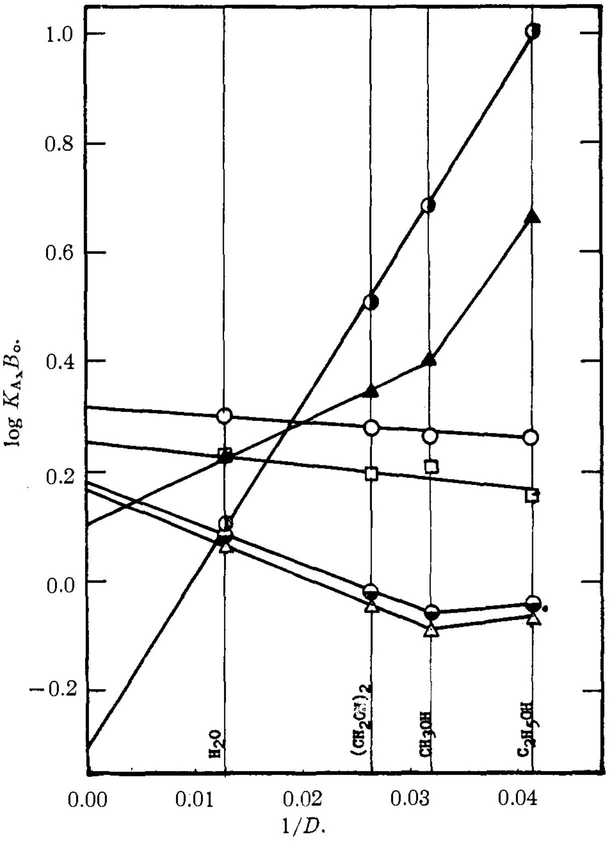

Fig. 1.—Effect of substituents upon the acid strength of cyclohexanecarboxylic acid: ◑, *cis*-2-OH; ▲, *trans*-2-OH; ○, *cis*-3-OH; ⊖, *trans*-3-OH; △, *cis*-4-OH; □, *trans*-4-OH.

D. Structural Considerations Based on the Dissociation of These Acids.—The dissociation constant of an acid has been shown to be dependent upon the structure of the molecule and will be a function of molecular resonance effects when present, the orientation and spatial interaction of dipolar groups, and the distance of the dipolar center from the ionizable proton. The acids under consideration in this investigation are non-resonating and, therefore, this specific effect will be excluded from the discussion. Before entering into a treatment of the theoretical interpretation of

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(19) F. G. Brockman and M. Kilpatrick, THIS JOURNAL, **56**, 1483 (1934).

(20) L. A. Wooten and L. P. Hammett, *ibid.*, **57**, 2289 (1935).

structure, the chemical methods used to differentiate the isomers from one another will be reviewed.

Chemical evidence has been used to identify and label the 1,3- and 1,4-hydroxy-substituted cyclohexanecarboxylic acids, in that there is only one isomer in each of the aforementioned pair that is able, under suitable conditions, to undergo a self-condensation to form a lactone. This indicates that the ease of formation of a new cycle without undue strain is determinative, and these molecules were called the *cis* isomers. Those unable to form the lactone were called *trans* isomers. As the properties of lactones are so widely different from those of carboxylic acids, a separation of the two was easily accomplished.

The problem is more difficult for the 1,2-isomeric pair, and was resolved by an observation of the difference in solubilities of the sodium salts of these acids.[7] It also appears that upon vigorous treatment with strong caustic, the *cis*-1,2-isomer is converted to the *trans*-1,2- which will be shown in the following discussion to possess the more stable configuration.

To facilitate the correlation of the structure of these stereoisomeric acids with their observed dissociation constants, an acceptable model will have to be constructed. Recent investigations have simplified this problem considerably.

