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ORTHO EFFECTS—VIII

THERMODYNAMICS OF THE IONIZATION EQUILIBRIA OF *o*- AND *p*-SUBSTITUTED BENZOIC ACIDS IN DIMETHYL SULFOXIDE–WATER MIXED SOLVENTS[1]

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Abstract—Thermodynamic quantities, ΔH° and ΔS°, in the ionization of various *o*- and *p*-substituted benzoic acids have been determined in 65 and 95 vol % aqueous dimethyl sulfoxide (DMSO) and in water. A linear correlation between ΔG° and ΔH° for both *o*- and *p*-substituted acids exists in 65 and 95 vol % DMSO, whereas in water the same plot shows wide scattering. For *p*-substituted acids, a trend can be seen that the ionization is controlled by ΔS° in water while in 65 and 95 vol % DMSO the ionization is evidently controlled by ΔH°. These facts can be interpreted as a result of strong solvation of the acid anions in water and of weak solvation in aqueous DMSO. The characteristic features of aqueous DMSO as a solvent for ionization of organic acids are clarified in terms of ΔH° and $-T\Delta S^\circ$.

THIS STUDY was undertaken as part of a series of investigations to elucidate the nature of the *ortho* effects in the ionization of benzoic acids. In the preceding works[1,2] the *ortho* effect has been discussed on the basis of p*K*a values, which is proportional to the free energy change, ΔG°, and is generally used for discussions of substituent effects on acidity. Although some justification for using ΔG° values rather than ΔH° values as a measure of substituent effects was discussed carefully by Bell,[3] the nature of the substituent effects would be better understood on the basis of ΔH° and ΔS° values: this is especially the case for the effects of *ortho* substituents which, owing to their proximity to the reaction site, are expected to have a significant influence on ΔS°.

In spite of the pioneering efforts of Hammett,[4] Everett and Wynne-Jones,[5] and of Zawidzki, Papee and Laidler,[6] and of considerable amounts of thermodynamic data, ΔH° and ΔS°, being available at present as to the ionization equilibria of substituted benzoic acids in water (Table I), there still remains much uncertainty.[3, 7, 8] Recently Wilson *et al.*[9] attacked this problem again with some additional data of high accuracy. Suggestive approaches to this problem are also presented by Hepler[10] for phenols and by Christensen *et al.*[11] for dicarboxylic acids. The results are still complicated and this is presumably due to the complex effects of solvents.

The present work deals with the effects of *ortho* and *para* substituents on both ΔH° and ΔS° for the ionization of benzoic acid. Three solvents, water, 65 and 95 vol % aq DMSO, were used to see the effects of solvents on these thermodynamic quantities, especially in the case of *ortho* substituents.

RESULTS

In order to calculate the thermodynamic quantities, we have taken the general van't Hoff equation: $\Delta H = RT^2(\mathrm{d}\ln K/\mathrm{d}T)$. Assuming that ΔH is nearly constant over the temperature range investigated, the above equation can be integrated, giving $\Delta H = 2{\cdot}303\, R(pKa(T_2) - pKa(T_1))/(1/T_2 - 1/T_1)$. This method of calculation is very easy but somewhat rough in comparison with those reported in the literature (Table 1), so the accuracy was examined as follows:

In water. According to the data of Everett and Wynne-Jones[5] and of Briegleb and Bieber,[12] values of ΔC_p for twenty-two substituted benzoic acids obtained on the assumption, ΔC_p = constant, fall in the range from −22 to −48 cal/deg mole. Therefore values of ΔH which are derived using ΔC_p from the differential equation, $d(\Delta H) = \Delta C_p dT$, will decrease by 0·2 to 0·5 Kcal/mole with the temp. rise of 10°. This expectation has been verified in the cases of *m*- and *p*-substituted acids by the data of Wilson *et al.*[9] but the reverse trend has been found in the cases of *o*-substituted acids. However, the values of $\Delta H°$ calculated for the *o*-substituted acids on the assumption, ΔH = constant, using pKa(35°) − pKa(25°), coincide with those calculated accurately at 25°

