Effect of Substituents at the 5-Position on the First and Second Dissociation Constants of Isophthalic Acid

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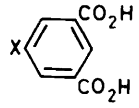
The dissociation constants of benzoic acid and 20 of its *meta*- or *para*-substituted derivatives and of isophthalic acid and ten of its 5-substituted derivatives have been measured in 50 wt % aqueous methanol. The Hammett ρ value for benzoic acid is 1.28; for isophthalic acid the ρ values are 1.21 (pK_1) and 1.20 (pK_2). The σ_{meta} values for hydroxy and acetoxy are −0.01 and +0.29, respectively, in this system. Values for σ_{meta} for CO_2H and CO_2^- are calculated to be +0.28 and −0.20, respectively; however there are indications that these values are not completely structure-independent.

In connection with other work we needed to know the effect of substituents at the 5-position on the first and second dissociation constants of isophthalic acid (1). The acid (1) and its 5-substituted derivatives constitute one of the few sets of diprotic acids in which the ionizing groups are effectively isolated from one another and in which the substituent is equidistant from the acidic centres. A great deal of attention has been given in the past to the ionization of isophthalic acid itself, but few of its derivatives have been examined. We have accordingly measured the p*K* values of a number of such compounds along with those for a series of benzoic acids in 50 wt % aqueous methanol, one of the two solvent systems which Eberson enjoined investigators to use when determining the strengths of carboxylic acids in media other than pure water.[1]



(1)

Experimental

(a) *Synthesis*.—The benzoic acids were either obtained commercially or prepared by standard procedures, as were isophthalic acid and its 5-hydroxy, 5-methyl, 5-nitro, 5-methoxy,[2] 5-acetamido,[3] 5-iodo,[4] and 5-chloro [5] derivatives.

5-*Bromoisophthalic acid*. Dimethyl 5-aminoisophthalate (2 g) in 50% methanol–6M-sulphuric acid (50 cm^3) was diazotized with sodium nitrite (2 g) in water (20 cm^3). After stirring at room temperature for 0.5 h, the diazonium salt solution was added to a solution of freshly prepared copper(I) bromide in 48% hydrobromic acid. The mixture was refluxed for 15 min. The solution was neutralized with sodium hydroxide and filtered while hot. The yellow filtrate was reacidified with hydrochloric acid (s.g. 1.18) producing a pale yellow precipitate. The solid was dissolved in 10% sodium hydroxide solution (15 cm^3) and then precipitated with hydrochloric acid and recrystallized from ethanol–water to give cream-coloured needles of 5-*bromoisophthalic acid* (40%), m.p. 281—283 °C (Found: C, 39.1; H, 2.1; Br, 32.45. $C_8H_5BrO_4$ requires C, C, 39.2; H, 2.05; Br, 32.6%).

5-*Fluoroisophthalic acid*. 3,5-Dimethylaniline (19.4 g) was diazotized in methanolic 48% tetrafluoroboric acid with aqueous sodium nitrite (12 g). The dried tetrafluoroborate diazonium salt was then thermally decomposed and the residue taken up in diethyl ether, washed, and dried. The ether was removed and the remaining 1-fluoro-3,5-dimethylbenzene distilled (at 144—145 °C and 750 mmHg). This product (2 g) was refluxed with potassium permanganate (8 g) and potassium carbonate (5 g) in water (70 cm^3) for 70 h [with additional potassium permanganate (6 g) after 30 h]. The manganese dioxide was filtered from the hot mixture, which was then cooled and acidified with hydrochloric acid. The precipitated solid was filtered off and recrystallized from water to give needles of 5-*fluoroisophthalic acid*, m.p. 298—301 °C (overall yield 10%) (Found: C, 52.4; H, 2.7. $C_8H_5FO_4$ requires C, 52.2; H, 2.75%); δ_H [$(CD_3)_2SO$] 7.94 (2 H, dd, 4- and 6-H, J_{HH} 2, J_{FH} 9 Hz) and 8.34 (1 H, t, 2-H, *J* 2 Hz); δ_F one triplet, J_{FH} 9 Hz.

5-*Acetoxyisophthalic acid*. 5-Hydroxyisophthalic acid (1 g) was heated in acetic anhydride at 80 °C for 3 h. The excess of anhydride was removed and the residue recrystallized from ethanol to give white crystals of 5-*acetoxyisophthalic acid* (30%), m.p. 238—240 °C (Found: C, 53.45; H, 3.8. $C_{10}H_8O_6$ requires C, 53.6; H, 3.6%).

(b) p*K Measurements*.—The dissociation constants of the isophthalic and benzoic acids were determined in 50% (w/w) methanol–water, with the concentration of the acids *ca.* 5×10^{-3}M. These were titrated with carbonate-free 0.195M-potassium hydroxide under nitrogen using a Radiometer Autoburette ABU1. The pH measurements were made with a Radiometer 26 pH meter which was standardized with aqueous buffer solutions.

The thermodynamic dissociation constants of the isophthalic acids were calculated using the method of Speakman [6] for overlapping p*K* values as adapted by Albert and Serjeant.[7] The ionization constants of the benzoic acids were calculated as described by Albert and Serjeant; [8] the concentrations of the ionic species were corrected by use of the corresponding activity coefficients, determined with Debye–Hückel constants, A and B, calculated using dielectric constant data reported for methanol–water systems by Albright and Gosting.[9] All calculations were carried out with an Apple II computer.