It has been shown by spectroscopic, X-ray diffraction[21] and more recent thermochemical studies[22] that substantially all of the cyclohexane molecule at room temperatures exists as the more symmetrical chair or staggered configuration, although the existence of a small percentage of the less symmetric boat form is not excluded. This has been described by Pitzer[23] as follows: "If the staggered position is the potential minimum for the rotation about single bonds, then the chair form would be expected to have a lower energy since it maintains the staggered position throughout, while the boat form twists two carbon-to-carbon bonds into an opposed configuration." The order of magnitude of the energy difference between the two forms has been shown to be 5.6 kcal. per mole.[22]

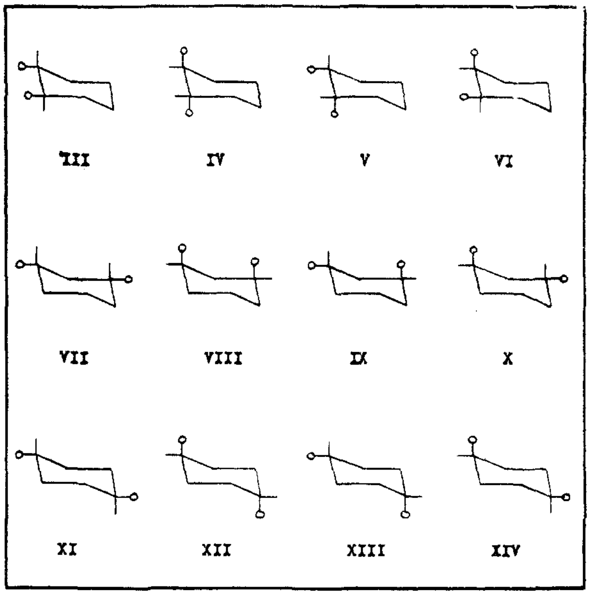

Fig. 2.—Total number of configurations in 1,2-, 1,3- and 1,4-disubstituted cyclohexanes: di-equatorial, III, VII and XI; di-polar, IV, VIII and XII; equatorial–polar, V, VI, IX, X, XIII and XIV.

Further examination of the geometry of the cyclohexane molecule has shown that six carbon-to-hydrogen bonds extend outwards from or form a belt around the ring, while the remaining six extend either above or below the ring. Those bonds projecting outwards or into the equator of the molecule have been labeled "equatorial" and those projecting up and down are called "polar."[22] In the chair form, three polar bonds are above and three are below the equator of the molecule.

In view of these considerations, the simplification of the selection of a reasonable model may now be understood. A disubstituted cyclohexane, or a molecule in which the substituents are bonded to different ring carbon atoms, may be limited to three possible configurations, *i.e.*, e–e, e–p, or p–p, where e–e refers to di-equatorial substitution, and e–p, equatorial–polar substitution, etc. In keeping with the conventional stereochemical concepts of *cis–trans* isomerism, an examination of the number of forms allowable for each, using the new terminology, is now in order and is shown in Fig. 2 and explained in Table VII.

The isomers of optical activity are not included in this discussion on the basis of the assumption, that there would be no difference between the dissociation constants of the (*d*) and (*l*) forms.

Table VII indicates that *cis*-1,2, *trans*-1,3 and *cis*-1,4 may be assigned a single configuration, namely, e–p, whereas two possibilities remain for *trans*-1,2, *cis*-1,3 and *trans*-1,4. The results of an investigation of the differences in energy between the latter three pairs, when both substituents are methyl groups, are reported in Table VIII.

TABLE VII

CONFIGURATIONS ALLOWABLE FOR EACH ISOMER

Acid	Configuration	Number
cis-1,2	Equatorial–polar (e–p)	V
	Equatorial–polar (e–p)	VI
trans-1,2	Di-equatorial (e–e)	III
	Di-polar (p–p)	IV
cis-1,3	Di-equatorial (e–e)	VII
	Di-polar (p–p)	VIII
trans-1,3	Equatorial-polar (e–p)	IX
	Equatorial-polar (e–p)	X
cis-1,4	Equatorial-polar (e–p)	XIII
	Equatorial-polar (e–p)	XIV
trans-1,4	Di-equatorial (e–e)	XI
	Di-polar (p–p)	XII

TABLE VIII

ENERGY DIFFERENCES IN DIMETHYLCYCLOHEXANES[22]

Isomer		ΔE, kcal./mole
trans-1,2	(p–p) − (e–e)	2.7
cis-1,3	(p–p) − (e–e)	5.4
trans-1,4	(p–p) − (e–e)	3.6

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(21) O. Hassel, *Tids. Kjemi Bergvesen*, **3**, 32 (1943).

(22) C. W. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1949).

(23) K. S. Pitzer, *Chem. Revs.*, **27**, 39 (1940).

