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# *ORTHO* EFFECTS—V

## *ORTHO* EFFECTS IN THE IONIZATIONS OF BENZOIC ACIDS IN DIMETHYL SULFOXIDE–WATER MIXED SOLVENTS[1]

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**Abstract**—The p*Ka* values of *o*- and *p*-substituted benzoic acids have been determined in 35, 50, 65, 85, and 95 vol % DMSO–water mixed solvents potentiometrically and/or spectrophotometrically. The *ortho* effect is evaluated with the use of the equation, *Ortho* Effects ≡ log *K*(*ortho*) − log *K*(*para*), minima of the *ortho* effects being observed near 65 vol % DMSO. Variation of the *ortho* effect with the change of the solvent is discussed in terms of solvent dependence of steric effects. Importance of desolvation of the benzoate anions due to bulky *ortho* substituents is suggested with the aid of solubility data.

SINCE Taft[2] presented the general quantitative method to separate polar and steric effects of *ortho* substituents on rates and equilibria of benzene derivatives, only a few cases[3–4] have been found to fit the Taft's equation:

$$\log K/K_o = \rho^*\sigma_o^* + \delta E_s$$

Of the four parameters the polar substituent constants, $\sigma_o^*$, have attracted the most attention and various sets of $\sigma_o^*$ values have been presented which appear to be approaching a set of conclusive polar substituent constants,[5] although some ambiguities still remain. The steric terms, $\delta E_s$, however, attracted much less attention[5] no doubt due to their complexity[4] and to the complex influence of solvents. Probably this is the main reason why Taft's equation does not fit the ionization equilibria of *o*-substituted benzoic acids.

While this paper was in preparation, Charton[6,7] reported that effects of *ortho* substituents in the ionizations of benzoic acids and in the hydrolysis of their esters can be attributable solely to inductive (or field) and resonance effects without intervention of any detectable amounts of steric effects.

This paper reports the results of further progress after our preliminary work[8] and, together with the succeeding three papers,[9] gives some new aspects on the *ortho* effects in the ionizations of benzoic acids.

### RESULTS

In Table 1 are listed p*Ka* values of benzoic acids and indicators in 35, 65 and 95 vol % DMSO determined by the indicator–spectrophotometric method together with those in water and in DMSO reported in literature. The p*Ka* values determined by the potentiometric titration are listed in Table 2. Where comparison is possible, relative acidities, p*Ka* (benzoic acid) − p*Ka* (substituted benzoic acids), obtained from the both methods show excellent agreements.

The p*Ka* values of 2,4-dinitrophenol in 35, 65, and 95 vol % DMSO, from which the rest of p*Ka* values were determined successively, were determined according to the literature[15] and used without correction for activity coefficients because the magnitude of the correction was found to be negligible from the Debye–Hückel equation.*

