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THE STEREOCHEMICAL STUDY OF DIPHENYL 2,2'-DISULFONIC ACID. VIII[1]

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The existence of optical isomers in substituted diphenyl compounds is, according to the obstacle theory, due to the fact that the ortho-substituted groups are sufficiently large to prevent free rotation. In a previous paper[2] it was shown that x-ray data on the sizes of atoms and groups of atoms may be used to calculate the relative interferences of the ortho substituents and thus to predict whether or not a compound might possibly be resolved. It was pointed out also that the values for each group should not be regarded as representing merely linear effects since the forces around an atom or group are certainly three dimensional in character. The interference values for certain definite molecules were designed to represent the interference due to the effective realms of influence of the various combinations of atoms or groups. Some confusion regarding the interpretation of the obstacle theory appears to exist, since Bergmann[3] suggests the obstacle theory is unnecessary and yet considers the "mutual influence of the electron shells of the atoms or groups" to be the chief consideration. The influence of the electron shells, in so far as they affect the size of the atom or group by causing it to have a larger or smaller realm of force or influence, has been an integral part of the obstacle theory as far as the interpretation in this Laboratory is concerned. By the size of the atom or group is simply meant the volume affected by the electrical forces of the atom, and it is this volume of force that is regarded as the obstacle. The volume of the electrical forces of the atom or group has dimensions and occupies space so that a second volume of force may not be superimposed upon or pass through the first, although the two volumes may approach each other closely. Hence the field of force of the first acts as an obstacle to the field of force of the second atom or group which may strive to pass through or occupy the same space. This is recognized as a simple mechanical interference and the term "obstacle theory" appears quite satisfactory for it. This is in contradistinction to the so-called electrical theory, which represents the atoms or groups as possessing residual affinity of either a negative or a positive electrical charge which, in turn, prevents free rotation in the diphenyl molecule. The attraction of ortho-substituted groups of unlike charge and the repulsion of groups similarly charged are thus assumed to

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[1] For the previous paper (VII) in this series see, Maxwell and Adams, THIS JOURNAL, 52, 2959 (1930).

[2] Stanley and Adams, *ibid.*, 52, 1200 (1930).

[3] Bergmann and Engel, *Z. physik. Chem.*, Abt. B, 8, 111 (1930).

be determined chiefly by the magnitude of such charges, and with no consideration of the size of the groups.

According to the obstacle theory the size of the group or atom, as determined by the fields of force without regard to the sign or amount of any residual affinity, is the determining factor as to whether or not interference occurs and thus makes resolution of such diphenyl compounds possible. It must be recognized that the angle at which substituents are attached to the benzene ring, as well as the angle between two benzene rings, may vary slightly according to the character of the substituents. This must be taken into consideration, as has been pointed out and exemplified in a previous article.[2]

Although diphenyl derivatives having three and four ortho-substituents have been and are the subject of considerable study, only one compound having but two ortho-substituents has been investigated. This compound, diphenic acid, failed to resolve. On the basis of x-ray data, the following possible interferences of the substituents in the 2,2′,6,6′-positions were obtained: C-H, 0.94Å.; C-COOH, 1.56Å.; C-C (2,2′ and 6,6′), 2.9Å. The carboxyl groups would fail to collide with the hydrogen atoms by 0.4Å.; 1.56Å. + 0.94Å. = 2.5Å. − 2.9Å. ⟶ −0.4Å. It is thus seen that resolution would not be expected. However, it should be possible to resolve such an α,α'-disubstituted diphenyl compound into optical isomers, provided the two substituting groups are sufficiently large and provided also that a hydrogen atom may serve as a blocking group. For example, if each of the two substituting groups was 0.4Å. or more larger than a carboxyl group, they would not only collide with each other but should also collide with the hydrogen atoms when the molecule becomes arranged so that the substituting groups are on opposite sides.