In the case of *cis*-1,3, the relatively large energy difference is due to the steric interaction in the di-polar form, and ΔE was sufficiently high for the investigators[22] to conclude that the p–p form may be ignored at room temperatures.

If these observations may be tentatively accepted, then an examination of the experimental data will be in order. The data for the cyclohexanedicarboxylic acids were taken from Kuhn and Wasserman[24] and are given in Table IX.

TABLE IX

RATIO OF DISSOCIATION CONSTANTS OF CYCLOHEXANEDICARBOXYLIC AND HYDROXYCYCLOHEXANECARBOXYLIC ACIDS IN WATER AT 25°

Acid	$K_{A_xB_0}$[a]	$K_{A_xB_0}$[b]
cis-1,2	1.28	3.5
trans-1,2	1.66	4.9
cis-1,3	2.00	4.3
trans-1,3	1.22	2.8
cis-1,4	1.17	2.4
trans-1,4	1.68	3.6

[a] Hydroxycyclohexanecarboxylic acids, this investigation. [b] Cyclohexanedicarboxylic acids.[24]

It is seen that in solvent water, all of the substituted acids are stronger than the parent acid, HCy, and what is perhaps more striking is that for each *cis–trans* pair, the acid with the di-equatorial substitution possibility is the stronger of the two.

E. Acids Substituted 1,3 and 1,4.—Extending these observations to non-aqueous solutions, it is seen that in the hydroxy-substituted cyclohexanecarboxylic acid system, *cis*-1,3 is stronger than *trans*-1,3, and *trans*-1,4 is stronger than *cis*-1,4, in all of the solvents studied. This does not follow with the 1,2-isomers, and an explanation of this phenomenon will be advanced later in the text. These observations are also in accord with those of Smith and Byrne[25] who investigated the acid-catalyzed esterification of the cyclohexanedicarboxylic acids in methanol. These authors observed the similarities in the rates of esterification and activation energies of the *cis*-1,3 and the *trans*-1,4-diacids, and the *trans*-1,3 and the *cis*-1,4-diacids, in agreement with the structural analogies suggested in this investigation.

The parallelism between these acids is again noted in Fig. 1, which represents the plot of the logarithm of the relative acid strength against the reciprocal of the dielectric constant. The slopes of the lines, or the nature of the change in $K_{A_xB_0}$ with $1/D$, for *cis*-1,3 and *trans*-1,4 are -1.51 and -2.07, respectively, while the slopes (between water and methanol) for *trans*-1,3 and *cis*-1,4 are -7.37 and -7.92, respectively. These data indicate small relative differences within each pair on changing the solvent. In addition to the similarity in slope, the curves for the latter two acids are not linear. The break occurs at methanol for the *trans*-1,3- and *cis*-1,4-hydroxy acids, with a change from a negative to a positive slope, proceeding from methanol to ethanol.

It is not unreasonable to conclude, therefore, that the structures of each of the two isomers in each pair are quite similar. Since it has been shown by Pitzer, *et al.*,[22] that the di-polar configuration of *cis*-1,3-dimethylcyclohexane has been eliminated on steric grounds and, since the repulsive forces between the carboxyl and hydroxyl groups would operate in the same direction as the steric interaction, it would appear that the molecule would prefer the greater separation enjoyed in the di-equatorial configuration. If this reasoning is correct, then it may be said that the *cis*-1,3-hydroxy acid is di-equatorial, as is the *trans*-1,4-hydroxy acid. The *trans*-1,3- and the *cis*-1,4-hydroxy acids are therefore obtained in the equatorial–polar configuration.

F. Acids Substituted 1,2.—The "anomalous" behavior of the 1,2-acids will now be examined. Although the *trans*-1,2-hydroxy acid is stronger in water than its *cis*-1,2 isomeride, it becomes weaker than the *cis*-1,2 as the dielectric constant of the solvent becomes less than that of water, as may be seen in Fig. 1. This cross-over in strength occurs at a point intermediate in dielectric constant between water and ethylene glycol, and is consistent with the data of Kuhn and Wasserman[24] for the 1,2-di-carboxylic acids in water–methanol mixtures. This is shown in Table X.

