

$P^{31}$  n.m.r. at 15-min. reaction time showed approximately equal amounts of ethyl hypophosphite ( $-37.1$ ,  $-14.8$ , and  $+8.3$  p.p.m.) and hypophosphorous acid ( $-28.8$ ,  $-6.9$ , and  $+15.2$  p.p.m.) with fairly large unidentified peaks at  $-40.6$ ,  $-34.9$ , and  $-19.4$  p.p.m. In 12 hr. the ethyl hypophosphite peaks were seen to be increasing at the expense of the others, and in 4 days the formation of ethyl hypophosphite was nearly complete. The rapid initial reaction rate and unidentified transient peaks suggest the possibility of an orthoester-hypophosphite ester intermediate species; as in the ketal reaction. This reaction mixture appeared to disproportionate more slowly at room temperature than the orthocarbonate or orthoformate reaction mixtures.

**Butyl Hypophosphite.**—Hypophosphorous acid (16.3 g., 0.25 mole) and butyl orthoformate (60.4 g., 0.26 mole) were combined as above. The temperature dropped to  $7^\circ$  and n.m.r. showed about 90% conversion after 30 min. at room temperature and complete conversion after 3 hr. The reaction mixture was evaporated at  $0^\circ$  and 0.2 mm. in a rotary evaporator for 2 hr. giving 43.8 g. of clear, colorless residue. This weight corresponds to a 69% solution of butyl hypophosphite in its reaction by-products. Identification was by n.m.r. (Table I).

**Usual Mixing Procedure.**—Most reactions for which separations were not anticipated were carried out in 5-mm. n.m.r. sample tubes. By forcing the open end of the tube into the crystalline acid and tapping the resulting plug of acid to the bottom of the tube, the very hygroscopic acid could be transferred and weighed with very little absorption of atmospheric moisture. The organic reactants were dropped in through a capillary pipet while weighing, and mixing was effectively accomplished with an oscillating vortex mixer. In this manner, reactions could be observed with n.m.r. within about 4 min. of mixing the reactants.

**Methyl 1-Hydroxy-1,1-dimethylmethylphosphinate.**—In the above manner, 0.444 g. (0.00673 mole) of hypophosphorous acid

and 1.400 g. (0.0135 mole) of acetone dimethyl ketal were combined. At 7-min. reaction time,  $P^{31}$  n.m.r. showed methyl hypophosphite peaks about twice as large as peaks of unreacted acid. Little change occurred in an additional hour. After 3 days, roughly 75% of the phosphorus was converted to phosphinate, but the remaining methyl hypophosphite peaks were still about twice as large as the acid peaks. After 20 days, conversion to phosphinate was complete. The reaction product was evacuated at room temperature, giving a clear, colorless residue of fairly pure phosphinate. Calcd. for  $C_4H_{11}O_3P$ : C, 34.8; H, 8.0; P, 22.4. Found: C, 33.9; H, 8.3; P, 22.2.  $P^{31}$  n.m.r.: doublet at  $-33.6$  and  $-56.3$  p.p.m.;  $J_{P-H} = 552$  c.p.s.  $H^1$  n.m.r. assignments, measured and theoretical areas (in H atoms), chemical shift in c.p.s., and coupling, respectively, are: HOC, 1.1, 1.0, 362,—;  $CH_3OP$ , 3.0, 3.0, 227, 11; unidentified, 0.2, 0, 199,—; HP (upfield peak only), 0.51, 0.50, —, —;  $(CH_3)_2CPH$ , 5.9, 6.0, 78, 16 c.p.s. to HP and 2.5 c.p.s. to HP. The downfield peak of the P-H doublet was observed, but was off-scale on this spectrum. From spectra of reaction mixtures, this doublet is centered at 385 c.p.s. and  $J_{P-H} = 513$  c.p.s.

