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ORTHO EFFECTS—VI

EFFECTS OF SULFUR-CONTAINING SUBSTITUENTS ON THE IONIZATION OF BENZOIC ACID IN DIMETHYL SULFOXIDE-WATER MIXED SOLVENTS[1]

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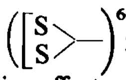
Abstract—The method presented in the preceding paper has been applied in order to examine the ortho effects for the sulfur-containing substituents. The ortho effect of *o*-MeS group has been found to be merely of a steric nature and that of *o*-$MeSO_2$ group to be quite similar to that of *o*-NO_2 group. However, the ortho effect of *o*-MeSO group has been found to behave quite differently. It increases steadily with the increase of dimethyl sulfoxide content of the solvents. This fact has been explained as due to the strong stabilization of the benzoate anion by the acid-strengthening field effect of the S → 0 dipole. A similar but more striking effect is observed for *o*-Me_2S^+ and *o*-OH groups. The acid-strengthening effect of *o*-Me_2S^+ group has been found to be abnormally weak in water.

Sulfur-containing substituents such as methylmercapto, methylsulfinyl, methylsulfonyl, and dimethylsulfonio groups are known to be capable of remarkable d-orbital conjugation.[2] On the other hand, interesting neighboring group participations are reported for the *o*-methylmercapto,[3,4] *o*-thiomethoxymethyl,[5,6] and *o*-dithiacyclopentyl [6] groups.

With these peculiar effects of sulfur-containing substituents in mind, the present work was undertaken as a part of our investigations into the ortho effects. This paper reports the ortho effects for the MeS, MeSO, $MeSO_2$, and Me_2S^+ groups on the ionization of benzoic acid in the dimethyl sulfoxide (DMSO)-water solvent system.

RESULTS AND DISCUSSION

The p*Ka* values are listed in Tables 1 and 2. The substituent effects, p*Ka*(H)−p*Ka*(X), obtained from the indicator-spectrophotometry and the potentiometric titration were found to be in satisfactory agreement with each other.

Activity coefficient correction. The tabulated p*Ka* values in H_2O are the thermodynamic values corrected for activity coefficients[8] or determined at high dilution, and the rest of the p*Ka* values in aqueous DMSO are the apparent values without correction. However, this will not affect the discussion at all, as far as the substituent effects are concerned.

Effects of para *substituents.* In Fig 1 are plotted p*Ka* values of the *p*-substituted benzoic acids against Hammett σ-constants. The data for the NO_2-, CN-, halo-, alkyl-, OMe-, and OH-substituted acids are taken from the preceding paper.[1] With these acids having common substituents satisfactory linear correlationships are established, their slopes being 1·55 in 65 vol % DMSO and 2·00 in 95 vol % DMSO.

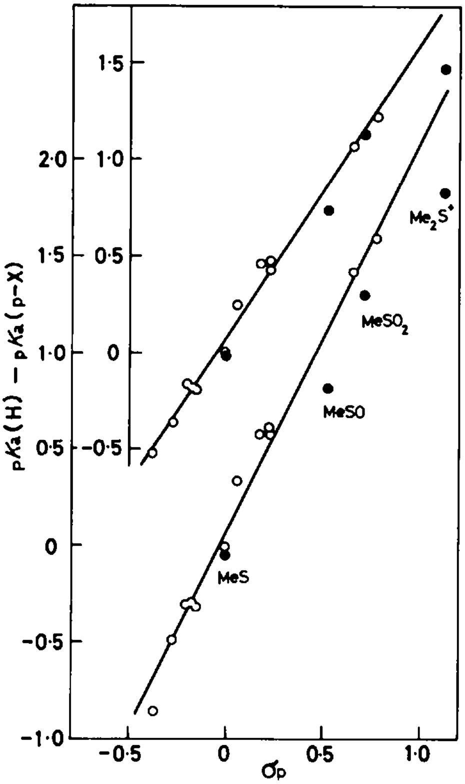


FIG 1. Hammett correlations with *p*-substituted benzoic acids in 65 and 95 vol % DMSO at 25°

The upper line (ρ = 1·55) shows correlation in 65 vol % DMSO and the lower (ρ = 2·00) in 95 vol % DMSO. See Tables 1 and 2. The data for the nitro-, cyano-, halo-, alkyl-, methoxy- and hydroxyl-substituted benzoic acids are taken from the preceding paper, Ortho Effects—V