TABLE I. THERMODYNAMIC QUANTITIES FOR THE IONIZATION OF BENZOIC ACIDS IN WATER AT 25°

Acids	pKa	$\Delta G°$ Kcal/mole	$\Delta H°$ Kcal/mole	$-T\Delta S°$ Kcal/mole	Ref.
o-OH	*2·973	4·05	0·73	3·32	[a]
	2·98	4·06	1·00	3·06	[b]
o-NO$_2$	2·18	2·98	−3·36	6·34	[b]
p-NO$_2$	*3·442	4·69	0·07	4·62	[c]
	*3·441	4·69	0·12	4·57	[d]
o-MeSO	3·10	4·22	−0·46	4·68	This work
p-MeSO	3·66	4·99	−0·50	5·49	This work
o-Cl	2·88	3·93	−2·47	6·40	[b]
p-Cl	*3·986	5·43	0·23	5·20	[c]
	*3·985	5·44	0·39	5·05	[d]
H	*4·21	5·74	0·09	5·65	[e]
	4·16	5·68	0·04	5·64	[b]
	*4·201	5·73	0·15	5·58	[f]
	*4·203	5·73	0·15	5·58	[d]
	4·213	5·74	0·42	5·32	[c]
o-Me	*3·91	5·33	−1·50	6·83	[e]
	*3·88	5·28	−1·40	6·68	[b]
	*3·893	5·31	−1·02	6·33	[d]
p-Me	*4·34	5·91	0·30	5·61	[e]
	*4·35	5·92	0·30	5·62	[c]
	*4·35	5·92	0·30	5·62	[b]
	*4·362	5·95	1·10	4·85	[d]
o-t.Bu	3·52	4·80	−2·52	7·32	This work
p-t.Bu	4·30	5·94	0·34	5·60	This work
p-OH	*4·582	6·25	0·54	5·71	[c]
	*4·580	6·25	0·39	5·86	[d]

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* Where plural values are listed, the values indicated by the mark * or the average values of those are adopted in this work.

[a] Z. L. Ernst, R. J. Irving and J. Menashi, *Trans. Faraday Soc.* **60**, 56 (1964)

[b] Ref 5 [c] Ref 12 [d] Ref 9 [e] Ref 8 [f] Ref 11

by Wilson *et al.*[9] to within 0·5 Kcal/mole. Values of $\Delta H°$ for *o*- and *p*-toluic acids reported by several authors fall beyond a spread of 0·4 Kcal/mole (Table I), and in practice, it is quite difficult to decide which value should be taken if one expects an accuracy of ±0·2 Kcal/mole. However, if an accuracy of ±0·4 Kcal/mole is allowable, one can be confident of determining an appropriate value by proper selection or by merely averaging them.

Therefore, the values of $\Delta H°$ for *o*-, *p*-Me, *o*-, *p*-t.Bu, and *o*-, *p*-methylsulfinylbenzoic acids can safely be used with an accuracy of ±0·4 to 0·5 Kcal/mole. The rest of the values taken from the literature in Table I can be used with an accuracy of ±0·1 to 0·2 Kcal/mole.

TABLE II. THERMODYNAMIC QUANTITIES FOR THE IONIZATION OF BENZOIC ACIDS AND INDICATORS IN 65 AND 95 VOL % DMSO AT 25°

Acids and Indicators No.	65 vol % DMSO				95 vol % DMSO			
	p*K*a	$\Delta G°$ Kcal/mole	$\Delta H°$ Kcal/mole	$-T\Delta S°$	p*K*a	$\Delta G°$ Kcal/mole	$\Delta H°$ Kcal/mole	$-T\Delta S°$
1. *o*-OH	3·49	4·75	0·75	4·0	5·64	7·66	3·5	4·2
2. *o*-Me_2S^+	—	—	—	—	4·95	6·73	3·3	3·4
3. *p*-Me_2S^+	4·27	5·81	1·8	4·0	7·29	9·91	4·9	5·0
4. *o*-NO_2	4·06	5·53	0·7	4·8	6·93	9·43	4·8	4·6
5. *p*-NO_2	4·52	6·15	1·6	4·6	7·53	10·25	6·5	3·8
6. *o*-MeSO	4·15	5·65	1·6	4·1	7·01	9·54	4·6	4·9
7. *p*-MeSO	5·00	6·80	1·8	5·0	8·30	11·28	6·6	4·7
8. *o*-Cl	4·80	6·52	1·3	5·2	7·97	11·28	6·9	4·4
9. *p*-Cl	5·26	7·15	2·3	4·9	8·54	11·62	8·0	3·6
10. H	5·74	7·80	2·7	5·1	9·12	12·41	8·2	4·2
11. *o*-Me	5·90	8·03	2·9	5·1	9·31	12·65	7·8	4·9
12. *p*-Me	5·92	8·05	2·8	5·3	9·41	12·80	7·9	4·9
13. *o*-t.Bu	5·80	7·89	3·1	4·8	9·06	12·33	7·5	4·8
14. *p*-t.Bu	5·90	8·03	3·4	4·6	9·42	12·81	8·2	4·6
15. *p*-OH	6·25	8·50	3·1	5·4	9·98	13·58	9·2	4·4
D.N.P.[a]	3·56	4·84	2·1	2·7	4·53	6·16	3·5	2·7
B.C.G.[b]	5·03	6·84	1·5	5·3	6·36	8·65	2·9	5·8
B.T.B.[c]	—	—	—	—	9·90	13·45	7·9	5·6
Precision	±0·005	±0·01	±0·2	±0·2	±0·005	±0·01	±0·4	±0·4