**Ethyl 1-Hydroxyethylphosphinate.**—A mixture of 1.43 g. (0.0216 mole) of hypophosphorous acid and 2.56 g. (0.0216 mole) of acetal failed to give a single-phase liquid after violent agitation for 10 min. Addition of a catalytic amount of finely ground ammonium chloride and more mixing produced no visible change. After standing for 4 days, the mixture was homogeneous, and  $P^{31}$  n.m.r. showed two approximately equal phosphinate doublets in addition to ethyl hypophosphite and hypophosphorous acid. In 5 months all hypophosphorous acid was consumed and the ethyl 1-hydroxyethylphosphinate doublet ( $-29.8$  and  $-51.9$  p.p.m.) was about three times as large as the 1-hydroxyethylphosphinic acid doublet ( $-23.4$  and  $-45.3$  p.p.m.). Some ethyl hypophosphite remained.

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## Ionization Constants of 3,5-Dimethyl 4-Substituted Benzoic Acids

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RECEIVED AUGUST 15, 1963

Ionization constants of a series of 4-substituted 3,5-dimethylbenzoic acids ( $X = N(CH_3)_2, NH_2, NHCOCH_3, OH, OC_2H_5, Br, Cl, CN, CO_2CH_3, NO_2$ ) have been measured and the  $pK_a$  values are interpreted in terms of steric inhibition of resonance. A comparison of "effective  $\sigma$ -values" with  $\sigma_I$  constants is made and approximate angles of twist for substituents are calculated.

The development and use of linear free-energy relationships represents one of the more significant contributions to organic chemistry since it has provided a critical test for, and facilitated the elucidation of, reaction mechanisms. Hammett,<sup>2</sup> utilizing the extensive data on the ionization constants of benzoic acids, defined parameters ( $\sigma$ -values) for each functional group which reflected its electronic influence at a reaction site either *meta* or *para* to it in a benzene ring; these  $\sigma$ -values were recognized as being compounded of both resonance and inductive effects which could act to reinforce or oppose each other.

Recently Taft<sup>3</sup> and his co-workers have devoted considerable effort to separating the inductive and resonance contributions of a group to the Hammett  $\sigma$ -value and have been able to calculate  $\sigma_I$  constants<sup>4</sup> which denote the portion of  $\sigma$  which is due solely to the inductive influence of a group. These values are certainly qualitatively correct and have at least a semiquantitative significance as demonstrated by the existence of a "linear inductive free-energy relationship" for a diverse series of reactions.<sup>4-6</sup> The reso-

nance contribution to  $\sigma$  can then be obtained by subtracting  $\sigma_I$  from  $\sigma$ . As the resonance interaction of a substituent with the aromatic ring is inhibited, it is to be expected that the apparent  $\sigma$ -value should approach  $\sigma_I$  as a limit.<sup>7</sup> To assess the experimental significance of Taft's parameters we have initiated a study of the variation of electronic influences of substituents with steric environment and now wish to report on the ionization constants of 3,5-dimethyl 4-substituted benzoic acids.

### Experimental

Most of the compounds in question were prepared by appropriate modifications of procedures in the literature and were assayed for purity by spectral methods and neutralization equivalents. Melting points are uncorrected.

**3,5-Dimethyl-4-nitrobenzoic Acid.**—To a 1-l. three-neck flask fitted with a stirrer, dropping funnel, and condenser were added 64 g. (0.38 mole) of nitromesitylene,<sup>8</sup> 300 ml. of glacial acetic acid, and 80 ml. of concentrated sulfuric acid. The mixture was heated to reflux and 120 g. of chromic acid in 400 ml. of water was added at such a rate that a moderate reflux was maintained. After the addition was completed, stirring at reflux was continued for an additional 30 min. and then the reaction mixture was poured onto 750 g. of ice. The crystals were suction filtered from solution, washed well with water, and transferred to a beaker

(1) This work is abstracted from the thesis of Terrence J. Miraglia, presented to the graduate college at the University of Arizona in partial fulfillment of the requirements for the Master of Science degree.

(2) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII.

(3) R. W. Taft in "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13; R. W. Taft, *J. Phys. Chem.*, **64**, 1803 (1960), and papers cited therein.

(4) R. W. Taft and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958).

