Substituent Effects. Part 11.[1] Anomalous Dissociation Constants of Benzoic Acids in Water–Organic Solvent Mixtures. An Extended Hammett Equation Comprising the Hydrophobic Constant as an Additional Parameter

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Thermodynamic dissociation constants of benzoic acids show deviations from the Hammett equation in ethanol–water and, more strongly, in t-butyl alcohol–water, with maxima at about 40% ethanol–water (16 mol%) and 32% t-butyl alcohol–water (8 mol%). The extended equation $\Delta = \rho\sigma + h\pi$, where π is Hansch's hydrophobic constant, covers the experimental data very well; h varies from 0 to -0.16. Similar behaviour is exemplified for other systems. In the solvents 80% methyl Cellosolve and 65% dimethyl sulphoxide the Hammett equation is followed closely. Some practical implications and an attempt at rationalization are given. Related data from the literature, including recent work of Fan and Jiang, are discussed briefly.

In previous papers[2–4] we have drawn attention to the strong solvent dependence of the Hammett σ values of alkyl groups, in particular 3-Bu^t, 4-Bu^t, and 3,5-di-Bu^t. In the alkaline hydrolysis of ethyl arylacetates, for example,[3] the σ values of 3,5-di-Bu^t are -0.14 and -0.53 in 85% ethanol–water and 60% acetone–water, respectively. Furthermore, we noticed that Hammett plots are usually less satisfactorily linear for data from 50% ethanol–water than for data from 10% or 75% ethanol–water.[3]

Such observations led us to work in various water–organic solvent mixtures in a number of compound series. The present paper deals mainly with dissociation constants of *meta*- and *para*-substituted benzoic acids in ethanol–water, denoted as E/H_2O, and t-butyl alcohol–water, TB/H_2O. Some data in methyl Cellosolve–water, MCS/H_2O, and dimethyl sulphoxide–water, DMSO/H_2O, are also given.

Results and Correlation Analysis

Tables 1 and 2 give data in E/H_2O and TB/H_2O. In order to facilitate comparisons we do not give pK_a values throughout, but only those of the parent, and we list the substituent effects as $100\Delta = 100(\mathrm{p}K_a^\circ - \mathrm{p}K_a)$. Solvent compositions are always in vol% organic solvent, 50E meaning 50 volumes of absolute ethanol in 100 volumes of final solution. We chose 22TB because it corresponds with 5 mol%, and 32TB (8 mol%) because it gives the maximum effect with 3-Bu^t-benzoic acid.

Figures 1 and 2 illustrate the variation of the Hammett σ value with solvent composition for some crucial groups. It is clear that the anomalies in E/H_2O and TB/H_2O are qualitatively similar. Both show maxima and minima at intermediate composition, and at higher alcohol concentrations the σ values tend to aqueous values. It is also obvious that the anomalies in E/H_2O are much smaller than in TB/H_2O; we shall, therefore, pay most attention to the latter solvent mixture.

As for the *meta*- (and *para*-) alkyl groups the anomalies appear in the order Me < Et < Pr^i < Bu^t < CEt_3. It is noteworthy that in 26TB, 3-CEt_3 and 3,5-di-Bu^t are as much acid-weakening as 3-NO_2 is acid-strengthening: $\Delta = -0.93$, -0.94, and $+0.95$, respectively.

The *meta*-halogen substituents behave in the same way as the alkyl groups. The anomalies are in the order F < Cl < (Br <) I and lead to at least four different orders of Δ in TB/H_2O. The ratio Δ(3-I)/Δ(3-NO_2) changes from 0.50 in water, to 0.40 in 50E, and 0.19 in 32TB, 'returning' to 0.50 in 85E and 0.44 in 90TB.

Substitution of the α-H atom of 3-$CHMe_2$ by OH to give 3-CMe_2OH practically removes the anomaly. The same substitution in 3-CH_3 to give 3-CH_2OH also raises σ; now the minimum in σ is converted into a maximum. It will be observed that the effects of 3-CH_2OH and 3-I are virtually equal in 32TB.

Close inspection of the data gives several indications that the maximum deviation moves to a lower percentage TB the larger the alkyl group, occurring at about 26TB for 3-CEt_3 and 3,5-di-Bu^t, and at 32TB for 3-Bu^t. We shall not pursue this aspect here.