TABLE 1. p*Ka* VALUES OF SUBSTITUTED BENZOIC ACIDS AND INDICATORS IN THE DMSO-WATER SYSTEM AT 25°

| Acids and Indicators | Water | 35 vol % DMSO | 65 vol % DMSO | 95 vol % DMSO | 100% DMSO[a] |
|---|---|---|---|---|---|
| D.N.P.[b] | 4·11[c] | 3·81 ($H_2SO_4$)[d] | 3·56 ($H_2SO_4$) | 4·53 ($H_2SO_4$) | 5·2[e] |
| *o*-OH | 3·00[f] | 2·99 (D.N.P.) | 3·49 (D.N.P.) | 5·64 (D.N.P.) | 6·9[g] |
| B.C.G.[h] | 4·90[g] | 4·87 (*o*-OH) | 5·03 (*o*-$NO_2$) | 6·36 (*o*-OH) | 7·4[g,e] |
| *o*-$NO_2$ | 2·17[i] | 2·89 (D.N.P.) | 4·06 (D.N.P.) | 6·93 (B.C.G.) | -- |
| *p*-$NO_2$ | 3·43[i] | 3·66 (D.N.P.) | 4·52 (B.C.G.) | 7·53 (B.C.G.) | 8·9[j] |
| *p*-CN | 3·54[k] | -- | -- | 7·70 (B.C.G.) | -- |
| *o*-I | 2·86[i] | -- | -- | 8·00 (B.C.G.) | -- |
| *o*-Br | 2·85[i] | -- | -- | 7·88 (B.C.G.) | -- |
| *o*-Cl | 2·94[i] | 3·65 (D.N.P.) | 4·80 (B.C.G.) | 7·96 (B.C.G.) | -- |
| B.T.B.[l] | 7·30[g] | -- | -- | 9·90 (*o*-Cl) | 10·2[g,e] |
| *o*-F | 3·27[i] | -- | -- | 8·08 (B.T.B.) | -- |
| *p*-I | 3·98[m] | -- | -- | 8·54 (B.C.G.) | -- |
| *p*-Br | 3·97[i] | -- | -- | 8·50 (B.C.G.) | -- |
| *p*-Cl | 3·97[i] | 4·36 (D.N.P.) | 5·26 (B.C.G.) | 8·54 (B.C.G.) | 10·1[j] |
| *p*-F | 4·14[i] | -- | -- | 8·78 (B.C.G.) | -- |
| H | 4·20[i] | 4·64 (D.N.P.) | 5·74 (B.C.G.) | 9·12 (B.C.G.) | 10·0[g]<br>11·0[j] |
| *o*-*t*-Bu | 3·53[n] | -- | 5·80 (B.C.G.) | 9·06 (B.C.G.) | -- |
| *o*-*i*-Pr | 3·64[n] | -- | -- (B.C.G.) | 9·17 (B.C.G.) | -- |
| *o*-Me | 3·91[i] | -- | 5·90 (B.C.G.) | 9·31 (B.C.G.) | -- |
| *p*-*t*-Bu | 4·40[i] | -- | 5·90 (B.C.G.) | 9·42 (B.C.G.) | -- |
| *p*-*i*-Pr | 4·35[i] | -- | -- | 9·43 (B.C.G.) | -- |
| *p*-Me | 4·37[i] | -- | 5·92 (B.C.G.) | 9·41 (B.C.G.) | -- |
| 2.6-$Me_2$ | 3·25[n] | -- | -- | 8·84 (B.C.G.) | -- |
| *o*-MeO | 4·09[i] | -- | -- | 9·40 (B.C.G.) | -- |
| *p*-MeO | 4·47[i] | -- | -- | 9·61 (B.C.G.) | -- |
| *p*-OH | 4·58[o] | 5·05 (B.C.G.) | 6·25 (B.C.G.) | 9·98 (B.C.G.) | -- |

[a] At 20–25° or at ambient temps.
[b] 2,4-Dinitrophenol.
[c] G. Schwarzenbach and R. G. Bates. *Helv. Chim. Acta* **37**, 1069 (1954).
[d] Reagents in the parentheses were used for the p*Ka* measurements.
[e] B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac and A. J. Parker, *J. Am. Chem. Soc.* **88**, 1911 (1966).
[f] J. F. J. Dippy, *J. Chem. Soc.* 2405 (1957).
[g] See Ref 15.
[h] Bromcresol green.
[i] J. F. J. Dippy, *Chem. Rev.* **25**, 151 (1939).
[j] C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.* **90**, 2821 (1968).
[k] S. Widequist, *Arkiv Kemi* **2**, 383 (1950).
[l] Bromthymol blue.
[m] J. M. Vandebelt, C. Hendrick and S. G. VandenBerg, *Analyt. Chem.* **25**, 726 (1954).
[n] J. F. J. Dippy, S. R. C. Hughes and J. W. Laxton, *J. Chem. Soc.* 1470 (1954).
[o] G. Briegleb and A. Bieber, *Z. Electrochem.* **55**, 250 (1951).

* Using the dielectric constant of DMSO (47),[16] the Debye–Hückel equation becomes $-\log f_{\pm} = 1{\cdot}1\sqrt{I}$ for 100% DMSO solvent. Since I = 0·0004, we obtain $-\log f_{\pm} = 0{\cdot}02$. For the mixed solvents $-\log f_{\pm}$ is expected to be less than 0·02, thus the correction must be less than 0·04.

The exact p*Ka* values of benzoic acids, HA, are calculated from the following equation including the activity coefficient term,

$$pKa(HA) = pKa(HIn) + \log(C_{A^-}/C_{HA}) - \log(C_{In^-}/C_{HIn}) + \log(f_{A^-} f_{HIn}/f_{In^-} f_{HA}).$$

Since the coefficient term is reasonably assumed to be nearly zero, the p*Ka* values in Table 1 were obtained directly without the correction. Fig 1 shows the correlation between the p*Ka* of benzoic acid and the solvent composition.