Since the calculations of the ionization constants were made using the pH meter reading, the p*K′* values obtained must be corrected by subtracting 0.11 to obtain the values shown in the Table, which refer to the true standard state p*K* value for this particular system.[10]

Results and Discussion

Benzoic Acid Dissociation in 50 *wt* % *Aqueous Methanol*.—The pK_{HA} values for dissociation of benzoic acids and 20 of its derivatives are listed in the Table. A Hammett plot [11] using σ values recommended by Perrin, Dempsey, and Serjeant [12]

Table. Dissociation constants of benzoic and 5-substituted isophthalic acids in 50 wt % aqueous methanol at 25 °C

	Benzoic acid		Isophthalic acid	
Substituent	*meta*	*para*	pK_1	pK_2
None	5.43	5.43	4.78	5.98
Acetoxy	5.02		4.43	5.68
Acetamido			4.61	5.91
Benzoyl		4.83		
Bromo	4.90	5.05	4.27	5.55
t-Butyl		5.61		
Chloro	4.91	5.09	4.27	5.57
Ethyl		5.62		
Fluoro	4.96		4.34	5.64
Hydroxy	5.41	5.82	4.79	6.08
Iodo		5.11	4.36	5.61
Methoxy	5.29	5.69	4.69	5.93
Methyl	5.51	5.63	4.86	6.12
Nitro	4.44	4.38	3.93	5.16
Phenyl		5.43		
Trifluoromethyl		4.72		

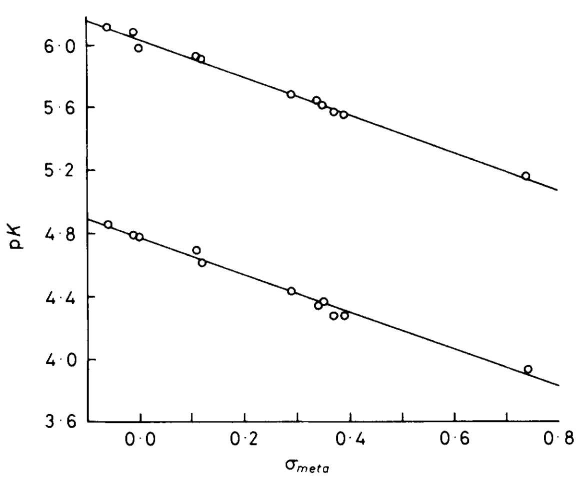


Figure. A plot of pK_1 (lower line) and pK_2 (upper line) for 5-substituted isophthalic acids in 50 wt % aqueous methanol against the Hammett *meta*-substituent constant; the ρ values are 1.21 (pK_1) and 1.20 (pK_2)

gives an excellent straight line except for the points for 3-hydroxy and 3-acetoxy, which were also anomalous in the case of the isophthalic acids discussed later. We have accordingly defined *meta*-substituent constants σ_m for these two groups by taking the values that would place them on the line. The values thus obtained are −0.01 for hydroxy and +0.29 for acetoxy; *cf.* +0.13 and +0.39 given by Perrin *et al.* (It is known that the substituent constant for the hydroxy group is solvent-dependent.[13])

The reaction constant ρ for the ionization of benzoic acid in 50 wt % methanol is 1.280; the correlation coefficient is 0.997 with the points for 3-hydroxy and 3-acetoxy omitted. This reaction constant is considerably larger than the value of 1.085 determined [14] from data obtained some considerable time ago.[15] The latter value appears anomalous in view of the values of 1.00 and 1.54 [14,16] found in pure water and methanol, respectively. (The value for 50% aqueous ethanol is roughly midway between those of the pure solvents.[17,18])

Dissociation of 5-Substituted Isophthalic Acids.—The pK_1 and pK_2 values for the dissociation of eleven isophthalic acids are given in the Table and are plotted against σ in the Figure. The ρ values for the first and second dissociations are virtually identical, 1.212 and 1.201, respectively. That is, a plot of pK_1 against pK_2 will be linear and of unit slope. This result has implications for other diprotic series, *e.g.* diazines, in which only one set, pK_1 or pK_2, may be readily accessible.

The ρ value for each of the isophthalic acid dissociations is fairly close to, but not identical with, that for benzoic acid dissociation, 1.28. (If only groups common to both series are used the discrepancy increases slightly.) Wepster has shown that charged substituents often fail conspicuously in Hammett correlations.[19,20] Our results show that the presence of a carboxylate unit does in fact have a small but real effect on ρ. However, its effect is identical, within experimental error, with that of the un-ionized carboxy group. If these two groups were perfectly behaved substituents the ρ values for all three dissociations would be identical; presumably, specific solvation effects of both groups are sufficient to cause their σ values to vary slightly as the substituent at the 3-position is altered. The σ values for CO_2^- and CO_2H are given by $\pm(\Delta pK - 0.30)/\rho$. Taking the pK values from the intercepts of plots of pK against σ gives $\sigma_m(CO_2H) = +0.28$ and $\sigma_m(CO_2^-) = -0.20$. Exner's tabulations [21] reveal a very wide range of reported values for the *meta*-CO_2^- group (+0.09 to −0.030), but much less variation for the *meta*-CO_2H group (recommended value +0.35), although the range of reported values of pK_1 for isophthalic acid suggests that this quantity is not firm.[22–27] Our results indicate that σ for both *meta*-carboxy and -carboxylate depends on the molecular environment.

Acknowledgements

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