It is clear that the above behaviour is not expressed in the Hammett equation:

$$\Delta = \rho\sigma \qquad (1)$$

or, in more detail,

$$\Delta_m = \rho\sigma_m \qquad (2)$$

and

$$\Delta_p = \rho\sigma_p \qquad (3)$$

The observed influence of the introduction of OH in $CHMe_2$ and CH_3 has led us to adopt Hansch's hydrophobic constant,[5] π, as an additional parameter. This was especially encouraged by the fact that the change in sign of the anomaly from CH_3 to CH_2OH is accompanied by a change in sign of π ($0.56 \longrightarrow -1.03$). The form of the extended Hammett equation containing π was chosen to be:

$$\Delta = \rho\sigma + h\pi \qquad (4)$$

or, in more detail,

$$\Delta_m = \rho\sigma_m + h_m\pi \qquad (5)$$

and

$$\Delta_p = \rho\sigma_p + h_p\pi \qquad (6)$$

The values of the substituent 'constants' π are defined (and determined) as:

$$\pi(Y) = \log P(\text{Y-benzene}) - \log P(\text{benzene}) \qquad (7)$$

where P is the partition coefficient between octanol and water

Table 1. Benzoic acids:[a] thermodynamic pK_a values of the parent, and substituent effects expressed as $100(\mathrm{p}K_a^{\circ} - \mathrm{p}K_a)$ in ethanol–water and some t-butyl alcohol–water mixtures, at 25 °C; π values of substituents.

			% Ethanol						% t-Butyl alcohol		
No.	Substituent	π	0	10	30	50	75	85	22	32	90
1	H	0	4.21	4.37^{q}	4.84	5.48	6.29	6.77	4.78	5.28	8.59
2	3-Me	0.56	−6.9^{e}	−7	−10	−12	−12	−13	−15	−24	−14
3	3,5-di-Me	1.07	−13^{f,g}	−14	−21	−26	−23	−26	−30	−44	−27
4	3-Bu^{t}	1.98	−7^{f}	−8^{r}	−21	−24	−18	−15	−40	−50	−20
5	3,5-di-Bu^{t}	3.96^{b}	−14^{b}		−43	−46	−37	−32	−79	−92	−44
6	3-CH_2OH	−1.03	7	8	11	13	10	8	13	21	13
7	3-CMe_2OH	−0.35^{c}	3	2	2	4	0	−1	−1	4	4
8	3-CHO	−0.65	44	48	56	64	73	74	58	66	88
9	3-COMe	−0.55	37.6	39	49	58	66	70	46	52	78
10	3-NO_2	−0.28	71.0	78	94	107	119	121	92	99	140
11	3-SO_2Me	−1.63	67^{h}	76	90	103	113	109	89	103	127
12	3-F	0.14	33.7^{i}	36	43	44	52	52	40	36	56
13	3-Cl	0.71	37.3	40	46	47	58	61	36	30	65
14	3-Br	0.86	39.1	41	47	51	60	61	35	30	65
15	3-I	1.12	35.2	37	40	43	55	60	27	19	61
16	3-Et	1.02	−6^{f}	−7		−17	−14	−14	−23	−32	
17	3-Pr^{i}	1.53	−8^{f}	−9		−23	−15	−15	−29	−38	
18	3-CN	−0.57	64^{h}	68		99	115	117	83	95	
19	3-CO_2Me	−0.01	33^{f}	36		45	53	53	33	36	
20	3-CF_3	0.88	41^{f}	45		59	71	75	39	39	
21	3-NHAc	−0.97	17^{f}	18		23	23	22	17	27	
22	3,5-di-NO_2	−0.64	137.9	149		203	227	234	182	195	
23	3-OMe	−0.02	12^{j}	12		11	10	8	14	10	
24	3-OEt	0.38	10^{f}	11		7	8	5	4	0	
	3-CEt_3	3.60^{d}		−22^{r}	−42	−37	−22	−22	−84	−80	−27
	3-Ph	1.96				2	14	10	−19	−17	
	3-$SiMe_3$	2.59				−22	−11	−8	−47	−48	
	3-OH	−0.67	7^{k}	8		3	−2	−6	6	6	
	3-OPh	2.08	25.2			16	21	22		−13	
	4-Me	0.56	−17.0^{e}	−17		−21	−21	−21	−21	−28	
	4-Et	1.02	−15.1	−15		−22	−20			−35	
	4-Pr^{i}	1.53	−15.1	−16		−23	−19			−39	
	4-Bu^{t}	1.98	−11^{f,l}	−12^{r}		−21	−16	−13	−33	−40	−21
	4-CEt_3	3.60^{d}				−28	−13	−11	−66	−57	
	4-CMe_2OH	−0.35^{c}		0		−1	−4			3	
	4-CHO	−0.65	52^{f}	56		77	80			80	
	4-COMe	−0.55	47^{f,m}	52		67	73	77	62	68	
	4-CN	−0.57	68	72		103	114		89	105	
	4-CF_3	0.88				78	87		55	63	
	4-$SiMe_3$	2.59				−1	6	4	−25	−21	
	4-NH_2	−1.23	−62^{n}			−79^{n}	−90^{n}			−64	
	4-NHPh	1.37				−68	−69			−81	
	4-NMe_2	0.18	−69^{n}			−92^{n}	−93^{n}			−91	
	4-NPh_2	3.61				−51	−37	−35		−70	
	4-NO_2	−0.28	77.8	83		119	133		104	117	
	4-OMe	−0.02	−26.8	−29		−31	−32		−33	−34	
	4-F	0.14	6.2^{o}	9		23	30		15	18	
	4-Cl	0.71	22.4	24		41	49		26	30	
	4-Br	0.86	23.2			42	54			30	
	4-I	1.12	21^{p}			37	50			27	
	3,5-$(CH_2OH)_2$	−2.06^{b}	15	16	20	24	20	16	21	36	28
	3-CH_2OH-5-Br	−0.17^{b}	44	48	54	58	65	64	45	46	68
	3,5-$(OH)_2$	−1.33	16	13		7	−2			12	
	3,5-Cl_2	1.25	71^{f}	77		102	122		74	69	132