[a] 2,4-Dinitrophenol [b] Bromcresol green [c] Bromthymol blue

In 65 *and* 95 *vol % DMSO*. Plot of p*K*a *vs.* $1/T$ for most of the acids in Table II generally shows a linear relationship within an experimental error of ±0·01 p*K*a unit. This fact suggests that the values of $\Delta H°$ are constant to within ±0·2 Kcal/mole in 65 vol % DMSO over the temp range from 15° to 35° and to within ±0·4 Kcal/mole in 95 vol % DMSO from 25° to 35°. Since we have neglected the activity coefficient correction in these aqueous DMSO solns, some uncertainty remains in the absolute magnitudes of $\Delta H°$ values in Table II. However, relative quantities such as substituent effects could be evaluated without any appreciable amounts of influence of this uncertainty. Thermodynamic quantities for the ionization of benzoic acids in the three solvents are listed in Table I and II.

DISCUSSION

Figs. 1, 2 and 3 show the correlations between ΔG° and ΔH° and between ΔG° and $-T\Delta S^\circ$, in water, 65 vol % DMSO, and 95 vol % DMSO, respectively.

Water as solvent (Fig. 1). For *o*-substituted acids the plot is widely scattered in the range of as large as 4·1 Kcal/mole in ΔH° and 4·0 Kcal/mole in $-T\Delta S^\circ$. However, for the *p*-substituted acids the corresponding range is fairly small (1·0 Kcal/mole and 1·2 Kcal/mole, respectively), and ΔG° for these acids are almost linearly correlated with $-T\Delta S^\circ$, except for the case of *p*-MeSO group where slight deviation is observed. Inspection of Fig. 1 also reveals that ionization of the *p*-substituted acids are controlled by entropy† rather than by enthalpy.

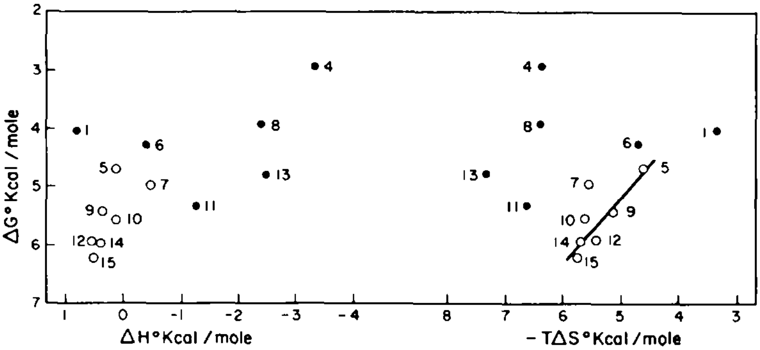

Fig 1. Plot of ΔG° against ΔH° and $-T\Delta S^\circ$ for *o*- and *p*-substituted benzoic acids in water at 25°. The numbers refer to the acids in Table II. The solid circles show the *o*-substituted acids and the open the *p*-substituted.

This fact seems to be best interpreted as a result of compensation of the two effects. Water molecules are bound strongly to the negative charge of the carboxylate group by electrostatic forces, hydrogen bonding, etc., and stabilize the anions with consequent enthalpy decrease and entropy decrease. On the other hand, the anions are stabilized (or destabilized) by electronic effects of the *p*-substituents mainly with the decrease (or increase) in enthalpy. The less stabilized anions by the *p*-substituents would be stabilized the more by the solvent and this kind of compensation would make the ionization entropy-controlled rather than enthalpy-controlled.