TABLE X

DISSOCIATION CONSTANTS OF CYCLOHEXANEDICARBOXYLIC ACIDS[24]

Acid	Water $-\log K_1$	50% Methanol $-\log K_1$
cis-1,2	4.36	5.26
trans-1,2	4.21	5.38

In order to substantiate the arguments for the configurations presented in this section, it was necessary to include the results of the calculations of the distances between the ionizable proton and the center of the dipolar (hydroxyl) group in the 1,2-isomers. Although a more extensive treatment of this subject will be given in Section G of this paper, the assumptions made in the selection of the models used will be treated here.

The equivalence of the ring carbon atoms in the highly symmetrical chair form of cyclohexane has been shown experimentally by Hassel and Ottar[26] and we have assumed that this equivalence will be maintained in a disubstituted cyclohexane molecule. It is perhaps more reasonable to assume that some distortion or bond deformation may exist in the 1,2-substituted acids. In the absence of quantitative information applicable to this case, the bond distances and angles will be considered to be the same as those reported for the unsubstituted molecule, 1.538 Å. and 109°28′, respectively.[26] Steric interaction, however, was reported only for the dipolar 1,3-dimethylcyclohexanes (*cf.* Fig. 2).[22]

The treatment of Kirkwood and Westheimer was used in defining the position of the ionizable proton, and it was located at the extension of the bond joining the carboxyl carbon atom to its nearest carbon neighbor. The distance between the proton

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(24) R. Kuhn and A. Wassermann, *Helv. Chim. Acta*, **11**, 3 (1928).

(25) H. A. Smith and F. P. Byrne, THIS JOURNAL, **72**, 4406 (1950).

(26) O. Hassel and B. Ottar, *Arch. Math. Naturvidenskab*, **45**, No. 10, 1 (1942).

and the carboxyl carbon atom is therefore assumed to be 1.45 Å.[27]

In determining the location of the center of the hydroxyl dipole, the normal carbon-to-oxygen bond distance of 1.43 Å. was used.[28] If the conditions for the free rotation of the oxygen-to-hydrogen bond around an axis through the carbon-to-oxygen bond are allowable, then it will be assumed that the mean center of the hydroxyl dipole will lie along this ring carbon-to-oxygen bond axis at a distance of 1.72 Å. from the ring carbon atom. This assumption is treated more fully in Section G.

If the distances between the proton and the nearest ring carbon atom, the center of the hydroxyl dipole and its nearest ring carbon atom and, finally, the distance between the two ring carbon atoms are known, together with the angles formed by the lines passing through these positions with each other, then the distances between the proton and the center of the dipole can be calculated for the isomers. The values obtained for the 1,2-hydroxy acids are given in Table XI.

TABLE XI

INTRAFUNCTIONAL GROUP DISTANCES IN 1,2-HYDROXY ACIDS[a]

Acid		r,[b] Å.
cis-1,2	(e–p)	3.96
trans-1,2	(e–e)	3.96
trans-1,2	(p–p)	5.42

[a] Calculated by W. Drost-Hansen. [b] r is the distance between the center of the dipole and the ionizable proton.

The *cis*-1,2-isomer can be assigned only one configuration, whereas the *trans*-1,2-isomer may have two. In the absence of large repulsive forces, as in the dimethylcyclohexanes (1,2-), the di-equatorial configuration is favored for the *trans* isomer over the di-polar form. The stability of *cis*-1,2 indicates that although steric interaction may be large, *i.e.*, the close proximity of the groups, the distance between the groups is sufficiently great for the compound to exist, as evidenced by its reported stability.[7] Similar reasoning may be applied to the di-equatorial *trans*-1,2-acid. The choice of a favored configuration for the *trans*-1,2-isomer may now rest not on the magnitude of the forces operating between the hydroxyl and carboxyl groups, but on the dielectric constant of the solvent which will act either to diminish or intensify these forces. Since a decrease in the dielectric constant of a solvent causes an increase in the strength of the *cis*-1,2-acid over that of the *trans*-1,2-acid, and a decrease in dielectric constant is in the direction of intensification of the repulsive forces, the more stable configuration will be one in which the distance between groups is larger, thus favoring p–p over e–e for the *trans*-1,2-acid. If the above conclusions are reasonable, it may then be said that *trans*-1,2-hydroxy acid is di-equatorial in water, but di-polar in the non-aqueous solvents investigated. Previous calculations[29] have shown the *trans*-1,2-dicarboxylic acid to be di-equatorial in water, in agreement with the above deductions.