[a] Values of π: see ref. 5. 10% Ethanol means 10 cm^3 of absolute ethanol in 100 cm^3 final solution; *etc.* First row (No. 1, H): pK_a values of benzoic acid. Second row (No. 2, 3-Me): *e.g.* 50E − 12 from pK_a of 3-methylbenzoic acid, 5.60, and pK_a parent, 5.48; *etc.* Values (in water) to 1 decimal place were taken from J. F. J. Dippy, *Chem. Rev.*, 1939, **25**, 151; L. G. Bray, J. F. J. Dippy, and S. R. C. Hughes, *J. Chem. Soc.*, 1957, 265; L. G. Bray, J. F. J. Dippy, S. R. C. Hughes, and L. W. Laxton, *ibid.*, 1957, 2405; J. F. J. Dippy and S. R. C. Hughes, *Tetrahedron*, 1963, **19**, 1527. Additional data (% E; pK_a or 100Δ): H, 20, 4.57; 3-CEt_3, 20, −23 (pot.); H, 40, 5.17; 3,5-di-Bu^{t}, 40, −50; 3-NO_2, 40, 100; 3-CEt_3, 40, −41. [b] Additivity assumed. [c] Calculated as $\pi(CH_2OH) + [\log P(Me_3COH) - \log P(EtOH)] = -1.03 + 0.37 + 0.31 = -0.35$. [d] Calculated as $\pi(Bu^t) + 3[f(CH_2) - f(\text{bond})] = 1.98 + 3(0.66 - 0.12) = 3.60$. [e] Present work: by extrapolation of pK_a in 4E and 2E; 3-Me, −6; 4-Me, −16. [f] Estimated as 100Δ(10E)/ρ(10E). [g] Dippy and co-workers (note *a*): −9.8. [h] By extrapolation of pK_a in 10E, 4E, and 2E. [i] Present work: 34. [j] Dippy and co-workers (note *a*): 11.5. [k] Dippy and co-workers (note *a*): 12.0. [l] Dippy and co-workers (note *a*): −19.7 (*cf.* text and footnote). [m] Dippy and co-workers (note *a*): 50.2. [n] B. van de Graaf, A. J. Hoefnagel, and B. M. Wepster, *J. Org. Chem.*, 1981, **46**, 653. [o] Present work: 5. [p] P. D. Bolton, K. A. Fleming, and F. M. Hall, *J. Am. Chem. Soc.*, 1972, **94**, 1033. [q] Potentiometry and spectroscopy. [r] Spectroscopy (4×10^{-5} mol dm^{-3}; λ 280–290 nm).