(5) J. L. Roberts and H. H. Jaffé, *ibid.*, **81**, 1635 (1959).

(6) Application of the linear inductive free-energy relationship,  $\log$

$k_m/k_o = \alpha \log k_p/k_o - \sigma_I(\rho_I^m - \alpha\rho_I^p)$ , is complicated by the assignment of an appropriate value to  $\alpha$  which is a weighting factor indicating the degree to which resonance of a *m*-substituent with the aromatic ring affects the electron density at the reaction site with which it is not necessarily conjugated. In addition it must be assumed that  $\rho_I^m = \rho_I^p$  and that inductive effects of groups in the *m* and *p* positions are equal (these are probably good first approximations). The utility of the equation is limited.

(7) R. W. Taft and H. D. Evans, *J. Chem. Phys.*, **27**, 1427 (1957).

(8) G. Powell and F. R. Johnson in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 449.

TABLE I  
 IONIZATION CONSTANTS OF 4-SUBSTITUTED 3,5-DIMETHYLBENZOIC ACIDS<sup>a</sup>

4-Substituent	$pK_a$	$\sigma^b$	$\Sigma\sigma^c$	$\Delta\sigma^d$	$\sigma_R^e$	$\sigma - \Delta\sigma^f$	$\sigma_I$
N(CH <sub>3</sub> ) <sub>2</sub>	6.23	-0.83	-0.97	-0.63	-0.93	-0.20	+0.10
NH <sub>2</sub>	6.88	-.66	-.80	-.03	-.76	+.63	+.10
NHCOCH <sub>3</sub>	5.68	.00	-.14	-.16	-.28	+.16	+.28
OH	6.47	-.37	-.51	0	-.62	-.37	+.25
OC <sub>2</sub> H <sub>5</sub>	6.02	-.24	-.38	-0.18	-.49	-.06	+.25
Cl	5.59	+.227	+.09	0	-.24	+.23	+.47
Br	5.55	.232	+.09	0	-.22	+.23	+.45
CO <sub>2</sub> CH <sub>3</sub>	5.44	.45	+.31	0.13	+.15	+.32	+.30
CN	4.90	.660	.52	0	.08	+.66	+.58
NO <sub>2</sub>	4.91	.778	.64	0.11	.15	+.67	+.63
Benzoic acid	5.71	.000					

<sup>a</sup> All measurements are in 50 volume % ethanol and are uncorrected for liquid junction potentials. <sup>b</sup> Ref. 14. <sup>c</sup>  $\Sigma\sigma$  was obtained by adding the  $\sigma$ -value for the 4-substituent to -0.138 to correct for the two *m*-methyl groups. <sup>d</sup>  $\Delta\sigma$  was obtained by subtracting from  $\Sigma\sigma$  the value of  $\Sigma\sigma$  predicted from the slope of the line ( $\rho = 1.522$ ) and the  $pK_a$  of the acid. <sup>e</sup> These values were obtained by subtracting  $\sigma_I$  values (ref. 4) from  $\sigma$ . <sup>f</sup>  $\sigma - \Delta\sigma$  is the "effective  $\sigma$ -value" for the group in the above molecule.

containing 100 ml. of 10% sodium hydroxide solution to dissolve the acidic components. Filtration gave unreacted starting material which was steam distilled for further use.

Acidification of the filtrate with concentrated hydrochloric acid and cooling precipitated the crude acid which, after repeated recrystallizations from 95% ethanol, gave 8-15 g. of light yellow crystals, m.p. 225.5-227° (lit.<sup>9</sup> 214-220°).

**3,5-Dimethyl-4-aminobenzoic acid** was prepared by reduction of the nitro compound in ethanol using 5% rhodium-on-charcoal in a Parr shaker. After crystallization from 95% ethanol the long white needles had m.p. 257-257.5° dec. (lit.<sup>9</sup> 242°).

**3,5-Dimethyl-4-acetaminobenzoic acid** was prepared by refluxing the amine for 24 hr. in benzene with an excess of acetic anhydride, the product being crystallized from 95% ethanol; m.p. 270-272.5°.