TABLE 2. p*Ka* VALUES OF SUBSTITUTED BENZOIC ACIDS DETERMINED BY THE POTENTIOMETRIC TITRATION AT 25°

| Acids | 35 vol % DMSO | 50 vol % DMSO | 65 vol % DMSO | 85 vol % DMSO |
|---|---|---|---|---|
| *o*-OH | -- | -- | ... | 5·91 |
| *o*-$NO_2$[a] | . | | 5·33 | 7·00 |
| *p*-$NO_2$[a] | - | 4·80 | 5·73 | 7·49 |
| *o*-I | . | 4·98 | 6·20 | 7·98 |
| *o*-Br | .. | 4·88 | 6·08 | 7·94 |
| *o*-Cl[a] | - | 4·93 | 6·01 | 7·90 |
| *o*-F | -- | 4·99 | 6·02 | 7·98 |
| *p*-I | | 5·44 | 6·51 | 8·39 |
| *p*-Br | . | 5·44 | 6·54 | 8·42 |
| *p*-Cl[a] | 4·87 | 5·48 | 6·50 | 8·42 |
| *p*-F | .... | 5·67 | 6·72 | 8·70 |
| H[a] | 5·15 | 5·87 | 6·97 | 8·97 |
| *o*-*t*-Bu | | 5·80 | 7·05 | 9·01 |
| *o*-*i*-Pr[a] | 5·04 | 5·90 | 7·07 | 9·04 |
| *o*-Me[a] | 5·17 | 6·03 | 7·15 | 9·22 |
| *p*-*t*-Bu | ... | 6·05 | 7·15 | 9·23 |
| *p*-*i*-Pr[a] | 5·33 | 6·03 | 7·16 | 9·17 |
| *p*-Me[a] | 5·31 | 6·07 | 7·17 | 9·22 |
| 2,6-$Me_2$ | | 5·46 | 6·78 | 8·80 |
| *o*-MeO[a] | 5·23 | 6·03 | 7·20 | 9·28 |
| *p*-MeO[a] | 5·45 | 6·18 | 7·33 | 9·41 |
| *p*-OH | | .. | 7·53 | 9·57 |

[a] The preliminary paper[8] reported the p*Ka* values of these substituted benzoic acids.

## DISCUSSION

*Effects of* p-*substituents.* Effects of *p*-substituents are well correlated with the Hammett equation, giving $\rho$ values of 1·24, 1·32, 1·55, 1·84 and 2·00 in 35, 50, 65, 85 and 95 vol % DMSO, respectively. This fact suggests that even in highly nonaqueous 95 vol % DMSO there occurs no anomaly so far as the effects of *p*-substituents are concerned. The deviations found in the Hammett correlations are the minor magnitudes in comparison with the solvent dependence of the *ortho* effects. The deviation of the OH group is comparable to that found in ethanol–water,[17] but much less than that found for 4-hydroxy-bicyclooctane-1-carboxylic acid in DMSO.[18]

*Estimation of* ortho *effects.* In the Taft equation,[2] $\log K/K_o = \rho^*\sigma_o^* + \delta E_s$, we may regard the $\rho^*\sigma_o^*$ term as the normal effects and the $\delta E_s$ term as the anomalous effects, or the *ortho* effects.* In the present and the subsequent papers the following

* V. Maremae (*Reakts. Sposobnost Org. Soedin.* **4** (1), 96 (1967)) has proposed similar equation to get the quantitative measure of the *ortho* effects and shown that the *ortho* effects for the basic hydrolysis of aryltosylates are considerably dependent upon solvents and temperature.

expression is used to define and estimate the *ortho* effects. *Ortho* effects $\equiv \log K(ortho) - \log K(para)$, because $\rho\sigma_p$[3,19–21] can be regarded nearly equal to $\rho^*\sigma_o^*$ and also because of its simplicity. In fact the authors have not noticed any significant difference between the two results derived from the above two definitions although they are somewhat different numerically.

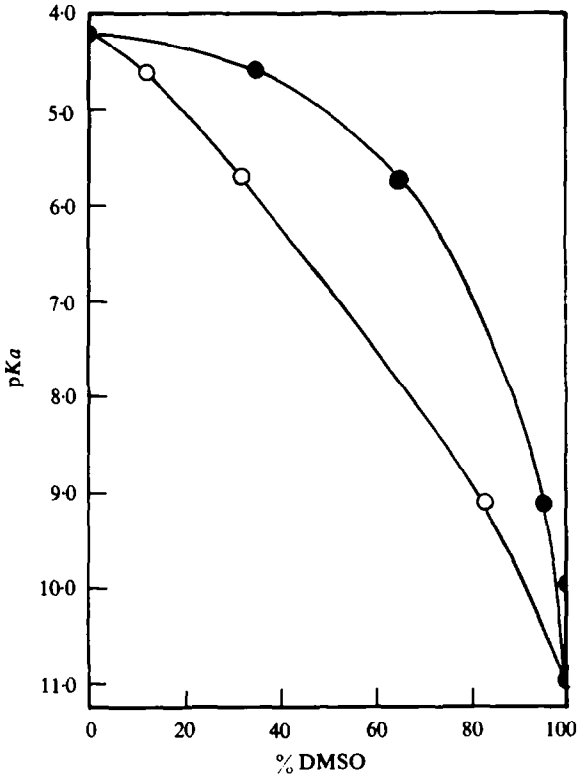


FIG 1. Plot of p*Ka* of benzoic acid against solvent composition. The solid circles correspond to vol % and the open to mole %.

