

which the restraining influence of higher neurons is expressed.

The identification in the central nervous system of cholinergic and adrenergic mechanisms responsive to doses within the range of physiological interest makes it reasonable to pursue further and energetically the inquiry into the possibility of central humoral transmission along the lines that Loewi has been so instrumental in developing.

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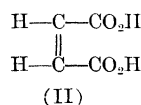
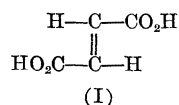


# Hydrogen Bonding as a Factor in the Ionization of Dicarboxylic Acids

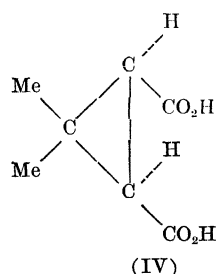
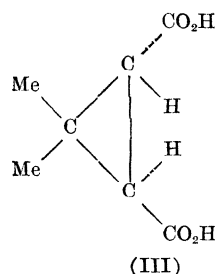
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THE ratios of the first to the second ionization constant of many dicarboxylic acids show a remarkable variation with structure. Thus the ratio  $K_1/K_2$  is 23.2 for fumaric acid (I), whereas it is 20,200 for maleic (II).



Similarly the ratio is 31.8 for *trans*-caronic (III) and 929,000 for *cis*-caronic (IV).



These and related data are summarized in Table I.

The deviation of the  $K_1/K_2$  ratio of symmetrical dicarboxylic acids from the statistically expected value

<sup>1</sup> Fellow on a National Science Foundation grant at Purdue University.

TABLE I  
IONIZATION CONSTANTS FOR DICARBOXYLIC ACIDS IN WATER AT 25° C

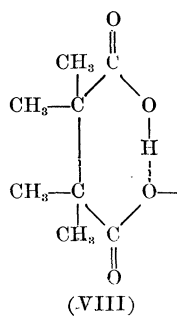
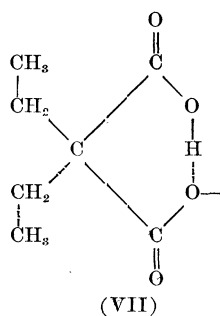
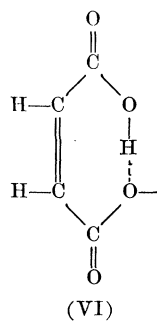
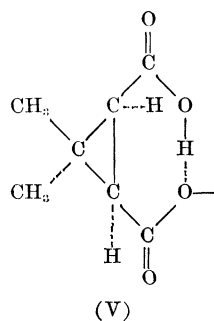
| Acid                                        | $10^4 K_1$ | $10^7 K_2$ | $K_1/K_2$ |
|---------------------------------------------|------------|------------|-----------|
| Fumaric (17)                                | 9.57       | 413        | 23.2      |
| Maleic (17)                                 | 120        | 5.95       | 20,200    |
| <i>trans</i> -Cyclopropanedicarboxylic (16) | 2.2(24° C) | 74(24° C)  | 29.7      |
| <i>cis</i> -Cyclopropanedicarboxylic (16)   | 4.7        | 3.4(24° C) | 1,380     |
| <i>trans</i> -Caronic (4)                   | 1.52       | 47.8       | 31.8      |
| <i>cis</i> -Caronic (4)                     | 45.9       | 0.0494     | 929,000   |
| Malonic (2)                                 | 14.9       | 20.3       | 734       |
| Dimethylmalonic (2)                         | 6.83       | 8.72       | 783       |
| Methylethylmalonic (2)                      | 13.8       | 3.86       | 3,580     |
| Diethylmalonic (2)                          | 61.5       | 0.51       | 121,000   |
| Succinic (2)                                | 0.64       | 33.3       | 19.2      |
| Tetramethylsuccinic (2)                     | 3.19       | 0.52       | 6,130     |

of four was explained by Bjerrum as due to the electrostatic effect of the negative carboxylate ion acting through the solvent medium on the remaining carboxylic hydrogen (1). From this assumption Bjerrum was able to calculate reasonable values for the separa-

tion of the carboxyl groups. However, the distances calculated in this way were much too short for a number of short chain acids, particularly maleic acid, the disubstituted malonic acids, and tetramethylsuccinic acid, acids which are distinguished by a high value for the  $K_1/K_2$  ratio (Table 1).

