

that the silver chloride was non-radioactive. From this preliminary experiment and the half-life of radioactive chlorine, it was possible to calculate the most advantageous dilution for any subsequent time. With the strength of the sample of radioactive chlorine that was available to us, it was possible to remain in the optimum counting range for six hours even though the first count was not made until two hours after irradiation of the sample.

In Table I and Fig. 2 we show the data for typical determinations.

TABLE I

Results from two experiments. For both, the solutions were 0.0187 molar silver chloride and 0.5 molar ammonium hydroxide. Each count is the result of a ten minute period of counting.

Sample	Time, min.	Dil.	Net count per minute	Net count times the dil.
1a	0	200	158.8 ± 4.5	31760 ± 900
1b	125	20	147.2 ± 4.4	2944 ± 88
1c	280.5	2	81.2 ± 3.6	162.4 ± 7.2
2a	0	80	134.0 ± 4.0	10520 ± 320
2b	82	20	101.3 ± 3.7	2026 ± 74
2c	193	2	134.0 ± 4.0	268.0 ± 8
2	241	1	102.5 ± 3.7	102.5 ± 3.7
2	305.5	1	41.9 ± 2.8	41.9 ± 2.8

The use of this method for any material that can be brought into solution is obvious. It may be worthwhile to point out that the diluent should be chemically identical with the stock radioactive solution in order to eliminate any errors due to differential absorption.

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RECEIVED MAY 18, 1936

### 5,7-Diiodo-8-hydroxyquinoline

BY VIKTOR PAPESCH AND ROBERT R. BURTNER

5,7-Diiodo-8-hydroxyquinoline, which is of therapeutic interest, has been prepared previously by the interaction of iodine and sodium iodide with 8-hydroxyquinoline in alkaline solution.<sup>1</sup> Although the yield is satisfactory, the procedure requires working in rather dilute solution, thus involving the use of large-scale equipment even for semi-commercial production. A different procedure was therefore developed which is distinctly more economical with respect to ease of manipulation and materials required.

A solution of 2105 g. (14.5 moles) of 8-hydroxyquinoline in 5800 cc. of 15% (by weight) hydrochloric acid is added in a slow stream with stirring

(1) British Patent 351,805.

at laboratory temperature to 4872 g. (30.0 moles) of iodine monochloride dissolved in 6000 cc. of 15% hydrochloric acid. Stirring is continued for four hours longer and the mixture then allowed to stand for twelve hours. The product is washed by decantation with 5% hydrochloric acid to remove excess iodine monochloride, followed by a washing with water and finally with a 2% solution of sodium hydrosulfite to reduce traces of free iodine. An additional amount of product may be recovered by combining the liquors of the first two washings and allowing them to stand for several days. The total yield of product melting at 198–200° is 4900–5300 g. or 83.5–92.5% of the theoretical, the purity of which is approximately 98.5% as determined by iodine analysis.

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RECEIVED APRIL 23, 1936

### On a Relation between the Dissociation Constants of Substituted Aliphatic Acids and the Distance between the Dissociating and the Substituted Groups

BY JESSE P. GREENSTEIN

A relationship between the dissociation of a substituted acid and the distance between the carboxyl and substituted groups was suggested by MacInnes<sup>1</sup> in 1928 in which  $pK_{\infty}$  represents the

$$pK = pK_{\infty} + S(1/d) \quad (1)$$

value of the dissociation constant for an acid whose substituent is removed an infinite length along the chain, and  $d$  has the value 1 for an  $\alpha$ -, 2 for a  $\beta$ - and 3 for a  $\gamma$ -substitution. This inverse linear relationship held for the hydroxy and the chloro substituted acids, and was extended by subsequent authors<sup>2-4</sup> to the variously substituted amino acids, diamines, dicarboxylic acids and amino acid esters.

In the endeavor to introduce physical quantities into equation (1), an interesting relation developed. If in place of  $d$  in the equation there is substituted the square of the distance,  $l^2$ , in Ångströms, from the center of the group dipole to the carboxyl center on the assumption of an extended chain, there is found for the substituted aliphatic acids an inverse linear relationship between  $pK$  and  $l^2$ .

(1) MacInnes, *THIS JOURNAL*, **50**, 2587 (1928).

(2) Edsall and Blanchard, *ibid.*, **55**, 2337 (1933).

(3) Greenstein, *J. Biol. Chem.*, **96**, 499 (1932).

(4) Schmidt, Appleman and Kirk, *ibid.*, **81**, 723 (1929).