**3,5-Dimethyl-4-dimethylaminobenzoic acid** was prepared by alkylating the amine with 40% aqueous formaldehyde and formic acid to give colorless crystals, m.p. 186.5-190.5° dec., from 95% ethanol.

**3,5-Dimethyl-4-bromobenzoic acid** was prepared by diazotizing the amine and decomposing the diazonium salt with cuprous bromide. Purification by recrystallization from 95% ethanol gave the desired product, m.p. 219.5-220.5° (lit.<sup>10</sup> 214-215°).

**3,5-Dimethyl-4-chlorobenzoic acid** was prepared from the above diazonium salt and cuprous chloride. The product was a white crystalline compound, m.p. 217.5-218.5° (lit.<sup>11</sup> 220° dec.).

**3,5-Dimethyl-4-cyanobenzoic acid** was prepared from the above diazonium salt and cuprous cyanide solution. The product had a m.p. 216.5-218°.

**3,5-Dimethyl-4-hydroxybenzoic acid** was obtained by decomposition of the diazonium salt in the presence of hot dilute sulfuric acid; m.p. 226.5-227.5° (lit.<sup>12</sup> 218°).

**3,5-Dimethyl-4-ethoxybenzoic acid** was prepared by alkylating the phenol with ethyl iodide in the presence of sodium carbonate which, after work-up and crystallization gave a white product, m.p. 186-188°.

**3,5-Dimethyl-4-carbomethoxybenzoic acid** was prepared by the method of Feist<sup>13</sup> and recrystallized from water; m.p. 152.5-154° (lit.<sup>13</sup> 154°).

**Determination of  $pK_a$ 's.**—The samples to be studied were dried at 50° for 24 hr. at 4-7 mm. pressure. Duplicate determinations were made on each compound and good agreement of values was obtained. Neutralization equivalents corresponded in all cases to the calculated values.

In a typical determination, a Teflon-covered magnetic stirring bar and 50-125 mg. of sample were placed in the titrating vessel. Exactly 50 ml. of anhydrous ethanol was pipetted into the titrating vessel and the sample was allowed to dissolve. As soon as solution of the sample was complete, 50 ml. of ion-free water was pipetted into the titrating vessel. The potentiometric titrations were followed on a Beckman Model G pH meter, standardized before each run with Beckman pH 4 buffer. After each addition of base, an equal volume of anhydrous alcohol was added before the pH was recorded. The solutions were constantly stirred and all titrations were carried out at 25°.

Carbonate-free sodium hydroxide was used as titrant. It was standardized by titrating against potassium acid phthalate samples in 50% ethanol solution. The  $pK_a$  values were determined graphically and checked numerically by using the data around the half-neutralization point. Values listed in Table I

are apparent  $pK_a$  values uncorrected for liquid junction potentials.

## Discussion

Table I summarizes the apparent  $pK_a$  values of the compounds studied in the solvent system 50% ethanol-water at 25°. These data are plotted as a function of  $\Sigma\sigma$  in Fig. 1 and a line corresponding to  $\rho = 1.522$  has been drawn through the value measured for benzoic acid.<sup>14</sup>

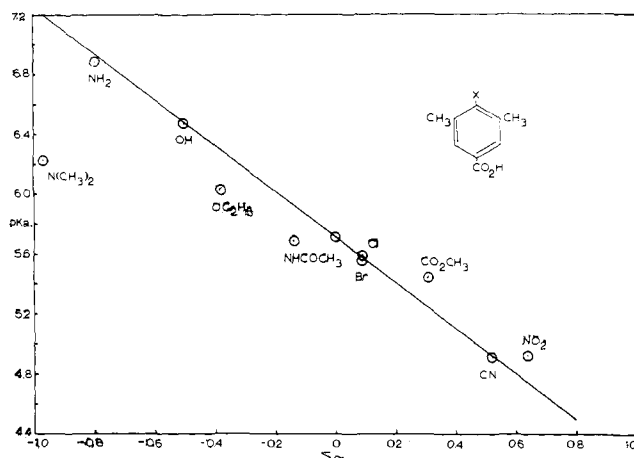


Figure 1.