*Influence of solvents on steric effects in* ortho *effects.* To investigate effects of steric origin involved in the *ortho* effects, alkyl groups were chosen because their polar effects are uniform and sufficiently small. As can be seen from Table 3 and Fig 2 the minimum points near 65 vol % DMSO are quite remarkable and the magnitudes of the decrease* and the increase in the *ortho* effects are enlarged as the bulkiness of alkyl groups become greater.

Desolvation of the benzoate anions due to the presence of bulky *ortho* substituents seems to be responsible for this decrease in *ortho* effects. This kind of desolvation should be more effective as the *ortho* substituents become bulkier and also would be enhanced on changing the solvent gradually from water to the less aqueous organic solvents because solvating power toward the acid anions is surely weakened in

* As for the similar decrease in *ortho* effects some data are reported[22–25] in other organic solvents.

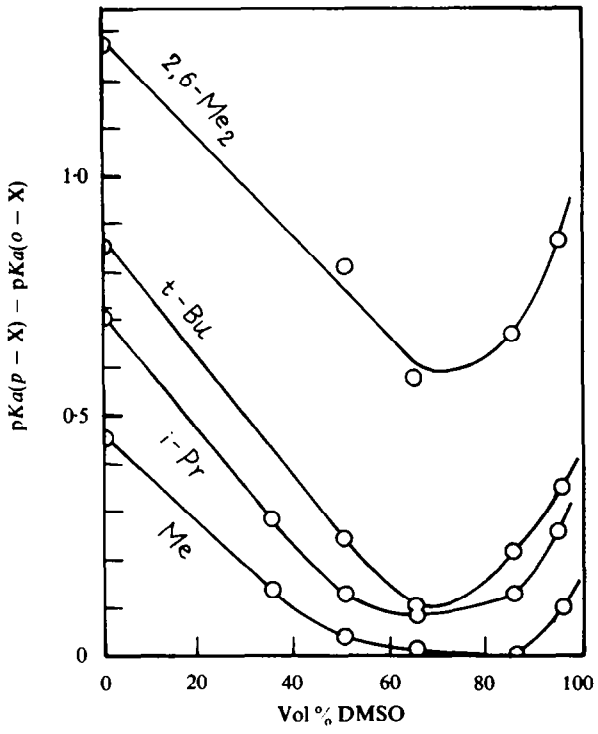


FIG 2. Plots of *ortho* effects for the alkyl groups against solvent composition.

accordance with this solvent change. Thus the inherently high acidities of the *ortho* substituted acids which are ascribable to the steric inhibition of resonance in the acid molecules are reduced gradually to minimize the observed *ortho* effects near 65 vol % DMSO.

Although the concept of steric inhibition to solvation has been used to interpret some ionization data,[26–29] further support[1] by check of its solvent dependence, physico-chemical data, etc., have never been given. We have two facts in favor of this

TABLE 3. ORTHO EFFECTS, p*Ka* (*p*-X) − p*Ka* (*o*-X), IN THE DMSO–WATER SYSTEM AT 25°

| Substituents | Water | 35 vol % | 50 vol % | 65 vol % | 85 vol % | 95 vol % DMSO |
|---|---|---|---|---|---|---|
| $NO_2$ | 1·26 | 0·76 | - | 0·46 | 0·49 | 0·60 |
| I | 1·12 | | 0·46 | 0·31 | 0·41 | 0·54 |
| Br | 1·12 | - | 0·56 | 0·46 | 0·48 | 0·62 |
| Cl | 1·03 | 0·71 | 0·55 | 0·46 | 0·52 | 0·58 |
| F | 0·87 | | 0·68 | 0·70 | 0·72 | 0·70 |
| Me | 0·46 | 0·14 | 0·04 | 0·02 | 0·00 | 0·10 |
| i-Pr | 0·71 | 0·29 | 0·13 | 0·09 | 0·13 | 0·26 |
| t-Bu | 0·87 | | 0·25 | 0·10 | 0·22 | 0·36 |
| 2,6-Me[a] | 1·29 | - | 0·81 | 0·59 | 0·67 | 0·86 |
| MeO | 0·38 | 0·22 | 0·15 | 0·13 | 0·13 | 0·21 |