Table 2. Benzoic acids:[a] thermodynamic pK_a values of the parent, and substituent effects expressed as 100(pK_a° − pK_a), in t-butyl alcohol–water mixtures, at 25 °C.

		% t-Butyl alcohol										
No.	Substituent	10	22	26	30	32	36	40	50	60	75	90
1	H	4.35[b]	4.78	4.97	5.17	5.28	5.43	5.55	5.87	6.24	7.06	8.59
2	3-Me	−9	−15			−24		−24	−22	−18	−13	−14
3	3,5-di-Me	−16	−30			−44		−44	−40	−35	−27	−27
4	3-Bu^t	−14	−40	−46	−48	−50	−48	−43	−38	−36	−26	−20
5	3,5-di-Bu^t		−79	−94	−92	−92	−87	−85	−76	−67	−53	−44
6	3-CH_2OH	6	13			21		20	20	21	19	13
7	3-CMe_2OH	1	−1	−1	3	4		3	6	8	8	4
8	3-CHO	48	58			66		70	72	78	86	88
9	3-COMe	39	46			52		54	62	67	76	78
10	3-NO_2	79	92	95	98	99	102	106	112	116	128	140
11	3-SO_2Me	71	89			103		107	112	118	127	127
12	3-F	36	40			36		36	38	46	52	56
13	3-Cl	39	36			30		35	40	48	57	65
14	3-Br	40	35			30		33	39	46	57	65
15	3-I	34	27	24	21	19	24	28	33	41	53	61
	3-CEt_3	−23[c]	−84	−93	−86	−80		−75	−63	−50	−40	−27
	4-Bu^t		−33			−40		−36	−31	−25	−20	−21
	3,5-$(CH_2OH)_2$	11	21			36		39	42	44	41	28
	3-CH_2OH-5-Br	46	45			46		48	52	60	66	68

[a] See note *a* Table 1. Additional data (% TB; pK_a or 100Δ): H, 20, 4.67; 24, 4.87; 28, 5.06; 34, 5.36; 38, 5.50; 3-Bu^t, 20, −33; 24, −44; 28, −47; 34, −49; 38, −46; 3,5-di-Bu^t, 28, −94; 34, −89; 3-CMe_2OH, 20, −1; 3-NO_2, 20, 88; 24, 93; 28, 96; 34, 100; 38, 104; 3-I, 34, 23; 38, 26; 3-CEt_3, 20, −65; 24, −90; 28, −90. [b] Potentiometry and spectroscopy. [c] Spectroscopy (4×10^{-5} mol dm^{-3}; λ 278–284 nm).

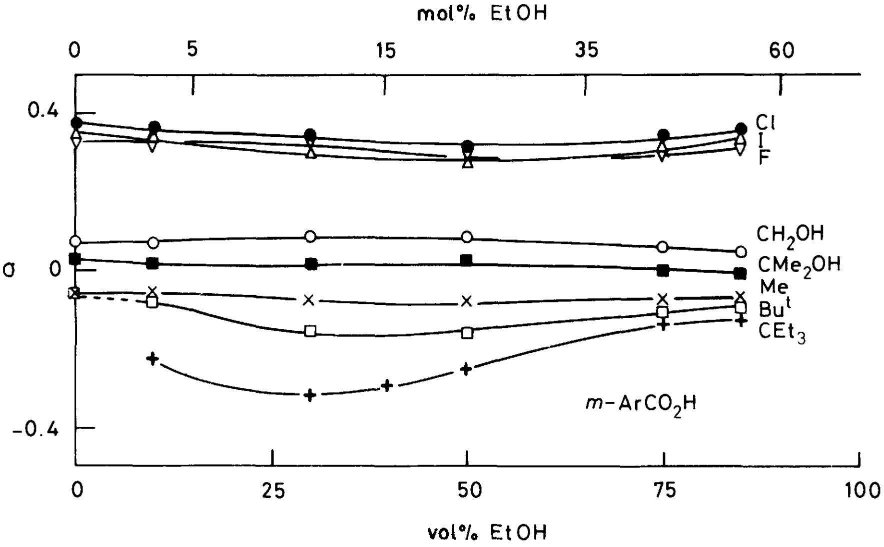

Figure 1. Variation of Hammett σ values ($\sigma_m = \Delta/\rho_m$) with solvent composition: ethanol–water. Values of ρ_m were taken as Δ(3-NO_2)/σ(3-NO_2) = Δ(3-NO_2)/0.71; see text for this assumption.