As was mentioned earlier[2] steric inhibition of resonance is an important contribution to the high acidities of *o*-nitro, *o*-chloro- and *o*-alkylbenzoic acids and this effect will cause much diminution in ΔH° together with some increase in $-T\Delta S^\circ$.[6, 9] Fig. 1 shows that this is actually the case for these *o*-substituted acids. Although steric inhibition to solvation can be anticipated for these acids, this effect should result in an increase in ΔH° and a decrease in $-T\Delta S^\circ$, which are contrary to observation. This directly means that the steric inhibition to solvation is not significant in water owing to the strong solvating power of water, which is certainly in good agreement with the conclusion derived in our previous works.[2]

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† This was first pointed out by Hammett as a result of temperature dependence of the dielectric constant of solvents, purely on the basis of the electrostatic theory.[4,8]

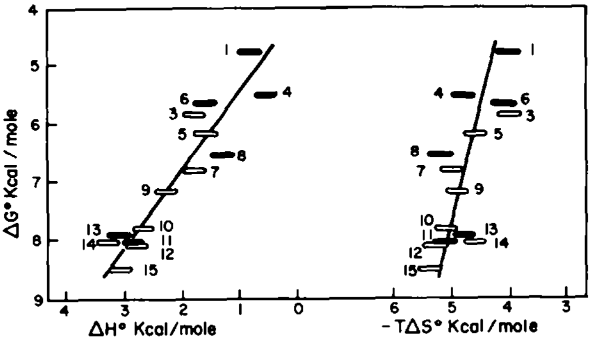

Fig 2. Plot of ΔG° against ΔH° and $-T\Delta S^\circ$ for *o*- and *p*-substituted benzoic acids in 65 vol % DMSO at 25°. The numbers refer to the acids in Table II. The solid symbols show the *o*-substituted acids and the open the *p*-substituted.

The fact that the points for the *o*-hydroxyl group are situated at the opposite extreme to those for the *o*-nitro, *o*-chloro and *o*-alkyl groups (Fig. 1) shows the importance of entropy-controlled effects, its ΔH° value differing only slightly from that for *p*-hydroxyl or unsubstituted benzoic acid. Of course, this phenomenon can be attributed solely to intramolecular stabilization of the acid anion by hydrogen bonding, *i.e.*, a kind of intramolecular solvation of the carboxylate group by the *o*-hydroxyl substituent. The intermediate situation for the *o*-methylsulfinyl group (Fig. 1) reasonably suggests that it stabilizes the carboxylate group by its strong dipole

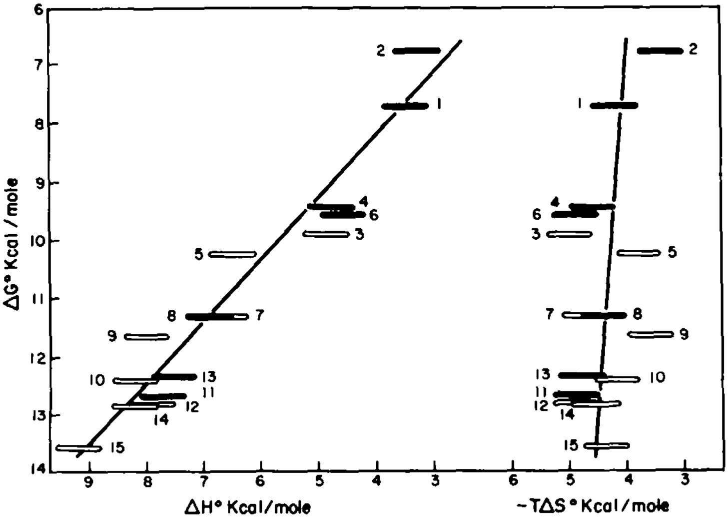

Fig 3. Plot of ΔG° against ΔH° and $-T\Delta S^\circ$ for *o*- and *p*-substituted benzoic acids in 95 vol % DMSO at 25. The numbers refer to the acids in Table II. The solid symbols show the *o*-substituted acids and the open the *p*-substituted.

which was also shown previously.[2] It seems of much importance to note that although acid-strengthening *ortho* effects due to bulky *o*-substituents and those due to strong intramolecular stabilization cannot be distinguished in terms of $\Delta G°$, they are well discriminated in terms of $\Delta H°$ and $-T\Delta S°$.

65 *vol % DMSO as solvent* (Fig. 2). Since the acid anions are less strongly solvated in 65 vol % DMSO than in water, thermodynamic data in 65 vol % DMSO are of great importance in connection with the above reasoning. As can be seen in Fig. 2, the free-energy changes for *p*-substituted acids are controlled mainly by the enthalpy changes with small cooperative effects of the entropy changes. This fact is satisfactorily interpreted as the result of weak solvation of the acid anions in 65 vol % DMSO. "Weak solvation" here means a situation that solvent molecules are held less intimately and less specifically around the acid anions. In such a situation the acid anions are stabilized less effectively by the solvent and therefore intramolecular stabilization by the electronic effects of *p*-substituents becomes the more important, which would make the ionizations in this solvent strongly enthalpy-controlled, in contrast with the entropy-controlled ionizations in water. Another feature seen in this solvent is that the substituent effects on $\Delta H°$ are considerably larger than in water. This is partly a direct consequence of the increased substituent effect on $\Delta G°$ (larger ρ value), but partly is thus due to the decreased contribution of $-T\Delta S°$ to $\Delta G°$ in this solvent.