[a] O.E. (2,6-$Me_2$) = p*Ka* (*p*-Me) + *pKa*(*p*-Me) − *pKa*(H) − *pKa*(2,6-$Me_2$).

interpretation. One is the solubility data which indicate the importance of the acid–anion solvation and are shown in the appendix of this paper and the other is the thermodynamic data to be reported.[9c]

Dippy *et al.*[22] and Davis *et al.*[24] interpreted this *ortho* effect–decreasing effect as being due to the resonance effect; recovery of the resonance between phenyl and carboxyl groups will be achieved as a result of the diminished solvation of the carboxyl group when the solvent is changed from water to aqueous or pure organic solvents. However, this interpretation does not account for our present results.

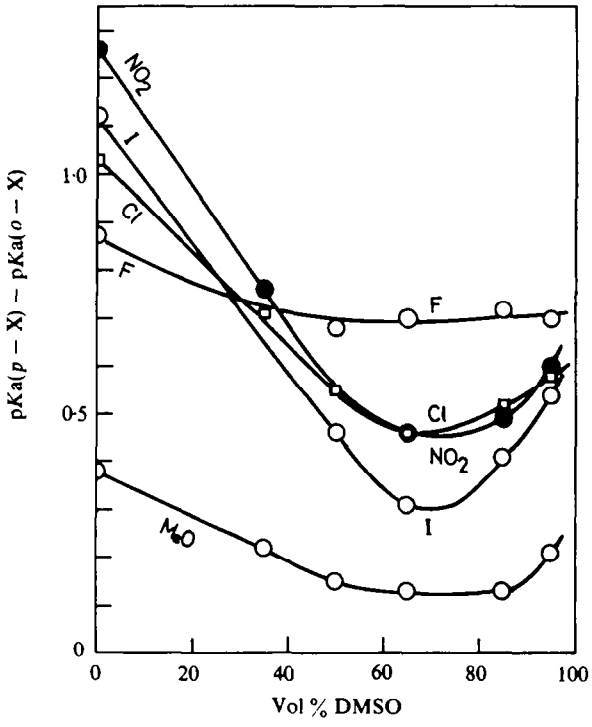


FIG 3. Plots of *ortho* effects for the polar groups against solvent composition.

Firstly, in view of the UV spectral data* of the related compounds it seems improbable that the resonance can recover to such an extent as to cause disappearance of almost all of the acid-strengthening *ortho* effects, which is the case for *o*-t-butyl- or *o*-i-propylbenzoic acids in 65% DMSO (Fig 2). Secondly, the solubility data in the appendix indicate that this solvent dependence is responsible for the acid anions and not for the acid molecules.

The *ortho* effects increase in the range from 65 to 100% DMSO.[8] Suppose two extreme solvents, one of which is excellent and the other is poor in solvating specifically

* The UV spectra of *o*-alkyl substituted nitrobenzenes clearly show the resonance inhibition due to the bulky ortho substituents (Me, i-Pr, t-Bu) in isooctane as well as in water.[30a] Similarly, the UV spectra of *o*- and *p*-toluic acids in cyclohexane show the existence of the resonance inhibition, although the magnitude is reduced considerably and the situation is complicated owing to the dimer formation.[30b]

the acid anions, for instance, by hydrogen bonding. Solvation by the former solvent would be too strong and by the latter too weak to differentiate the two acid anions, i.e. *ortho* substituted and *para* substituted benzoate anions. However, in those solvents of intermediate solvating power, e.g. in a mixture of the two extreme solvents, the two acid anions could be distinguished by the difference in the degree of the specific solvation, the acid anion with *ortho* substituents being less solvated by steric hindrance. This reasoning suggests that while steric inhibition to solvation occurs most efficiently in the solvents of the weakest solvating power it can be observed most evidently in the solvents of medium solvating power. This is probably the reason why the acid-strenghtening *ortho* effects increase again when DMSO content exceeds over 65%.

Similarly but by far the less obviously, these phenomena can be observed in ethanol–water[31] and dioxane–water[32] systems, too, the minimum points being situated 65 wt % ethanol and near 65 vol % dioxane, respectively.