If the *trans*-1,2-hydroxy acid is stabilized in non-aqueous solvents as the di-polar configuration, the increase in distance between the center of the dipole and the proton, as shown for this form in Table XI, will favor its becoming a weaker acid than the unchanged *cis*-1,2-acid, in agreement with the experimental results.

G. Quantitative Calculations of Relative Acid Strengths.—The influence of a polar substituent on the dissociation constant of an organic acid, according to Bjerrum,[30] is primarily electrostatic in origin, and he suggested that the ratio of the dissociation constants of two similarly constituted acids may be calculated from the electrostatic work necessary to transfer a proton from the first acid to the anion of the second acid. This was applied to the dicarboxylic acids with fair success. A treatment similar to that of Bjerrum, but for acids with dipolar substituents, was formulated by Eucken[31] and Schwarzenbach and Egli[32] and is shown in equation 2.

$$\ln K_{A_xB_0} = \frac{eu \cos \theta}{r^2 kTD} \qquad (2)$$

In the above expression, e is the electronic charge, u is the dipole moment of the substituent group, θ is the angle between the dipolar axis and the line joining its center with the proton, r is the length of this line, k is the Boltzmann constant, T is the absolute temperature and D is the dielectric constant of the solvent.

More recently, Kirkwood and Westheimer[27] described the acid molecules as forming cavities of low dielectric constant in a medium of continuous dielectric constant (the solvent). An effective dielectric constant (D_E) was defined to depict that portion of the solution under examination. D_E now replaces D in equation 2 and is, therefore, a function of the dielectric constant of the solvent, the dielectric constant of the molecule itself (D_i), and the dimensions of the cavity. The latter parameter is defined in part by the model chosen and their models, for the purpose of mathematical convenience, were either spherical or ellipsoidal.

The parameters chosen for this newer treatment also include D_i, which was arbitrarily assigned a value of 2.00, based upon the observed dielectric constants of liquid paraffin hydrocarbons, and x, which is equal to the square of r divided by the square of b, the radius of the molecule.

A physical concept of the hydroxycyclohexanecarboxylic acids obtained from the previous discussion was used to construct a model of the acids, so that the distances and angles between substituent groupings could be calculated trigonometrically. The bond distances and angles in the cyclohexane molecule were obtained from the precise measurements of Hassel.[21,26] In this manner, the parameters of equation 2 were evaluated, and the fit between the experimentally determined values and theory could be obtained.

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(27) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506, 512 (1938).

(28) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 167.

(29) D. H. Barton, *J. Chem. Soc.*, 1197 (1943).

(30) N. Bjerrum, *Z. physik. Chem.*, **106**, 219 (1923).

(31) A. Eucken, *Angew. Chem.*, **45**, 203 (1932).

(32) G. Schwarzenbach and H. Egli, *Helv. Chim. Acta*, **17**, 1183 (1934).

In order to be consistent with Kirkwood and Westheimer, spherical model or cavity was assumed for the hydroxy acids, and the proton by definition[27] was placed on the extension of the bond between the carboxyl carbon and the nearest carbon neighbor, at an upper limit of 1.45 Å. away. A simplified picture of the hydroxyl dipole, in the absence of more complete information, was one in which free rotation was assumed to take place about an axis passing through the carbon-to-oxygen bond. The dipole was considered as a cone whose apex lay in the center of the oxygen atom, and the sides of which formed an angle of 105° with an extension of the axis. Free rotation of this dipole may not be an unreasonable assumption for the distantly substituted positions, and the center of the dipole was taken as coincident with the midpoint of the axis of the cone. The dipole moment of the hydroxyl group is $-1.70\ D$[33] (*cf.* Fig. 3).

Further comparison of the observed data with that calculated reveals that the fair agreement in solvent water (*cf.* Table XII) is indicative of a reasonable choice of parameters for this computation. Namely, the selection of a spherical model for the hydroxy acids, as opposed to an ellipsoidal one, gives this agreement and the use of the latter model would add little to rectify the discrepancies between experiment and theory on changing solvents.