A number of modifications of Bjerrum's theory have been proposed to explain the above difficulties (2, 3). Among these, the treatment of Westheimer and Kirkwood has proved most satisfactory (3). These authors considered the transmission of the electrostatic effect through the molecule itself as well as through the solvent. Since the hydrocarbon chain must have a low dielectric constant, the internal transmission was considered to be very important in short, highly alkylated acids. They were thus able to obtain reasonable values for the separation of the carboxylate groups in the alkylated malonic and succinic acids.

In 1936 Jones and Soper (4) suggested that internal hydrogen bonding might account for the large  $K_1/K_2$  ratio in *cis*-caronic acid (V). This reasonable explanation appears to have been overlooked by workers in the field. We have been making a survey of the factors affecting acid strength and have come to the conclusion that this proposal can be extended to a general explanation for the high  $K_1/K_2$  factors observed in many dicarboxylic acids (VI-VIII).



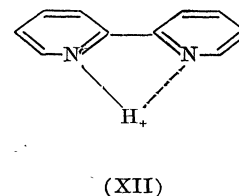
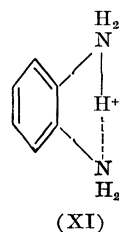
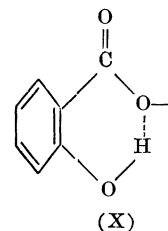
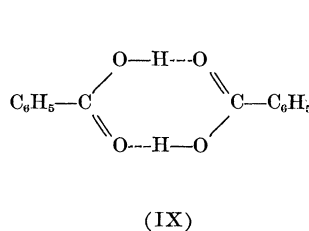
Stabilization of the carboxylic acid ion through internal hydrogen bonding should result in an increased tendency for the ionization of the first proton and a decreased tendency for the second. This is in accord with the results (Table 1). We attribute the large effect of the gem-dimethyl group in *cis*-caronic acid to their effect in minimizing rotation of the carboxyl groups, thereby stabilizing the chelate structure. In dimethylmalonic acid, the two methyl groups do not

interfere with the rotation of the carboxyl groups and there is little increase in the  $K_1/K_2$  ratio over that observed for the parent acid. The geometrical requirements of the two ethyl groups (5), however, are such as to act as a barrier to the rotation of the carboxyl groups (VII)—a very large  $K_1/K_2$  value is observed (Table 1).

Finally, tetramethylsuccinic acid is related to hexamethylethane, a molecule which is highly strained (6, 7). The strain should be reduced in the hydrogen-bonded chelate structure (VIII). For an alternative explanation of the effect of alkyl groups in favoring ring closure, see Bartlett (8). It follows that hydrogen bonding furnishes a reasonable, logical explanation for the  $K_1/K_2$  ratios under discussion.

Recently Hunter, following publication of evidence for hydrogen bonding in the crystal structure of maleic acid (9), proposed such hydrogen bonding as an explanation of the anomalous strength of maleic and similarly constituted acids (10). Subsequently, this interpretation was attacked by Davison (11). He questioned whether the internal hydrogen bond in the maleic acid ion could be sufficiently strong to withstand competition from hydrogen bonding to water. Davison based his argument upon his observation that maleic acid in ether shows an infrared absorption pointing to the presence of a nonhydrogen-bonded carbonyl, whereas in the crystalline acid and in ethanol solution the absorption corresponds to a hydrogen-bonded carbonyl. Since chelation observed in the crystalline acid (9) does not survive competition with ether, he concludes that similar hydrogen bonding in the maleate acid ion would not survive competition with water. This conclusion does not necessarily follow. The oxygen atom in ethyl ether may be considerably better as the donor atom in a hydrogen-bond than the oxygen atom in water. Moreover, the carboxylate ion, with its negative charge, should form far more stable hydrogen bonds than the neutral carboxyl group.