*Influence of solvents on polar effects in* ortho *effects.* Fluorine may serve as a typical polar substituent since it is only a little bulkier than hydrogen and can be regarded as having essentially no steric effects.* The *ortho* effects for fluorine varies little in comparison with those for alkyls or other halogens when the solvent is changed from water to aqueous DMSO (Table 3 and Fig 3). This phenomenon may be interpreted as due to the absence of appreciable amounts of steric effects in the *ortho* effects for fluorine. Solvent effects observed for other halogens, nitro and methoxy substituents differ somewhat from those for alkyl substituents of comparable bulkiness (Table 3 and Figs 2 and 3). These phenomena may be due mainly to the change in field effect with the change of the solvent, as is more clearly shown in the cases for *o*-sulfinyl and *o*-sulfonio substituents which will be reported in the succeeding paper.[9a]

## EXPERIMENTAL

pKa *Measurements.*[10] The p*Ka* values in 35, 65 and 95 vol % DMSO were determined by the indicator–spectrophotometric method and those in 35, 50, 65 and 85 vol % DMSO were measured by the potentiometric titration.

*Indicator–spectrophotometric method.* Into 10 ml volumetric flasks 5 ml aliquots of the $5 \times 10^{-5}$ *M* 2,4-dinitrophenol soln were pipetted and the calculated volumes of 0·005 N $H_2SO_4$ were added from a microburet and the flasks were filled to the mark with the solvent. Thus 7 indicator solns of different hydrogen-ion concentrations were prepared to determine the ratios of the basic form, $In^-$, to the acidic form, HIn, spectrophotometrically. Into another 10 ml volumetric flask the alkaline soln was added instead of the $H_2SO_4$ soln to obtain the absorbance of the basic form. A Hitachi UV spectrophotometer (self-recording) was used to obtain the spectra between 360 and 500 mμ. The absorbance was determined by a Shimadzu QV-50 UV spectrophotometer (manual) using stoppered 1 cm length cells. The temp was measured by a thermistor dipped into the cell[11] and maintained at 25·0° ± 0·2° by circulating temp-controlled water through the jacket. Beer's law held for the indicator in the mixed solvent. The p*Ka* value of the indicator was calculated from the following equation.

$$pKa(HIn) = -\log C_{H^+} - \log(C_{In^-}/C_{HIn}).$$

where C denotes the concentration in mole $l^{-1}$. The six p*Ka* values calculated from the different hydrogen-ion concentrations corresponding to the range from $\log(C_{In^-}/C_{HIn}) = 0{\cdot}5$ to $-0{\cdot}5$ agreed within ±0·01 p*Ka* unit.

The p*Ka* values of substituted benzoic acids in the mixed solvents were determined from the general equation.

$$pKa(HA) = pKa(HIn) + \log(C_{In^-}/C_{HIn}) - \log(C_{A^-}/C_{HA}).$$

* Evidence is obtained from the UV spectra of *o*- and *p*-fluorobenzoic acids.[33]

In this case 7 values of the ratio ($C_{In^-}/C_{HIn}$) were taken in the substituted benzoate buffers ranging from ($C_{A^-}/C_{HA}$) = 8/2 to 2/8 which were prepared by adding the calculated amounts of carbonate-free KOH aq. The acid was weighed exactly and dissolved in a 50 ml volumetric flask together with the indicator. The acid concentration was 0·25 ~ 1 × $10^{-2}$ *M* and the indicator concentration was 1 ~ 5 × $10^{-5}$ *M*. The ratios of ($C_{A^-}/C_{HA}$) were determined stoichiometrically and corrected for acid ionization if necessary, assuming an appropriate p*Ka* value. The correction was found to be necessary when the p*Ka* value was smaller than about 5·5 at the acid concentration of 0·25 × $10^{-2}$ *M*. The correction for the acid ionization was done as follows:

$$\mathrm{HA} \overset{K}{\rightleftharpoons} \mathrm{H^+} + \mathrm{A^-}$$

$$a(1 - x - y) \quad ax \quad a(x + y)$$

where *a* denotes the initial concentration of an acid, *x* the degree of ionization for the acid, *y* the degree of neutralization and *K* the ionization constant. Therefore,

$$ax^2 + (ay + K)x - (1 - y)K = 0.$$

Since *a* is a constant and *y* is varied only from 0·2 to 0·8, *x* can be calculated for various *K* values.

The p*Ka* values of less acidic indicators such as bromcresol green (B.C.G.) and bromthymol blue (B.T.B.) were determined in buffers of appropriately substituted benzoic acids.