TABLE XII

LOG $K_{A_xB_0}$ CALCULATED FROM EQUATION 2 AND COMPARED WITH EXPERIMENTAL VALUES

Acid	Water (D = 78.5) Calcd.	Obsd.	D_E	Ethylene glycol (D = 37.7) Calcd.	Obsd.	D_E
cis-2-OH	0.261	0.107	6.54	0.333	0.508	5.13
trans-2-OH	.261[a]	.220	6.54	− .143[b]	.346	1.74
cis-4-OH	.127	.068	4.18	.144	− .042	3.70
trans-4-OH	.322	.225	4.42	.371	.193	3.84

Acid	Methanol (D = 31.5) Calcd.	Obsd.	D_E	Ethanol (D = 21.4) Calcd.	Obsd.	D_E
cis-2-OH	0.360	0.681	4.74	0.409	1.001	4.18
trans-2-OH	− .146[b]	.401	1.70	− .153[b]	0.661	1.62
cis-4-OH	.145	− .083	3.54	.162	− .061	3.25
trans-4-OH	.388	.212	3.67	.412	.158	3.38

[a] Assuming a di-equatorial configuration. The di-polar value is −0.133. [b] Assuming a di-polar configuration.

Serious disagreement, however, is observed as the dielectric constant is decreased. An explanation of this phenomenon does not lie in the shape of the model selected as the distances between atoms should not markedly change with the solvent. Davies and Monk,[34] who examined the effect of some hydroxylic solvents on ionic radii, corroborate this hypothesis.

The findings in this investigation show that log $K_{A_xB_0}$ decreases with decreasing D and suggest the inapplicability of the Kirkwood–Westheimer theory to account for the effect of non-aqueous hydroxylic solvents on the relative strengths of the hydroxy acids.

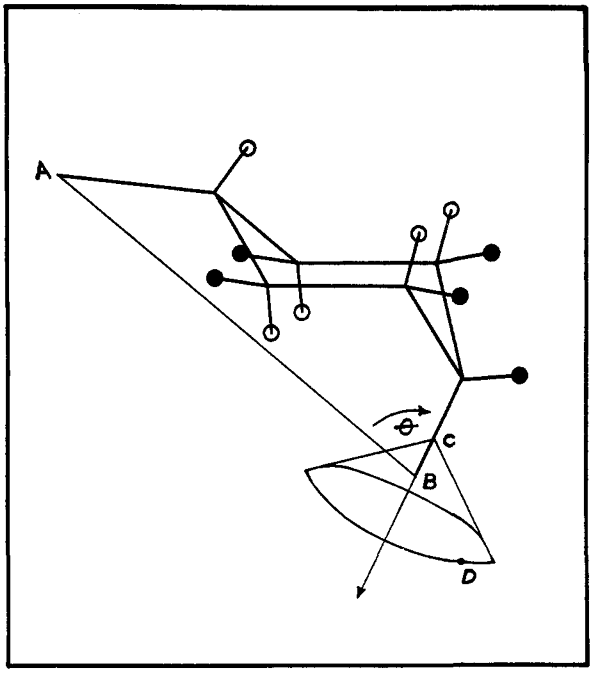

Fig. 3.—Model of *cis*-4-hydroxycyclohexanecarboxylic acid. A represents the carboxylic proton; B, the assumed center of the hydroxyl dipole (CD); ● and O are "equatorial" and "polar" hydrogens, respectively; θ is the angle between $\overline{AB}$ and the axis of the hydroxyl dipole.

This theory apparently does not completely account for the short range interactions between ions and molecules and the effect of solvation of these species. Wynne-Jones and Rushbrook,[35] report that the advantages of this theory, although real, are actually small in comparison with the serious discrepancies found between theory and experiment. The decided lack of agreement in accounting for the effect of temperature, in addition to the effect of the dielectric constant upon the relative dissociation constant, was also noted. The latter is in agreement with the conclusions of this investigation.

The treatment of Sarmousakis,[36] although representing an improvement over that of Kirkwood and Westheimer,[37] is applicable to aromatic systems only and cannot be used here.

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(33) R. J. W. Le Fevre, "Dipole Moments," Methuen, London, 1938.

(34) P. B. Davies and C. B. Monk, *J. Chem. Soc.*, 2718, 2723 (1951).

(35) W. F. K. Wynne-Jones and G. S. Rushbrooke, *Trans. Faraday Soc.*, **40**, 99 (1944).

(36) J. N. Sarmousakis, *J. Chem. Phys.*, **12**, 277 (1944).

(37) J. G. Kirkwood and F. H. Westheimer, *Trans. Faraday Soc.*, **43**, 77 (1947).