A necessary criterion for the application of the Hammett equation for quantitative evaluation of substituent effects is that the  $\sigma$ -values for "normal substituents" be additive. That this is so can be seen by the proximity of the 4-bromo, 4-chloro, and 4-cyano compounds to the line defined by the simple benzoic acids. Since the halogens and the cyano group extend linearly from the benzene ring and since the electron distribution around these groups is symmetrical, no steric hindrance to resonance should be observed; therefore these are called "normal substituents."<sup>15</sup>

More noteworthy is that, within experimental error, the 4-hydroxy and 4-amino compounds show no deviation from the predicted acidities. These facts can be related to the steric requirements of the proton.

It is obvious that the major factor controlling the electronic influence of the hydroxyl and amino substitu-

(14) This value has been adopted on the recommendation of D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958), from their reevaluation of  $\sigma$ -constants based only on the ionization constants of benzoic acids and the available data pertaining to the ionization constants of benzoic acids in 50% ethanol-water.

(15) Similar behavior of these groups under related circumstances has been noted by other workers: e.g., G. W. Wheland, R. M. Brownell, and E. C. Mayo, *J. Am. Chem. Soc.*, **70**, 2492 (1948).

(9) H. L. Wheeler and C. Hoffman, *Am. Chem. J.*, **44**, 118 (1910).

(10) H. J. Schmitz, *Ann.*, **193**, 174 (1878).

(11) R. Fittig and S. Hoogewerff, *ibid.*, **150**, 325 (1869).

(12) J. Thiele and H. Eichwede, *ibid.*, **311**, 372 (1900).

(13) F. Feist, *ibid.*, **433**, 61 (1923).

ents in the  $p$ -position to a reaction center is its resonance interaction with that center (for  $\text{NH}_2$ ,  $\sigma_p = -0.66$ ,  $\sigma_I = +0.10$ ,  $\sigma_R = -0.76$ ; for  $\text{OH}$ ,  $\sigma_p = -0.37$ ,  $\sigma_I = 0.25$ ,  $\sigma_R = -0.62$ ). From the excellent correlation of the observed and predicted  $\text{p}K_a$  values for the acids bearing these substituents we can conclude that steric hindrance to resonance, and therefore to free rotation about the C-X bond, is negligible in these compounds. These data also add convincing evidence to the arguments of Hammond<sup>16</sup> and Wepster<sup>17</sup> in their contention that B-strain is not an important factor in determining the basicities toward a proton of aromatic amines<sup>18</sup> of this type since it is probable that the steric requirements for the anilinium ion are not significantly different from that of aniline itself.<sup>17</sup>

For the 4-nitro and 4-carbomethoxy derivatives we would expect the acids to be weaker than the value predicted from a simple summation of  $\sigma$ -constants since the substituents are comparatively large and steric interactions with the  $o$ -methyl groups should be sufficient to prevent coplanarity of the substituent and the ring, thereby diminishing possible resonance interactions. In Table I the  $\Delta\sigma$  values for these substituents, which reflect the degree of steric inhibition of resonance, lie rather close to the values predicted by Taft's<sup>3</sup>  $\sigma_R$  values; that is  $\sigma - \Delta\sigma$ , the "effective  $\gamma$ -value" for the substituents flanked by two  $o$ -methyl groups approaches  $\sigma_I$ . A value of  $+0.68$  can be calculated for the "effective  $\sigma$ -value" of the nitro group from the data of Westheimer and Metcalf<sup>19</sup> on the saponification rate of ethyl 3,5-dimethyl-4-nitrobenzoate; this compares well with the value determined in this investigation ( $+0.67$ ).

Since the dimethylamino group is a powerful electron donor, steric inhibition of resonance should result in a pronounced increase in the acidity of 3,5-dimethyl-4-dimethylaminobenzoic acid above the calculated normal value. Examination of Fig. 1 indicates that it is a stronger acid by about one  $\text{p}K_a$  unit, a dimethylamino group having an "effective  $\sigma$ -value" of  $-0.20$  compared to  $-0.83$  for this group in a normal environment; however, this still differs significantly from the  $\sigma_I$  value of  $+0.10$ .