Considerable evidence can be quoted to support our position that hydrogen bonding of this kind can persist in aqueous and alcoholic solutions:



(1) Hydrogen bonding in the benzoic acid dimer (IX) apparently withstands competition with water. Its dimerization constant,  $K_D = [(\text{HA})_2]/[\text{HA}]^2$ , has been determined to be 0.75 l/mole in water (12).

(2) The ionization constants ( $\times 10^5$ ) for the isomeric hydroxy- and methoxy-benzoic acids in water at 25° are (13):

|                    | <i>ortho</i> | <i>meta</i> | <i>para</i> |
|--------------------|--------------|-------------|-------------|
| HO—                | 105          | 8.3         | 2.9         |
| CH <sub>3</sub> O— | 8.1          | 8.2         | 3.4         |

The enhanced ionization of the *ortho* hydroxy and its absence in the corresponding methoxy derivative is reasonably interpreted in terms of the hydrogen bonded intermediate (14) (X).

(3) One mole of acid effectively prevents the reaction of *o*-phenylenediamine with methyl iodide in methanol solution (15); two moles are required for the *meta* and *para* isomers (XI).

(4)  $\alpha$ ,  $\alpha'$ -Bipyridyl reacts with but one mole of acid, whereas the  $\beta$ - and  $\gamma$ -isomers neutralize two moles (18) (XII).

Other data could be quoted. However, the evidence strongly supports the conclusion that hydrogen bond-

ing in such systems can persist in aqueous solution and that hydrogen bonding offers a simple, reasonable explanation for the high  $K_1/K_2$  ratios observed in many dicarboxylic acids.

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## News and Notes

### International Hydraulics Convention

THE Minnesota International Hydraulics Convention, which combined the fifth plenary meeting of the International Association for Hydraulic Research and the second separate meeting of the Hydraulics Division of the American Society of Civil Engineers, introduced several innovations in meetings of this character. It was held at the University of Minnesota in Minneapolis September 1-4, 1953, and was attended by delegates from 35 states and the District of Columbia and other eminent scientists and engineers from eighteen countries. Preceding the Convention by one day, there was also in session a Hydrology Meeting of the North Central Regional Branch of the American Geophysical Union.

A unique feature of the Convention was the prepublication of all technical papers in a large illustrated volume, with 49 comprehensive hydraulics papers by 75 authors from some 20 countries. The preprinting of the *Technical Proceedings* proved to be exceptionally effective in scheduling the technical sessions and stimulating discussion.

The theme of the congress was directed toward four geophysical aspects of hydraulics: (a) Basic Relationships of Sediment Transportation by Flowing Water; (b) Density Currents; (c) Air Entrainment by Flowing Water; and (d) Waves, Beach Erosion, and the Hydromechanics of Shore Structures. Countries par-

ticipating for the first time since World War II included Yugoslavia and Japan. A half-day tour was made through the St. Anthony Falls Hydraulic Laboratory, displayed in full operation.

Dr. Theodore C. Blegen, Dean of the Graduate School of the University of Minnesota, made the welcoming address and stressed the importance of freedom of thinking and international cooperation in all research work, whether fundamental or applied. Dr. E. C. Stakman, world-renowned plant pathologist, addressed the opening session on a topic phrased, "Land and Water—May They Get Together Better." He discussed the unbalance in the international sphere of the world's increasing population and the distribution of land for agricultural needs. Emphasis was placed on further development of water resources for irrigation, recognizing the diverse needs of either increase or decrease in water on various lands to enhance their utility, and the development of plant types that will require less water than many types now in prevalent use. The speaker at the concluding luncheon meeting of the Convention was Major General S. D. Sturgis, Jr., Chief of Engineers of the U.S. Army, who discussed "Water Resource Development."

The International Association for Hydraulic Research selected Delft, Netherlands, for its next plenary meeting to be held in September, 1955. A new Constitution was also adopted by the IAHR. The officers elected at the concluding session were: President, Dr.