In this investigation diphenyl-2,2′-disulfonic acid was prepared in an attempt to secure groups larger than the carboxyl groups. Pauling[4] and Goldschmidt[5] have calculated the ionic radii of the sulfur ion in sulfates as 0.29 and 0.34Å., and the ionic radii of the carbon atom in carbonates as 0.2Å. The C-O distance in a carbonate group has been estimated by means of crystal analysis as 1.08 Å.,[6] the S-O distance in a sulfate group as 1.55Å.,[7] the C-C distance in aromatic compounds as 1.45Å. and the S-S distance in gaseous S_2 as 1.81Å. and as 2.08Å.[8] in Fe_2S. This indicates that the sulfur atom is from 25 to 50% larger than the carbon atom, or from 0.38 to 0.76Å. larger. If other factors do not interfere and the increase in the sulfonic acid group as indicated by the C-O and the S-O dis-

[4] Pauling, This Journal, **49**, 765 (1927).

[5] Goldschmidt, *Trans. Faraday Soc.*, **25**, 253 (1929).

[6] Lennard-Jones, *Proc. Roy. Soc.* (London), A113, 673, 690 (1927).

[7] "Annual Reports," **1926**, p. 274.

[8] Mecke, *Z. Physik*, **42**, 390 (1927).

tances is effective, the total sulfonic acid group should be more than 0.4Å. larger than the carboxyl group. Interference with the hydrogen atoms would thus be made possible with the subsequent possibility of resolution of the compound. However, it was found impossible to resolve diphenyl-2,2′-disulfonic acid through the di-brucine, di-quinine and di-morphine salts. These salts were fractionated from several different solvents and gave no indication of resolution. An intermediate product, 4,4′-diamino-diphenyl-2,2′-disulfonic acid was also found to be unresolvable in the form of the di-brucine and di-strychnine salts. It would appear, therefore, that the sulfonic acid group may not be sufficiently large to interfere with a hydrogen atom and prevent free rotation. It may have a more compact structure than was supposed or else the hydrogen atom may be smaller as a blocking group than has previously been assumed. The second possibility appears plausible because the hydrogen atom represents a special case, in that it is different from all other substituting groups by not having an electron shell.

Other possible atoms or groups which, substituted in the α,α' positions in diphenyl, might make free rotation impossible are the bromine atom, the iodine atom and certain ring structures. Thus, 2,2′-dibromodiphenyl should be resolvable for the C-Br distance is approximately 2.11Å., which would cause the bromine atoms to interfere with the hydrogen atoms approximately 0.15Å. A 2,2′-di-iododiphenyl, if no abnormality occurs in the iodine atom when substituted in the benzene ring, should also resolve, for the C-I distance is about 2.2Å. This would cause the iodine atoms to interfere with the hydrogen atoms by 0.24Å. Diphenyl compounds having rings as the large disubstituted groups, may also be prepared. These conclusions depend on the validity of the assumption that the hydrogen atom has an appreciable interfering effect (0.94Å.). Representatives of the above type are now under investigation.

The diphenyl-2,2′-disulfonic acid was prepared by the sulfonation of nitrobenzene to *m*-nitrobenzene sulfonic acid, reduction to azobenzene disulfonic acid by means of zinc dust and alkali and further reduction and rearrangement by means of stannous chloride and hydrochloric acid to 4,4′-diaminodiphenyl-2,2′-disulfonic acid. Removal of the two amino groups by diazotization and treatment with copper powder in ethyl alcohol gave diphenyl-2,2′-disulfonic acid. Several attempts to prepare the disulfonic acid by reducing *m*-nitrobenzene sulfonic acid in alkaline solution to the hydrazo compound and filtering rapidly into concentrated hydrochloric acid to cause rearrangement to 4,4′-diaminodiphenyl-2,2′-disulfonic acid resulted in failure.

Experimental Part

***m*-Nitrobenzene Sulfonic Acid.**—*m*-Nitrobenzene sulfonic acid was prepared by the sulfonation of nitrobenzene.[9]

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[9] Holleman, *Rec. trav. chim.*, **24**, 198 (1905).