In applying this consideration to substituted aliphatic acids, we may assume tetrahedral symmetry for the carbon atoms, and the estimates of Pauling and Sherman<sup>5</sup> that the interatomic distance from the carboxyl carbon to the two oxygens is 1.29 Å. and the bond angle 124°. The linear component of the carboxyl group will be, therefore, 0.6 Å. In the case of the amino and hydroxyl substituents the mid-point of the dipole may be located in the center of the nitrogen and oxygen atoms, respectively. On the other hand, for the halogen substituents the dipole will lie somewhere along the halogen-carbon bond and we may for all purposes designate its center as midway along this bond. Using the value of the half tetrahedral angle and Pauling's single bond distances,<sup>6</sup> and expressing the straight line distance  $l$  from the dipole center to the carboxyl center in terms of Ångströms, there is found for the variously substituted molecules the following data for  $l^2$ :

Position	Substituted groups					
	OH $l^2$	NH <sub>2</sub> $l^2$	Cl $l^2$	Br $l^2$	I $l^2$	COOH $l^2$
$\alpha$	9.18	9.36	6.66	6.97	7.34	13.84
$\beta$	18.40	18.66	14.75	15.21	15.76	24.80
$\gamma$	30.80	31.14	26.01	26.63	27.35	38.94
$\delta$		46.79	40.45	41.22	42.12	56.25
$\epsilon$		65.61				76.74
$\zeta$						100.4
$\eta$						127.2
$\theta$						157.8

Substitution of the above values in the formulation

$$pK = pK_{\infty} + S(1/l^2) \quad (2)$$

leads to an excellent linear agreement between  $pK$  and  $1/l^2$  (Fig. 1), where the values of  $pK$  have been derived from Cohn<sup>7</sup> and from Simms.<sup>8</sup>

Examination of the values in Table I suggests the linear integer relation of MacInnes,  $l^2$  for a  $\beta$ -substitution appears to be about twice that for the  $\alpha$ -substitution, for a  $\gamma$ -substitution  $l^2$  is about three times that for the  $\alpha$ -value, etc. Similar to MacInnes' findings, the lines for the chloro, bromo and iodo acids are identical. Furthermore, within the limits of accuracy of this type of calculation the  $pK_{\infty}$  values derived from either equation (1) or (2) are identical. For the dicarboxylic acids only the value for malonic acid, where both carboxyls are attached to the  $\alpha$ -

carbon falls widely off the curve and has been omitted from the graph. The inability to fit this acid into any relation involving its higher isomers has been discussed by Gane and Ingold.<sup>9</sup>

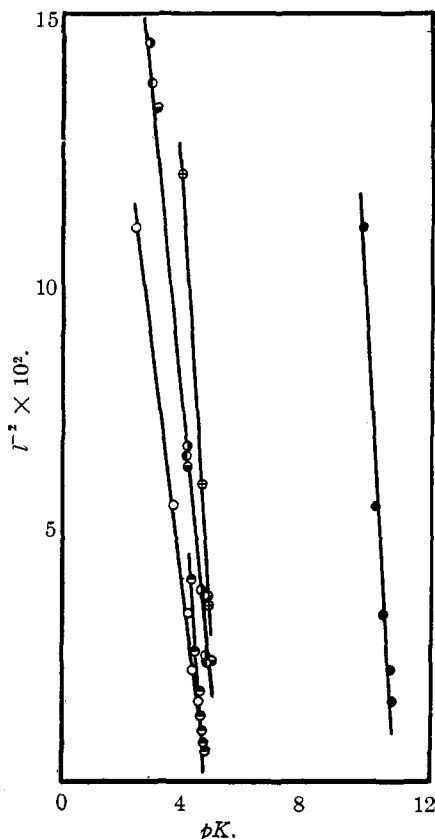


Fig. 1.—Amino acids,  $pK_1$  ○,  $pK_2$  ●; hydroxy acids, ⊕; chloro acids, ⊙; bromo acids, ⊖; iodo acids, ⊗; dicarboxylic acids, ⊗.

The constants in equation (2) for the variously substituted acids are gathered in Table II.<sup>10</sup>

Substituent	Ionizing group	$pK_{\infty}$	$-S$
OH	COOH	5.2	0.085
COOH	COOH	4.7	.081
COOH	NH <sub>2</sub>	10.9	.089
Halogens	COOH	5.1	.067
NH <sub>2</sub>	COOH	4.8	.040

Equation (2) recalls the formulation of the field due to a dipole at a distance from its center large in comparison to the distance of separation of the two charges:  $V = (\mu/d_0^2) \cos \theta$ , where  $\mu$  is the

(9) Gane and Ingold, *J. Chem. Soc.*, 1594 (1928).

(10) If the interatomic zigzag distance in Ångströms through the chain from the center of the substituent to the center of one of the oxygens of the carboxyl group be considered, an analogous inverse square relation between dissociation constant and distance is revealed in all the cases discussed above. Only malonic acid again provides an exception.

(5) Pauling and Sherman, *Proc. Nat. Acad. Sci.*, **20**, 340 (1934).

(6) Pauling, *ibid.*, **18**, 293 (1932).