at 25 °C. The actual figures have been taken from compilations by Hansch and Leo,[5] and are specified in Table 1. This implies that $\pi_m = \pi_p$ whereas for the other substituent 'constant' sigma, $\sigma_m \neq \sigma_p$. Hence *h* must carry the burden of any *meta–para* differentiation, $h_m \neq h_p$. Again, *h* may be expected to vary with compound series and reaction type, with temperature, and, of course, with solvent.

The σ values are defined as usual from the pK_a values of $ArCO_2H$ in water at 25 °C; some of these had to be calculated from data in 10E or by extrapolation as detailed in Table 1. It follows that $h \equiv 0$ for $ArCO_2H$ in water at 25 °C. We note that, unless indicated otherwise, we calculate ρ routinely from data for *meta*-substituted compounds only and assume that $\rho_m = \rho_p$.

Figure 3 shows the values of σ_m and π for the 24 groups which are used as a basis, their spread, and their lack of correlation. The square bracket ('inside') defines a set of ten substituents with a range of one π unit; the purpose of this set will appear below.

Table 3 lists the least-squares data pertaining to equations (2) and (5). They have been arranged in pairs for ease of comparison; thus set 1a gives the results with equation (2), set 1b those for the same set of data with equation (5). In the $ArCO_2H$ sets 1–6 all groups numbered 1–24 in Table 1 have been used as far as is suitable. Sets 7–19 cover the complete range of E/H_2O and TB/H_2O solvent mixtures for $ArCO_2H$ with the substituents numbered 1–15. The sets 20–22 and 23–25 will be discussed separately.

These data show that equation (5) performs well in all solvent

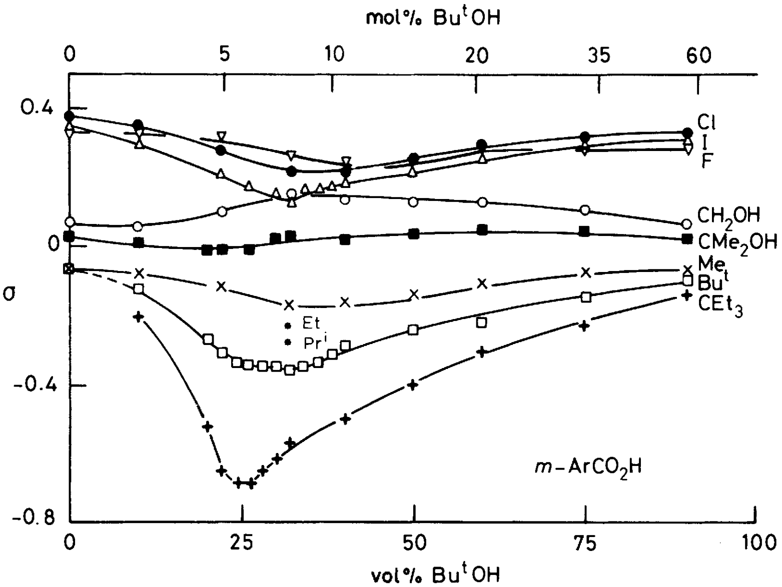

Figure 2. Variation of Hammett σ values with solvent composition: t-butyl alcohol–water; *cf.* Figure 1.