Azobenzene Disulfonic Acid.[10,11]—A mixture of 200 g. of potassium *m*-nitrobenzene sulfonate and 255 g. of sodium hydroxide in 1700 g. of water was heated on a steam cone and 204 g. of powdered zinc was added during six hours. The mixture was filtered hot and washed with hot water. The wash water was combined with the filtrate and saturated with carbon dioxide and then concentrated by evaporation until crystals appeared. After cooling a 40-g. crop of white crystals was removed and the filtrate was concentrated to about one liter. On cooling overnight a crop of 115 g. of yellow crystals of the sodium salt of azobenzene disulfonic acid came out. These were removed by filtration and used without drying in the next step.

4,4′-Diaminodiphenyl-2,2′-disulfonic Acid.[11]—A solution of 80 g. of stannous chloride in 160 cc. of concentrated hydrochloric acid was slowly added to a solution of 115 g. of the sodium salt of azobenzene disulfonic acid in 400 cc. of hot water. Upon addition of the stannous chloride the solution gradually loses its yellow color, finally becomes colorless and then white crystals of 4,4′-diaminodiphenyl-2,2′-disulfonic acid precipitate out. After standing overnight these were removed, dissolved in dilute ammonium hydroxide, filtered from a small amount of insoluble material, and reprecipitated by the addition of hydrochloric acid. The run was repeated and the total yield was 160 g.

Diphenyl-2,2′-disulfonic Acid.[11]—Dilute sodium hydroxide was added to a mixture of 100 g. of 4,4′-diaminodiphenyl-2,2′-disulfonic acid in 1.5 liters of ice water until solution was effected. Then 41 g. of sodium nitrite was added and after solution was complete a cold solution of 120 cc. of concentrated sulfuric acid in 500 cc. of water was slowly added and the clear solution allowed to remain at 0° for three days. During this time long yellow needles crystallized out. These were removed, washed with 100 cc. of cold water and air dried for fifteen minutes. The weight of the partially dried product was 100 g. The product was placed in an 800-cc. beaker, covered with 200 cc. of 95% ethyl alcohol and copper bronze added slowly with stirring. The mixture warmed up and nitrogen was evolved. When the reaction was ended, the mixture was heated on the steam cone for fifteen minutes and filtered from the unreacted copper bronze. The filtrate was concentrated until practically free of alcohol and then taken up in 200 cc. of water. A solution of 80 g. of barium hydroxide in 600 cc. of water was then added and the 800 cc. of solution was filtered hot from a small amount of black insoluble material. On cooling a 50-g. crop of white crystalline barium salt of diphenyl-2,2′-disulfonic acid came out. This precipitate was removed and warmed with 12 g. of concentrated sulfuric acid in 200 cc. of water and filtered from the precipitated barium sulfate. Dilute sulfuric acid was then added dropwise to the filtrate until the addition gave no additional white precipitate of barium sulfate. The precipitated barium sulfate was then removed by filtration and the filtrate evaporated to a thick sirup which solidified on standing over phosphorus pentoxide for two days. Diphenyl-2,2′-disulfonic acid is very soluble in water and alcohol, soluble in acetone, and insoluble in chloroform, benzene and petroleum ether. It is very deliquescent.

Preparation and Fractionation of the Alkaloid Salts

Brucine Salt of Diphenyl-2,2′-disulfonic Acid.—A mixture of 5 g. of diphenyl-2,2′-disulfonic acid and 12.5 g. of brucine was boiled with 100 cc. of water until complete solution was effected. On cooling the salt separated as an oil which solidified after standing for a day. The salt was washed with water and then with 100 cc. of hot benzene. After drying the weight of the salt was 17.5 g. and the melting point was 244–246°. *Rotation.* (a) 0.3121 g. made up to 25 cc. in chloroform at 20° gave $\alpha_D = -0.8°$;

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[10] Mahrenholtz and Gilbert, *Ann.*, **202**, 332 (1880).

[11] Limpricht, *ibid.*, **261**, 327 (1891).