(7) Cohn, *Ergebnisse Physiol.*, **33**, 781 (1931).

(8) Simms, *THIS JOURNAL*, **48**, 1251 (1926).

electric moment and  $\theta$  the angle between  $d_0$  and the dipole axis. It would be difficult, in view of the changes in orientation of the dipole along the chain to derive at present any closer basis of relation other than analogy between the two formulations. It is interesting to note, however, that the value for the slope constant  $S$  in equation (2) is practically identical for the three halogen acids. The electric moments of the C-halogen bond for the three halogens are likewise very nearly equal. The relative magnitude of the slope constants, however, bears no obvious relation to that of the electric moments of the substituents.

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RECEIVED MARCH 16, 1936

### The Mechanism of the Diene Synthesis

BY EDWIN R. LITTMANN

The observation of Diels and Alder<sup>1</sup> that a yellow color appears during the synthesis of the

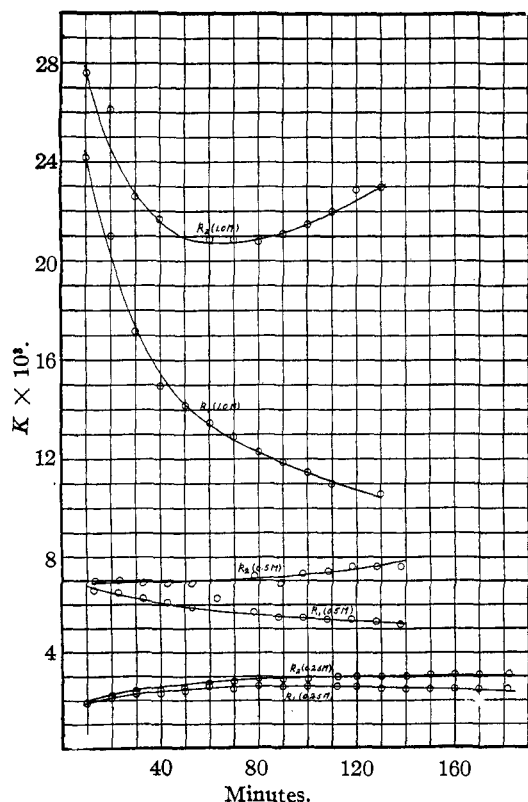


Fig. 1.—Reaction rate constants of  $\alpha$ -phellandrene-maleic anhydride.

(1) Diels and Alder, *Ann.*, **460**, 98 (1927).

colorless  $\alpha$ -phellandrene-maleic anhydride suggests that the reaction mechanism involves a colored intermediate compound. Such a mechanism would imply a second order followed by a first order process, and in the absence of side reactions the observed reaction rate constants should approach those for a first order reaction as the concentration increases.

To test this matter measurements of the rate of reaction between  $\alpha$ -phellandrene and maleic anhydride in acetone solutions have now been carried out at 0.25, 0.50 and 1.0 molality.

The  $\alpha$ -phellandrene (Schimmel and Company) had the following properties: specific rotation (sodium light),  $-110.7^\circ$ ; refractive index (white light), 1.4775, and density, both at  $20^\circ$ , 0.856. The maleic anhydride (Eastman Kodak Company) was completely soluble in benzene and was used without further purification. The solutions, cooled to  $25^\circ$ , after thoroughly mixing were transferred to 2-dm. polarimeter tubes and observations of the rotation taken at definite intervals. The temperature of the polarimeter tube was maintained at  $25 \pm 0.5^\circ$  by means of an air jet directed on the tube.

The results obtained are given in Fig. 1 in which the rate constants were calculated from the integrated forms of the standard rate equations. The values of the computed constants indicate that the reaction is more nearly unimolecular in the dilute than in the concentrated solutions and therefore it appears either that some other reaction mechanism is involved or that side reactions take place.

In order if possible to isolate the hypothetical polymer formed in the reaction, 6.8 g. of  $\alpha$ -phellandrene and 4.9 g. of maleic anhydride were mixed without the use of any solvent and heated to  $55$ – $65^\circ$  whereupon a violent reaction ensued which subsided in a few minutes. After standing for fifteen minutes the mixture was distilled at 3–5 mm. from an oil-bath at  $250^\circ$  until no more distillate was formed. The non-volatile residue was extracted repeatedly with ether, but only a small portion dissolved. The residual white powder when washed with methanol and dried gave, on analysis, 68.7% carbon and 7.27% hydrogen. Its molecular weight by the Rast method was found to be approximately 1220. These data agree with an empirical formula approximating either  $C_{46}H_{66}O_{12}$  or  $C_{60}H_{74}O_{15}$ , giving 69.0 or 69.6% carbon, 7.00 or 7.17% hydrogen, and a molecular weight of 800 or 1034, respectively.

Since  $\alpha$ -phellandrene and maleic anhydride were the only substances present, and since the