*Potentiometric titration.* The p*Ka* values were obtained from the p*H* readings at the half-neutralization point on titration curves. The acid concentration was 1 × $10^{-3}$ *M* and the alkaline titrant was 1 × $10^{-2}$ M in the mixed solvents. This simplified method was not applicable to strong acids in 35, 50 and 65 vol % DMSO on account of acid ionization. The reproducibility of the measured p*Ka* was within ±0·02 p*Ka* unit. The p*H*-meter and other accessories will be described in the succeeding paper.[9b]

*Solvents.* DMSO was dried over molecular sieves and distilled under $N_2$ at a pressure of a few millimeters through a Widmer column of 30 cm in length packed with glass helices and porcelain rings. The distillation was repeated from $CaH_2$ until the water content became less than 0·015 wt % (Karl Fischer method) and the specific conductance less than $10^{-7}$ $ohm^{-1}$ $cm^{-1}$. Water as solvent was deionized with ion-exchange resins and checked with the specific conductance ($< 10^{-7}$ $ohm^{-1}$ $cm^{-1}$).

*Indicators.* Commercial indicators were used. Bromcresol green and bromthymol blue were of Merck chemical grade.

*Acids.* All commercial acids were purified by repeated recrystallizations. o-*i-Propylbenzoic acid* was prepared according to the method of Crawford and Stewart[12] starting with i-propylbenzene. m.p. 59·5–60·5° (lit.[13] 58·5 ~ 59·5). (Found: C, 72·99; H, 7·74. Calcd for $C_{10}H_{12}O_2$: C, 73·14; H, 7·37%). o-*t-Butylbenzoic acid* was prepared from the para acid by treatment with bromine and silver sulfate to give the *o*-bromo acid and then by conversion into the corresponding amine by the Schmidt reaction. The remaining procedure was the same as that for the *o-i*-propyl acid. m.p. 69·5 ~ 71·0° (lit.[13] 68·5°). (Found: C, 73·70; H, 8·33. Calcd for $C_{11}H_{14}O_2$: C, 74·13; H, 7·92%). 2,6-*Dimethylbenzoic acid.* was obtained from 2,6-dimethylaniline via corresponding nitrile and the amide, m.p. 115 ~ 116° (lit.[13] 116°). (Found: C, 71·32; H, 6·54. Calcd for $C_9H_{10}O_2$: C, 71·98; H, 6·71%). Commercial anthranilic acid was converted into the ethyl ester and diazotized. The diazo compound was isolated as a fluoroborate and submitted to pyrolysis to give o-*fluorobenzoic* acid.[14] m.p. 127·0 ~ 127·5° (lit.[13] 125 ~ 126°). Commercial *p*-aminobenzoic acid was used as the starting material and converted to p-*fluorobenzoic acid* by the same procedure as for the ortho isomer, m.p. 184·8 ~ 185·8° (lit.[13] 184 ~ 186°). Ethyl *o*-aminobenzoate was diazotized and iodinated to o-*iodobenzoic acid*, m.p. 162° (lit.[13] 162°). Ethyl *p*-aminobenzoate was diazotized and iodinated to p-*iodobenzoic acid*, m.p. 270 ~ 271° (lit.[13] 269 ~ 270°).

## APPENDIX

The relative acidity of the two acids, HA and HB, is shown by the following equilibrium.

$$\mathrm{HA} + \mathrm{B^-} \rightleftharpoons \mathrm{A^-} + \mathrm{HB}$$

$$K_{HA}/K_{HB} = (a_{HB}/a_{HA})(a_{A^-}/a_{B^-})$$

where $a_X$ is activity of the component, X, and $K_{HA}$ and $K_{HB}$ are the acid ionization constants of HA and HB, respectively. Then the solvent effect on the relative acidity is shown by

$$\frac{(K'_{HA}/K'_{HB})}{(K''_{HA}/K''_{HB})} = \frac{(a'_{HB}/a''_{HB})(a'_{A^-}/a''_{A^-})}{(a'_{HA}/a''_{HA})(a'_{B^-}/a''_{B^-})}$$

where the subscripts ′ and ″ refer to the first and second solvents, respectively. Here we introduce the distribution coefficient, $D_X$, of the component, X, between the two solvents,[34]

$$D_{HA} = a'_{HA}/a''_{HA}, \quad D_{HB} = a'_{HB}/a''_{HB}$$

$$D_{M^+}D_{A^-} = a'_{M^+}a'_{A^-}/a''_{M^+}a''_{A^-}, \qquad D_{M^+}D_{B^-} = a'_{M^+}a'_{B^-}/a''_{M^+}a''_{B^-}$$

where $M^+$ designates a metal ion. Substitution of the distribution coefficients for the activities gives