TABLE 1 p*Ka* VALUE OF SUBSTITUTED BENZOIC ACIDS IN THE DMSO–WATER SYSTEM AT 25°

Acids	Water	35 vol % DMSO	65 vol % DMSO	95 vol % DMSO
H	4·19[a]	4·64 (D.N.P.)[b]	5·74 (B.C.G.)	9·12 (B.T.B.)
o-Me$_2$S$^+$	2·18[a]	—	2·7 (D.N.P.)	4·95 (D.N.P.)
o-MeSO$_2$	2·53[c]	3·24 (D.N.P.)	—	7·27 (B.C.G.)
o-MeSO	3·10[d]	3·36 (D.N.P.)	4·15 (D.N.P.)	7·01 (B.C.G.)
o-MeS	3·67[c]	4·50 (D.N.P.)	—	8·84 (B.C.G.)
p-Me$_2$S$^+$	3·06[a]	3·49 (D.N.P.)	4·27 (D.N.P.)	7·29 (B.C.G.)
p-MeSO$_2$	3·48[e]	3·72 (D.N.P.)	—	7·82 (B.C.G.)
p-MeSO	3·66[d]	4·03 (D.N.P.)	5·00 (D.N.P.)	8·30 (B.T.B.)
p-MeS	4·19[e]	4·66 (D.N.P.)	—	9·16 (B.T.B.)

[a] See succeeding paper, ref. 8, determined by the potentiometric titration. Thermodynamic

[b] See preceding paper

[c] Determined by UV spectrophotometry. Thermodynamic

[d] Determined by conductivity method. Thermodynamic

[e] Evaluated from $\rho\sigma$; $\rho = 1{\cdot}00$, $\sigma_{p\text{-MeSO}_2} = 0{\cdot}72$, $\sigma_{p\text{-MeS}} = 0{\cdot}00$ from ref. 25

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

Acids	65 vol % DMSO	85 vol % DMSO
H	6·97	8·97
o-Me_2S^+	—	5·31
o-$MeSO_2$	5·63	7·40
o-MeSO	5·41	7·05
o-MeS	6·92	8·87
p-Me_2S^+	5·50	7·20
p-$MeSO_2$	5·84	7·72
p-MeSO	6·22	8·19
p-MeS	6·98	9·00

The MeS group is situated close to the line, showing no anomaly in its substituent effect in the solvents used. By contrast, the MeSO and Me_2S^+ groups deviate downward appreciably and their substituent constants are found to decrease as the solvent is changed from H_2O to 95 vol % DMSO. Thus for p-MeSO σ-constants are 0·53, 0·46, 0·40, and for p-Me_2S^+[15, 16] they are 1·13, 0·94, 0·90 in water, 65, and 95 vol % DMSO, respectively.

The $MeSO_2$ group also shows similar trend in 95 vol % DMSO. These facts suggest some specific interactions between these substituents and the DMSO molecules. However, magnitudes of the deviations are much less than that of the ortho effects listed in Table 3.

Ortho *effects*. We have defined the ortho effects by the following equation.[1]

$$\textit{Ortho}\text{ effects} = \mathrm{p}Ka\,(\mathrm{p}-\mathrm{X}) - \mathrm{p}Ka(o-\mathrm{X}).$$

The *ortho* effects calculated in this manner are listed in Table 3 and plotted in Figs 2 and 3 against solvent change.

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

Substituents	Water	35 vol %	65 vol %	85 vol %	95 vol % DMSO
Me_2S^+	0·88	—	1·6	1·89	2·34
$MeSO_2$	0·95	0·48	0·21	0·32	0·55
MeSO	0·56	0·67	0·85	1·14	1·29
MeS	0·52	0·16	0·06	0·13	0·32
OH[a]	1·53	2·06	2·78	3·66	4·34

[a] The p*Ka* values are reported in the preceding ppaper, Ortho Effects-V.[1]

o-*MeS*. Variation of the ortho effects of o-MeS group with the change of solvents shows more resemblance to that of the o-Me or o-i-Pr groups rather than to that of the o-MeO group. Any special effect, such as intervention of the d-orbital in stabilizing the carboxylate group directly from the ortho position, cannot be recognized, at least in the ionization of o-methylmercaptobenzoic acid.

o-*MeSO*$_2$. Fig 2 shows that the ortho effects of the o-$MeSO_2$ group behaves similarly to that of the o-NO_2 group and, interestingly, quite different to that of the o-MeSO group. Sterically the o-$MeSO_2$ group will assume a conformation in which two oxygens are close to the carboxylate group since oxygen is smaller than Me.