From the data available on the rate of saponification of ethyl 3,5-dimethyl-4-dimethylaminobenzoate,<sup>19</sup> Taft<sup>3</sup> has estimated the "effective  $\sigma$ -value" of the dimethylamino group to be  $-0.11$ . The discrepancy between  $-0.20$  and  $-0.11$  would correspond to a combined experimental error of 60% which is unreasonable in view of the agreement obtained with the nitro compound and, therefore, we believe that this difference is real.<sup>20</sup> An explanation for this discrepancy which we favor is as follows.

In Table II we have calculated the angle of twist ( $\theta$ ) of the conjugating orbitals of the hindered substituent with the plane of the  $\pi$ -electrons of the benzene ring, using the assumption that the fraction of steric hindrance of resonance measured by  $\Delta\sigma/\sigma_R$  is a function of  $\cos^2 \theta$ .<sup>21</sup>

From the data in Table II relating to the ultraviolet absorption spectra it appears that the angle of twist of a particular group is a function of the electron demand or enriching ability of the substituent with which it is

TABLE II<sup>7,17,22</sup>

Entry <sup>d</sup>	Group	$\Delta\sigma/\sigma_R$	$\cos^2 \theta$	$\theta$
1	N(CH <sub>3</sub> ) <sub>2</sub>	0.63/0.98	0.68	56°
2	N(CH <sub>3</sub> ) <sub>2</sub>	0.72/0.93	0.75	62
3	N(CH <sub>3</sub> ) <sub>2</sub>			59
4	N(CH <sub>3</sub> ) <sub>2</sub>			64
5	N(CH <sub>3</sub> ) <sub>2</sub>			68
6	NO <sub>2</sub>	0.11/0.15	0.73	59
7	NO <sub>2</sub>	0.10/0.15	0.67	55
8	NO <sub>2</sub>			56
9	NO <sub>2</sub>			60
10	NO <sub>2</sub>			66
11	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	0.13/0.15	0.87	69
12	OC <sub>2</sub> H <sub>5</sub>	.18/ .49	.37	37
13	NHCOCH <sub>3</sub>	.16/ .28	.57	49
14	NH <sub>2</sub>	.03/ .76	.04	11

<sup>a</sup> Source of data: 1,  $\text{p}K_a$  of 3,5-dimethyl-4-dimethylaminobenzoic acid; 2, saponification of ethyl 3,5-dimethyl-4-dimethylaminobenzoate; 3, ultraviolet spectrum of 3,5-dimethyl-4-dimethylaminobenzene; 4, ultraviolet spectrum of ethyl 3,5-dimethyl-4-dimethylaminobenzoate; 5, ultraviolet spectrum of N,N-dimethyl-2,6-xylidene; 6,  $\text{p}K_a$  of 3,5-dimethyl-4-nitrobenzoic acid; 7,  $\text{p}K_a$  of 3,5-dimethyl-4-nitroaniline or saponification of ethyl 3,5-dimethyl-4-nitrobenzoate; 8, ultraviolet spectrum of 3,5-dimethyl-4-nitroaniline; 9, ultraviolet spectrum of nitrobenzylidene; 10, ultraviolet spectrum of 2,6-dimethylnitrobenzene; 11-14, this investigation on ionization constants of acids.

partially conjugated. To illustrate, for the nitro group the angles of twist decrease (steric interactions with the  $o$ -methyl groups increase) as the electron donating ability of the  $p$ -substituent increases ( $\text{NH}_2 > \text{CH}_3 > \text{H}$ ; entries 8, 9, and 10). This indicates that the increase in steric repulsion energy accompanying the decreased angle of twist is compensated for by the gain in extra resonance energy arising from the increased conjugation possible between  $p$ -substituents. Similar arguments apply for the dimethylamino group (entries 3, 4, and 5).