$l = 2$; $[\alpha]^{20}_{D}$ −32.0; (b) 0.3382 g. made up to 15 cc. in chloroform at 20° gave $\alpha_D =$ −0.76°; $l = 1$; $[\alpha]^{20}_{D}$ −33.6.

The salt was washed with 50 cc. of acetone. *Rotation.* 0.2413 g. made up to 20 cc. with chloroform at 20° gave $\alpha_D =$ 0.38°; $l = 1$; $[\alpha]^{20}_{D}$ −31.6. This product was analyzed after drying over phosphorus pentoxide for an hour at 100° and 10-mm. pressure.

Anal. Calcd. for $C_{68}H_{62}O_{14}N_4S_2$: S, 5.81; neut. equiv., 551.3. Found: S, 5.62; neut. equiv., 548.2.

Petroleum ether was added to a solution of 4 g. of the salt in 50 cc. of chloroform until about half of the salt was precipitated out. The remainder of the salt was obtained by evaporation of the filtrate. Both fractions gave essentially the same rotation and melting point as the original material. A solution of 8 g. of brucine salt in 100 cc. of hot water was allowed to cool to 30° with stirring. A 3.5-g. crop of crystals which separated was removed by filtration. On standing overnight a second crop of 0.85 g. of crystals had separated from the filtrate. These were removed and the filtrate was evaporated to 40 cc. and on cooling a 3.2-g. crop of crystals was obtained. The rotation and melting points of all three fractions were identical. A third portion of di-brucine salt was fractionated by crystallization from 95% ethyl alcohol. Both fractions melted at 245–248° and had a rotation in chloroform of $[\alpha]^{20}_{D}$ −33.2.

Quinine Salt of Diphenyl-2,2′-disulfonic Acid.—A mixture of 5 g. of diphenyl-2,2′-disulfonic acid and 10.3 g. of quinine was boiled with 400 cc. of water without effecting solution. The water was removed by evaporation on a steam cone and the residue was dissolved in 200 cc. of chloroform. The addition of petroleum ether caused a 7.5-g. portion of salt melting at 188–192° to precipitate. *Rotation.* 0.3045 g. made up to 15 cc. with chloroform at 20° gave $\alpha_D =$ −1.6°; $l = 1$; $[\alpha]^{20}_{D}$ −78.9.

This salt was washed with 100 cc. of ether and analyzed after drying over phosphorus pentoxide for two hours at 100° and 10-mm. pressure. The melting point was then 191–193° with sintering at 185°. *Rotation.* 0.285 g. made up to 15 cc. with chloroform at 20° gave $\alpha_D =$ −1.63°; $l = 1$; $[\alpha]^{20}_{D}$ −85.9.

Anal. Calcd. for $C_{62}H_{58}O_{10}N_4S_2$: S, 6.66; neut. equiv., 481.3. Found: S, 6.41; neut. equiv., 485.4.

The further addition of petroleum ether caused a 7-g. portion of di-quinine salt melting at 188–193° to precipitate. *Rotation.* 0.2453 g. made up to 15 cc. with chloroform at 20° gave $\alpha_D =$ −1.3°; $l = 1$; $[\alpha]^{20}_{D}$ −79.5. A solution of the di-quinine salt in 40% ethyl alcohol was fractionated into two fractions of 3.3 and 3.7 g. Both fractions melted at 189–192° and the rotations were −83.5 and −81.2, respectively.

Morphine Salt of Diphenyl-2,2′-disulfonic Acid.—A mixture of 3 g. of diphenyl-2,2′-disulfonic acid and 1.65 g. of morphine was boiled with 75 cc. of water until complete solution was effected. The solution was cooled and filtered from 0.01 g. of insoluble material and further evaporated. The salt was so soluble that it was impossible to fractionate it from water, so the aqueous solution was evaporated to a sirup. This sirup was dissolved in 150 cc. of hot ethyl alcohol. On cooling the solution a 0.75-g. portion of salt came out. This fraction of salt began to swell at 240° and melted at 260–265° with decomposition. *Rotation.* 0.1513 g. made up to 15 cc. with water at 20° gave $\alpha_D =$ −0.73; $l = 1$; $[\alpha]^{20}_{D}$ −72.5.