Including various kinds of *o*-substituents linear correlations between $\Delta G°$ and $\Delta H°$ and between $\Delta G°$ and $-T\Delta S°$ are quite satisfactory and any anomaly of *o*-substituents is not discernible at least in Fig. 2, although *ortho* effects are actually existing in this solvent.[2] As was fully discussed in the earlier paper[2a] steric inhibition to solvation will occur gradually when the solvent is changed from water to 65 vol % DMSO, accompanied with an increase in $\Delta H°$ and a decrease in $-T\Delta S°$. Therefore this effect will cancel partly or completely $\Delta H°$ and $-T\Delta S°$ due to steric inhibition of resonance.

95 *vol % DMSO as solvent* (Fig. 3). All features recognized in 65 vol % DMSO can be observed still more distinctly in 95 vol % DMSO. This result seems quite reasonable since solvation to the acid anions must become weaker in 95 vol % DMSO than in 65 vol % DMSO. It seems surprising that even *o*-OH, *o*-Me_2S^+ and *o*-MeSO groups, which have acid-strengthening *ortho* effects as high as 4·34, 2·34 and 1·29 *p*Ka units* in this solvent, respectively, do not show any anomaly in $\Delta G°$ vs. $\Delta H°$ and $\Delta G°$ vs. $-T\Delta S°$ correlations.

Effects of solvent on acid molecules. Whenever one is studying an ionization reaction as a function of solvent, one must consider the solvation of the neutral species as well and some mention seems necessary regarding this problem. In our earlier work[2c] solubility data of substituted benzoic acids and their salts were examined and analyzed in some detail, leading to the conclusion that so far as the effects of solvents on the relative acidities ($\Delta G°$) of the two acids are concerned, acid molecules are by far the less important compared to the corresponding acid anions. Presumably, $\Delta H°$ and $\Delta S°$ would also be controlled mainly by acid anions and not by acid molecules in these aqueous binaries.

EXPERIMENTAL

Values of $\Delta H°$ were determined by the temp variation method. The p*K*a values for *o*-, *p*-methylsulfinylbenzoic and *o*-, *p*-t-butylbenzoic acids in water were determined at 25 and 35° by conductimetry. The p*K*a

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* *Ortho* effects ≡ p*K*a(*p*-X) − p*K*a(*o*-X), see ref. 2a.

values for fourteen *o*-, *p*-substituted benzoic acids in 65 and 95 vol % DMSO-water mixed solvents were determined at 15, 25 and 35° or at 25, 30 and 35° by the indicator-spectrophotometry.[1, 2]

Conductimetry. General experimental techniques used here are those of Findlay[13] and of Albert and Serjeant.[14] The cell was of about 15 ml capacity equipped with Pt electrodes which were slightly coated with Pt-black and had a cell-constant of 0·4270 cm^{-1}. It was immersed in an oil bath thermostatted within ±0 02°. The measuring instrument was a Yanagimoto MY-7 conductivity instrument which incorporated a cathode tube indicator and a Wheatstone bridge capable of measuring up to 1,000,000 ohms to four sig. figs. Water was deionized with ion-exchange resins and carbonate-free NaOH soln used for the determination of the limiting conductance, Λ_0. The value of Λ_0 was obtained by extrapolation from the plot of Λ_c vs. $\sqrt{C}$, in which $\sqrt{C}$ was varied from 0·025 to 0·055. Following values of Λ_0 for acids at 25° were determined using $\Lambda_0(Na^+) = 50{\cdot}1$ and $\Lambda_0(H^+) = 349{\cdot}8$:[15] *o*-t.Bu, 377;[*] *p*-t.Bu 377; *o*-MeSO, 380; *p*-MeSO, 379. The Λ_0 values at 35° were determined using $\Lambda_0(Na^+) = 62$ and $\Lambda_0(H^+) = 397$:[15] *o*-t.Bu, 430; *p*-t.Bu, 430; *o*-MeSO, 434; *p*-MeSO, 433.

The concentration p*K*a value was submitted to the Debye-Hückel correction:[14] p*K*a(thermodynamic = p*K*a(concentration) − $2A\sqrt{\alpha C}$, where A is 0·509 at 25° and 0·519 at 35°, α the fraction ionized and *C* the concentration (mole/Kg).

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