In entries 1 and 2 the calculations suggest that the average angle of twist for the dimethylamino group is greater in the ester than in the acid; although this is more difficult to rationalize, we believe that the implications of this result can be justified. If, as a first approximation, we assume that resonance interactions of electron donor substituents with the carboxylate ion and the transition state for ester hydrolysis are negligible, the differences in the angle of twist calculated for the dimethylamino group from these two reactions can be related to the electron demand of the reacting functions of the starting materials (the acid and the ester). These assumptions appear to be reasonable since the carboxylate ion has a negative charge and the transition state for ester hydrolysis is probably close to saturated.<sup>23</sup>

Although  $\sigma$ -values for the carboxylic acid group are unreliable,<sup>14</sup> the electron demand of this group should be greater than that of the carbomethoxy group since alkyl substituents are better electron donors than hydrogen; this should result in a smaller angle of twist (more steric compression, more resonance interaction) in the acid. Similar arguments would lead to the prediction of the observed order in examples 6 and 7 but, owing to the magnitude of the numbers involved in the calculations, these results are probably not significant.

The remaining groups (ethoxy and acetamino) both show deviations in the expected direction and are stronger acids than would be predicted simply on the basis of the  $\Sigma\sigma$  value. The deviation is again due to steric inhibition of resonance, although the effect is

(16) G. S. Hammond in "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 9.

(17) B. M. Wepster, *Rec. trav. chim.*, **76**, 357 (1957).

(18) H. C. Brown and A. Cahn, *J. Am. Chem. Soc.*, **72**, 2939 (1950).

(19) F. H. Westheimer and R. P. Metcalf, *ibid.*, **63**, 1339 (1941).

(20) Since  $\rho = 2.31$ , the predicted relative rates of saponification for  $\sigma = -0.20$  would be  $\log k'/k_0 = 0.46$ . The actual value determined experimentally (55%) and used to calculate the "effective  $\sigma$ -value" of  $-0.11$  was  $\log k'/k_0 = 0.26$ . The difference between these values (0.20 log unit) corresponds to a ratio of rates of 1.6:1 or an error of the order of 60%.

(21) H. B. Klevans and J. R. Platt, *J. Am. Chem. Soc.*, **71**, 1714 (1949).

(22) B. M. Wepster, *Rec. trav. chim.*, **76**, 335 (1957).

(23) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951).

much smaller in these cases than for the nitro, carbethoxy, or dimethylamino groups. The angles of twist of 37 and 49°, respectively, seem reasonable, but it is difficult to discuss the behavior of these groups in more detail since the geometry of the groups and of the conjugating orbitals is open to question.

A further significant feature of Table II is the demonstration that the resonance interaction, as reflected by  $\sigma$ , of a functional group with a second substituent is a variable parameter which is very sensitive to the nature of the second substituent and the reaction process in question. For this reason it is impossible to assign a single  $\sigma$ -value to a group which can be used successfully to correlate all reaction data through the Hammett equation, as Wepster<sup>24</sup> has demonstrated.

Since the real value of the Hammett equation is not in correlating rate data but rather in elucidating reaction mechanisms, we feel that most applications of the Hammett equation should use only the  $\sigma$ -values based on the ionization constants of benzoic acids<sup>15</sup> and that investigators should then concentrate their efforts on analyzing the correlation or lack of correlation observed rather than defining new  $\sigma$ -values in an effort to obtain a straight line.

**Acknowledgment.**—The authors wish to thank the California Research Corporation for partial support of this work.

(24) H. von Békum, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.*, **78**, 815 (1959).