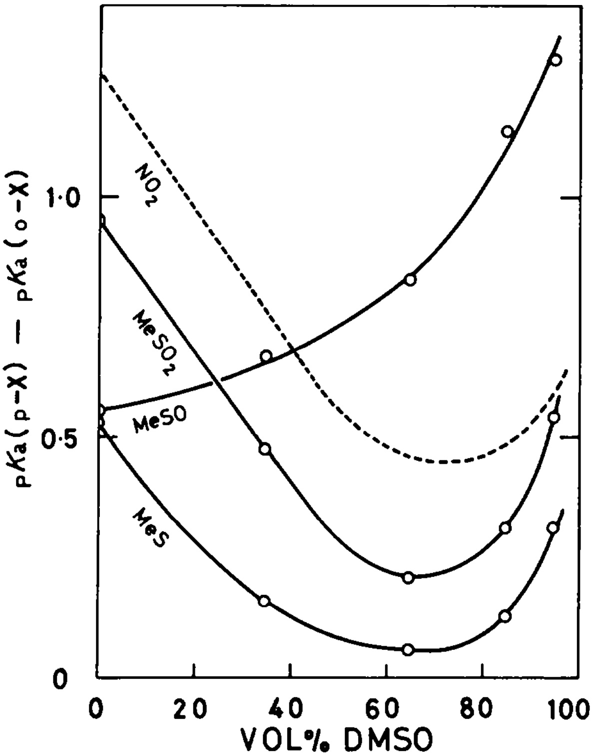


Fig 2. Plots of *ortho* effects for the MeS, MeSO and $MeSO_2$ groups against solvent composition

The curve for the NO_2 group is taken from the preceding paper. Ortho Effects—V

However, electrostatic repulsion will be maximum for this conformation. A similar situation exists in the *o*-NO_2 case. Conjugation keeps the NO_2 group coplanar with the Ph, while both steric hindrance and electrostatic repulsion cause tortion and bending of the former. Thus existence of two mutually opposing factors will make the effects of *o*-$MeSO_2$ and *o*-NO_2 groups less specific and less efficient (in either stabilization or destablization) compared with the case of *o*-MeSO group.

o-MeSO. This group shows particularly interesting behavior toward the solvent change. The ortho effect increases steadily with change of solvent from H_2O to DMSO. In this respect the group behaves rather like *o*-Me_2S^+ or *o*-OH group than like a *o*-$MeSO_2$ or *o*-MeS group, in spite of its resemblance to the latter groups (Figs 2 and 3). This phenomenon is presumably due to the strong stabilization of the acid anion by a direct dipolar field effect of the *o*-MeSO group.[17, 18] The most sterically favorable conformation of this group would be that where lone pair electrons of sulfur is in the closest position to the carboxylate group, and this conformation is also favorable for the S → O dipole to stabilize the negative charge of the carboxylate anion. This situation will make the effect of this dipole quite effective, in contrast with the case of *o*-$MeSO_2$ and *o*-NO_2 groups mentioned above.

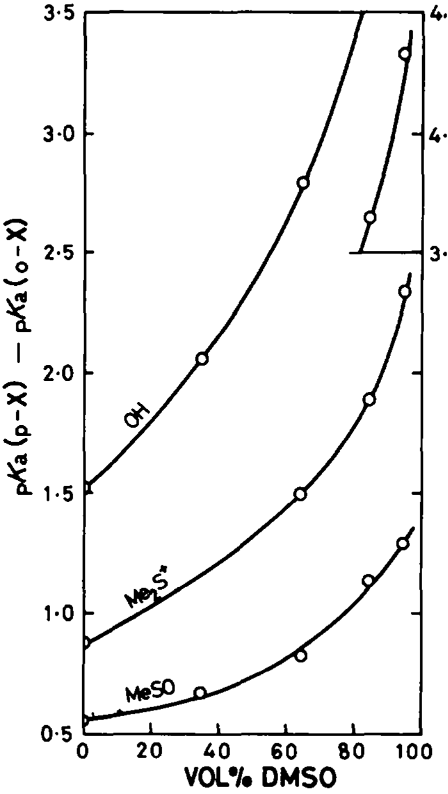


FIG 3. Plots of *ortho* effects for the MeSO, Me_2S^+ and OH groups against solvent composition