$$\frac{K'_{HA}/K'_{HB}}{K''_{HA}/K''_{HB}} = (D_{HB}/D_{HA})(D_{A^-}/D_{B^-}).$$

TABLE 4. DISTRIBUTION COEFFICIENTS

| Acids | $D_{HA}$ Water-50 vol % EtOH[a] | $D_{HA}$ Water-EtOH[b] | $D_{A^-}D_{A^-}$ Water-50 vol % EtOH[a] | $D_{A^-}D_{A^-}$ Water-EtOH[b] |
|---|---|---|---|---|
| Benzoic | 0·0288 | 0·00914 | 2·28 | 2410 |
| *o*-Nitrobenzoic | 0·0310 | 0·0109 | 2·05 | 4260 |
| *p*-Nitrobenzoic | | 0·00720 | | 416 |
| Salicylic | 0·0257 | 0·00537 | 0·562 | 205 |

[a] Ref 35.
[b] Ref 36.

TABLE 5. SUBSTITUENT EFFECTS, $\Delta pKa = pKa(H) - pKa(X)$

| Acids | $\Delta pKa'$ Water[a] | $\Delta pKa''$ 50 vol % EtOH[b] | $\Delta pKa''$ EtOH[c] |
|---|---|---|---|
| *o*-Nitrobenzoic | 2·03 | 1·6 | 1·83 |
| *p*-Nitrobenzoic | 0·78 | -- | 1·28 |
| Salicylic | 1·20 | 1·6 | 1·76 |
| *Ortho* effects = $pK(p\text{-}NO_2) - pK(o\text{-}NO_2)$ | 1·25 | -- | 0·55 |

[a] Ref 22.
[b] Ref 31.
[c] M. Kilpatrick and W. H. Mears, *J. Am. Chem. Soc.* **62**, 3051 (1940).

Taking the logarithmic form, we obtain

$$(pK'_{HB} - pK'_{HA}) - (pK''_{HB} - pK''_{HA}) = \Delta pK' - \Delta pK'' = \log(D_{HB}/D_{HA}) + \log(D_{A^-}/D_{B^-}).$$

Thus the solvent effect, $\Delta pK' - \Delta pK''$, can be separated into the initial state (acid molecule) term, $\log(D_{HB}/D_{HA})$, and the final state (acid aion) term, $\log(D_{A^-}/D_{B^-})$.

$D_{HA}$ and $D_{HB}$ for the uncharged molecules can be calculated from the solubility data for the acids, assuming the activity coefficients for the uncharged molecules being unity or nearly equal with each other in both solvents and correcting for the ionized part if necessary. The solubility data in dilute solutions are preferable for $D_{M^+}D_{A^-}$ and $D_{M^+}D_{B^-}$ because the solutions can be taken as ideal solutions although most of the non-ideality would be cancelled by taking the quotient, $D_{A^-}/D_{B^-}$. A summary of the distribution coefficient data taken from the works of Halford[35] and of Kolthoff *et al.*[36] are shown in Table 4. The substituent effects in the corresponding solvents are shown in Table 5.

The results summarized in Table 6 show satisfactory agreements of the two results, one from distribution

TABLE 6. INITIAL AND FINAL STATES CONTRIBUTION TO THE SOLVENT EFFECTS IN THE IONIZATIONS OF SUBSTITUTED BENZOIC ACIDS

| Solvents | Acids | $\log(D_{HB}/D_{HA})$ | $\log(D_{A^-}/D_{B^-})$ | Sum | $pK' - pK''$ |
|---|---|---|---|---|---|
| Water-50 vol % EtOH | *o*-Nitrobenzoic | −0·03 | 0·04 | 0·01 | 0·4 |
| | Salicylic | 0·05 | −0·61 | −0·56 | −0·4 |
| Water-EtOH | *o*-Nitrobenzoic | −0·08 | 0·24 | 0·16 | 0·20 |
| | *p*-Nitrobenzoic | 0·10 | −0·76 | −0·66 | −0·50 |
| | Salicylic | 0·23 | −1·07 | −0·84 | −0·56 |
| | *Ortho* effects = $pK(p\text{-}NO_2)$ − $pK(o\text{-}NO_2)$ | −0·18 | 1·01 | 0·83 | 0·70 |

coefficients and the other from ionization constants. Table 6 also indicates preponderant contribution of the initial state term $\log D_{A^-}/D_{B^-}$ over the final state term $\log (D_{HB}/D_{HA})$, which means that, so far as the effects of solvents on the relative acidities of the two acids are concerned, acid molecules are by far the less important compared to the corresponding acid anions.

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