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## Mass Spectra of O-Isopropylidene Derivatives of Pentoses and Hexoses<sup>1,2</sup>

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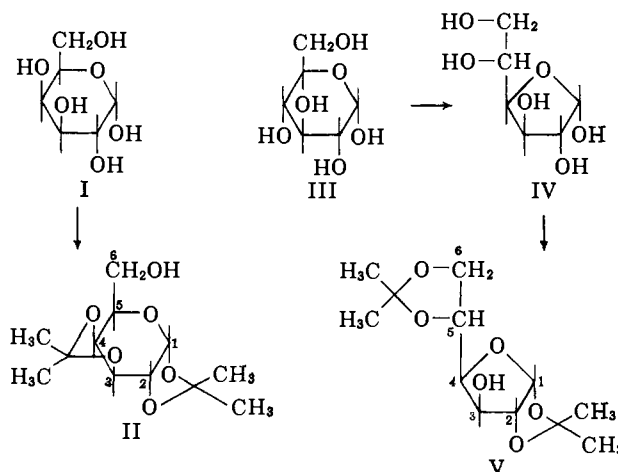
RECEIVED AUGUST 6, 1963

The mass spectra of O-isopropylidene derivatives of D-glucose, D-galactose, D-mannose, D-fructose, L-sorbose, L-arabinose, L-fucose, D-xylose, D-ribose, and D-lyxose are interpreted and their relationships to the stereochemistry of the parent monosaccharides are discussed. Both isotopic labeling and high resolution mass spectrometry are used to corroborate the proposed fragmentation mechanisms. As an application of the technique, the determination of the structure of a new di-O-isopropylidene derivative of D-galactose is presented.

The mass spectra of polyacetates of pentoses and hexoses,<sup>3</sup> of acetates of partially methylated derivatives thereof,<sup>4</sup> and of polymethyl ethers of monosaccharides<sup>5</sup> have recently been reported and interpreted. It was shown that it is possible to deduce from these spectra molecular weight and ring size of the compound, and, in the case of the O-methyl derivatives, also number and position of the methoxyl groups present in the molecules.<sup>3,4</sup> The spectra of these polyacetates are, however, very insensitive with respect to the stereochemistry of the molecule. This is not surprising as the only difference, for example, among the various epimeric aldohexopyranose pentaacetates is the spatial relationship between substituents attached *via* a single bond to the tetrahydropyran ring. The ensuing steric repulsions—or attractions—are, however, much too weak to lead to appreciable differences in the electron-impact-induced fragmentation of the molecule and thus in the mass spectrum. The differences which can be observed are too small to permit interpretations in terms of the stereochemistry, beyond direct comparison with the spectrum of an authentic sample.

Isopropylidene derivatives appeared to be much more promising in this respect,<sup>6</sup> as the formation of such a bi- or tricyclic ring system is greatly dependent on the availability of *cis*-1,2- or *cis*-1,3-diol systems.<sup>7</sup> Thus epimers may give isopropylidene derivatives which differ in actual bonding and are no longer merely stereoisomers but structural isomers; it is the latter to which mass spectrometry is very sensitive. As a well known

example, the case of D-galactose and D-glucose may be cited. While the former, in the  $\alpha$ -pyranoid form I, has two pairs of *cis*-1,2-diol groupings and therefore forms mainly a pyranoid 1,2:3,4-di-O-isopropylidene derivative (II),<sup>7</sup> D-glucopyranose has only one *cis*-diol group in the  $\alpha$ -form III (none in the  $\beta$ -form). The otherwise less favorable furanoid  $\alpha$ -isomer IV, on the other hand, is capable of reacting with two moles of acetone to form 1,2:5,6-di-O-isopropylidene-D-glucofuranose (V).<sup>7</sup> Similarly, D-mannose forms an isomeric di-O-isopropylidene-furanose (XXV).<sup>7</sup>



Comparison of isomers II and V reveals that—in contrast to I and III, or their pentaacetates (—OCOCH<sub>3</sub> instead of —OH)—the covalent bonds are arranged in a very different way. Of particular importance is the C-4, C-5 bond in V, a single bond connecting two parts of the molecule. Its cleavage, especially favorable because of the strong stabilization of the resulting positive charge on either C-4 or C-5 by the adjacent oxygen atom, is mainly responsible for the great difference in the mass spectra of V and II (Fig. 1 and 2).

While a situation similar to the one present in galactose (I) exists in  $\beta$ -L-arabinopyranose (VI), which also

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