The data for the OH group are taken from the preceding paper, *ortho* effects—V

Such an intramolecular stabilization is expected to be enhanced by decrease in intermolecular solvent stabilization. This is probably the cause of the steady increase of the ortho effects of the *o*-MeSO group, and more strikingly this kind of behavior can be seen in the cases of *o*-Me_2S^+ and *o*-OH groups. It seems of much importance to note that not only a formal charge (*o*-Me_2S^+) or hydrogen bonding (*o*-OH) but also a strong dipole (*o*-MeSO) is certainly quite effective in strengthening acidity and that this kind of strong intramolecular effect can be clearly discriminated from other ordinary effects by changing solvents.

Pasto and Kent[19] studied the solvent dependence of the acidities of phenylsulfinyl- and phenylsulfonylacetic acids in both EtOH-H_2O and dioxane-H_2O systems, and observed an inversion of the relative acidities of the two acids. Phenylsulfinylacetic acid is a weaker acid in pure-H_2O while it becomes the stronger acid of the two in solvents less aqueous than 80 wt % EtOH or 60 vol % dioxane. Although the magnitude of the inversion was very small and they explained it in terms of conformational effects and hydrogen bonding, their results seem to be explained best by our reasoning mentioned above.

Me_2S *and* OH. It seems natural to expect a strong acid-strengthening field effect for o-Me_2S^+ group and this effect would be the more enhanced in the less aqueous solvents as was noted in the o-MeSO case. The situation of the o-OH group is quite similar to that of the o-Me_2S^+ group since the o-OH group is capable of forming a strong intramolecular hydrogen bond with the carboxylate oxygen[20] and stabilize the anion. Similarly, but less remarkably, this phenomenon can be observed in EtOH-H_2O and in dioxane-H_2O mixed solvent systems[21] too.

Table 4 gives the steric and field effects involved in the ortho effects of o-Me_2S^+ group together with those of o-Me_3N^+ group determined in H_2O. The magnitudes of the steric effects were roughly approximated to those of alkyl groups of comparable bulkiness, and the magnitudes of the field effects were estimated as the differences between those of the steric and ortho effects. It is quite surprising that apparently the o-Me_2S^+ group exerts no field effect in H_2O although it is observed clearly in aqueous DMSO and of course it is evident for o-Me_3N^+ in H_2O, too.

TABLE 4. STERIC AND FIELD EFFECTS IN ORTHO EFFECTS IN WATER AT 25°

Substituents	*Ortho* effects[a]	Steric effect[b]	Field effect[c]
o-Me_2S^+	0·88	0·7 (i-Pr)	−0·2
o-Me_3N^{+}[d]	2·16	0·9 (t-Bu)	−1·3

[a] Evaluated by the equation, p*Ka*(p − X) − p*Ka*(o − X)

[b] Estimated from the ortho effect for the alkyl group of corresponding bulkiness

[c] The difference between the ortho and the steric effects. This may contain the inductive effect

[d] See the succeeding paper, Ortho Effects—VII

The Me_2S^+ group has been regarded as an analog of the Me_3N^+ group in their effects on the ionization of benzoic acid and their Hammett σ-constants are found to be essentially the same.[13, 22, 23]

Under these circumstances we were forced to re-examine the substituent effects of both groups and these results will be fully described in the following paper.[8]

EXPERIMENTAL

The p*Ka* values in 35, 65 and 95 vol % DMSO were determined by the indicator-spectrophotometric method and in 65 and 85 vol % DMSO by the potentiometric titration. Both methods are described in the preceding paper.[1] The p*Ka* values in H_2O for o-methylmercapto- and o-methylsulfonylbenzoic acids were determined by UV. The thermodynamic p*Ka* values in H_2O for o- and p-dimethylsulfoniobenzoic acids were determined by the potentiometric titration with correction for the activity coefficients estimated from the Debye–Hückel limiting law, $-\log f_{\pm} = 0{\cdot}505\sqrt{I}/(1 + 1{\cdot}6\sqrt{I})$, and the Ingold expression,[7] $-\log f_{\pm} = 4\,Ne^4Z^2dI/2303k^2(DT)^2$, for the zwitterions. Further details of the calculations are described in the succeeding paper.[8] The conductivity method was used for the p*Ka* values of o- and p-methylsulfinylbenzoic acids in water and is described elsewhere.[9]

The UV instruments were mentioned in the preceding paper.[1] The concentrations and the analytical wavelengths were 5×10^{-5} M and 234 mμ for benzoic, 1×10^{-4} M and 322 mμ for o-methylmercaptobenzoic, and 1×10^{-4} M and 218 mμ for o-methylsulfonylbenzoic acids.