The filtrate was evaporated to 75 cc. and a 0.5-g. portion of salt came out on cooling. This fraction began to swell at 240° and melted at 261–267° with decomposition. *Rotation.* 0.2237 g. made up to 15 cc. with water at 20° gave $\alpha_D =$ −1.11; $l = 1$; $[\alpha]^{20}_{D}$ −74.6.

The filtrate was evaporated to dryness and gave 1.65 g. of salt, which began to swell at 240° and melted at 261–267° with decomposition. *Rotation.* 0.1952 g. made up to 15 cc. with water at 20° gave $\alpha_D =$ −0.98; $l = 1$; $[\alpha]^{20}_{D}$ −75.1.

Anal. Calcd. for $C_{46}H_{48}O_{12}N_2S_2$: neut. equiv., 442. Found: 441.

The di-morphine salt was insoluble in chloroform, benzene, petroleum ether, ethyl acetate and acetone. The salt was also insoluble in absolute ethyl alcohol, but after moistening the salt with a small amount of water it dissolved in ethyl alcohol quite readily.

Strychnine Salt of 4,4′-Diaminodiphenyl-2,2′-disulfonic Acid.—A mixture of 5 g. of 4,4′-diaminodiphenyl-2,2′-disulfonic acid and 9.7 g. of strychnine was boiled for a half hour with 250 cc. of water. On cooling a 7.4-g. crop of salt melting at 310–318° (dec.) was obtained. *Rotation.* 0.2207 g. made up to 15 cc. with water at 20° gave $\alpha_D = -0.33$; $l = 1$; $[\alpha]^{20}_{D}$ -22.4.

Anal. Calcd. for $C_{54}H_{56}O_{10}N_6S_2$: Neut. equiv., 506.2. Found: 513.

The filtrate was evaporated to 120 cc. and on cooling 2.3 g. of salt was obtained. The filtrate was then evaporated to dryness, giving 3.3 g. of salt melting at 310–318° with decomposition. *Rotation.* 0.3060 g. made up to 15 cc. with water at 20° gave $\alpha_D = -0.43$; $l = 1$; $[\alpha]^{20}_{D}$ -21.4.

Brucine Salt of 4,4′-Diaminodiphenyl-2,2′-disulfonic Acid.—A mixture of 5 g. of 4,4′-diaminodiphenyl-2,2′-disulfonic acid and 11.4 g. of brucine was gently boiled for a half hour with 250 cc. of water. On cooling a 7.5-g. crop of dibrucine salt melting at 310–313° (dec.) was obtained. *Rotation.* 0.2715 g. made up to 15 cc. with water at 20° gave $\alpha_D = -0.38$; $l = 1$; $[\alpha]^{20}_{D}$ -21.0.

Anal. Calcd. for $C_{58}H_{64}O_{14}N_6S_2$: neut. equiv., 566.2. Found: 576.

The filtrate was evaporated to 190 cc. and on cooling a 5.5-g. crop of salt melting at 311–314° (dec.) was obtained. *Rotation.* 0.3010 g. made up to 25 cc. with water at 20° gave $\alpha_D = -0.24$; $l = 1$; $[\alpha]^{20}_{D}$ -20.0.

The filtrate was evaporated to dryness, giving 3 g. of salt melting at 310–314° with decomposition. *Rotation.* 0.3107 g. made up to 15 cc. with water at 20° gave $\alpha_D = -0.52$; $l = 1$; $[\alpha]^{20}_{D}$ -24.6.

Summary

The di-brucine, di-quinine and di-morphine salts of diphenyl-2,2′-disulfonic acid, and the di-brucine and di-strychnine salts of 4,4′-diaminodiphenyl-2,2′-disulfonic acid have been prepared. Fractionation of these salts from several different solvents gave no indication of resolution.

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