Solvents and indicators were the same as used in the preceding paper.[1]

o-Methylmercaptobenzoic acid. Sodium o-mercaptobenzoate was prepared by the method described by Allen and MacKay[11] and an alkaline solution of it was treated with dimethyl sulfate to give the acid, mp 168–169° (lit.[12] 169–170°).

p-*Methylmercaptobenzoic acid.* The method for the preparation of the ortho isomer was used. mp 189–190° (lit.[13] 189–190·5°).

p-*Methylsulfinylbenzoic acid.* According to the method of Price and Hydock,[14] *p*-Methylmercaptobenzoic acid was oxidized with dilute HNO_3, dec. 232 (lit.[14] 232·5–233·0 uncor.). (Calcd for $C_8H_8O_3S$: C, 52·16; H, 4·37; S, 17·40. Found: C, 52·31; H, 4·58; S, 17·14%). Purity from neut. equiv, 100·4%.

p-*Methylsulfonylbenzoic acid.* The method described by Price and Hydock[14] was adopted. *p*-Methylmercaptobenzoic acid was refluxed with AcOH and 30% H_2O_2 for 20 hr. mp 264–265° (lit.[14] 264–265 uncor.). Calcd for $C_8H_8O_4S$: C, 47·99; H, 4·03; S, 16·01. Found: C, 48·15; H, 4·27; S, 15·81%). Purity from neut. equiv, 99·8%.

o-*Methylsulfinyl- and* o-*methylsulfonylbenzoic acids.* Both acids were prepared by the method described by Arndt, Kirsch and Nachtwey.[12] *o*-Methylmercaptobenzoic acid was dissolved in hot glacial AcOH and appropriate amounts of 30% H_2O_2 added slowly to this solution.

o-*Methylsulfinyl-* dec 175° (lit.[12] 176–178°). (Found: C, 52·17; H, 4·59; S, 17·47%). Purity from neut. equiv, 100·4%.

o-*Methylsulfonyl-* mp 137·5–139° (lit.[12] 138–140°). Sintering, 131° (lit.[12], 135°). (Found: C, 47·69; H, 3·99; S, 15·74%). Purity from neut. equiv. 100·4%.

o- *and* p-*Dimethylsulfoniobenzoic acids.* The method described by Bordwell and Boutan[13] for the preparation of the para isomer was found to be successful for that of the ortho. The corresponding methylmercaptobenzoic acids were heated with twice molar quantity of methyl *p*-toluenesulfonate. The ortho isomer was recrystallized from absolute EtOH.

o-*Dimethylsulfonio-*: m.p 148·5° uncor. (Calcd. for $C_{16}H_{18}O_5S_2$: C, 54·22; H, 5·10; S, 18·09. Found: C, 54·48; H, 5·10; S, 18·03%). Purity from neut. equiv, 99·6%.

p-*Dimethylsulfonio-*: m.p. 197·5° uncor. (lit.[13] 176–177°). (Found: C, 54·26; H, 5·04; S, 18·21%). Purity from neut. equiv, 99·6%.

The observed m.p. (197·5°) for the para isomer was much higher than reported by Bordwell and Boutan (176–177°),[13] and almost identical with that for their meta isomer (196–197°).[13]

The acids prepared were checked by NMR spectra obtained at 60 Mc on a Japan Electron Optics JNM-C6OH spectrometer at room temp. Solutions were approximately 10 wt% in alkaline D_2O. Signals for the Me protons were sharp singlets for all acids and the chemical shifts were referenced from internal sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS).

TABLE 5. CHEMICAL SHIFTS OF Me PROTONS OF THE SUBSTITUTED BENZOATE ANIONS, δ-VALUES[a]

Substituents	MeS	MeSO	$MeSO_2$	Me_2S^+
Ortho	2·44	2·97	3·38	3·13
Para	2·50	2·91	3·32	3·25

[a] Measured in alkaline D_2O using DSS as an internal standard

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