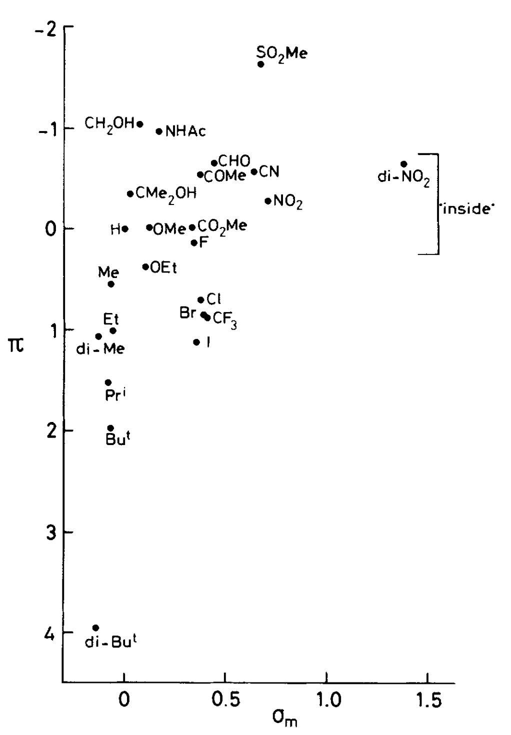

Figure 3. Showing the non-correlation between σ_m and π for the 24 numbered substituents of Table 1. The regression line has $s = 1.03$, $R = 0.51$; omitting 3,5-di-Bu^t and 3,5-di-NO$_2$ gives $s = 0.81$, $R = 0.49$; for the groups 1–15 $s = 1.17$, $R = 0.56$. The π range indicated 'inside' is from −0.73 to +0.27 and comprises ten groups with a σ range from 0.00 to 1.379.

mixtures and also when equation (2) fails. In 32TB, for example, equations (2) and (5) ($n = 24$) give correlation coefficients R of 0.961 and 0.998, respectively; the other statistical measures, s, F, s_ρ, and intercept, improve correspondingly.*,† The change in ρ should be noted, but, of course, ρ in equation (2) depends strongly on the substituents used. In the other solvent mixtures the improvements by equation (5) are from large to practically zero. In fact, in 10E, 75E, 85E, and 10TB the data leave little to be desired as regards adherence to the Hammett equation (or the accuracy of the measurements) so that the improvements by equation (5) are marginal or absent. In 90TB equation (5) still shows improvement although the halogens are back in their aqueous order.

Figure 4 shows the dependence of h_m on solvent composition and gives the anomalies of Figures 1 and 2 in terms of equation (5). The curves suggest h_m to be zero in the pure alcohols.

The success of equation (5) implies that for a set of compounds containing substituents with π values within a narrow range, equation (2) will perform well in all solvent mixtures. Figure 3 indicates an obvious choice, a π-range from +0.27 to −0.73 flanking H and NO$_2$ and comprising ten of the 24 substituents. Set 6e of Table 3 shows that in 32TB this 'inside' group follows equation (2) well; equation (5) (set 6f) is better, but h_m lacks precision. On the other hand, for sets 6c and 6d, with the 14 'outside' substituents ($-0.73 > \pi > 0.27$), equation (2) is not acceptable, but equation (5) is satisfactory with h_m and s_h close to those for set 6b with $n = 24$. Comparison of the sets 2a–f, for 50E, and 5a–f, for 22TB, gives similar conclusions. Finally, the sets 2g–h, 5g–h, and 6g–h, with a further narrowing down of the π-range to $-0.26 > \pi > -0.66$ (excluding H) show equation (2) to be near perfection, so that equation (5) can no longer give any improvement and the values of h_m are fortuitous.

It will be appreciated that the small value of $\pi = -0.28$ for

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* The equation $\Delta = \rho\sigma + h(f - 0.175)$, where f is (the sum of) Rekker's hydrophobic fragmental constants of the substituents (R. F. Rekker, 'The Hydrophobic Fragmental Constant,' Elsevier, Amsterdam, 1977) gives virtually the same results (see Supplementary Material,† Tables 8 and 9). This is as expected since the sources of π and f are the same and their values are well correlated; the least-squares line ($n = 24$) of f *versus* π has slope 0.990 ± 0.017; $s = 0.095$; $R = 0.997$. We have used π throughout because: (*a*) its definition [equation (7)] concurs with Hammett's definition [σ(H) ≡ 0] in giving π(H) ≡ 0; (*b*) it is more transparent and less ambiguous by the simplicity of equation (7); and (*c*) more π-values have been tabulated. Additional parameters that we found unsuccessful in, *e.g.*, 32TB, are: (*a*) size or volume (expected order of anomaly: Bu^t > CH$_2$OH > H); (*b*) weight (expected order: I > Bu^t > CH$_2$OH > H); and (*c*) polarizability (wrong sign: Bu^t would be acid-strengthening).

† The supplementary data referred to throughout this paper are presented in Supplementary Publication No. SUP 56758 (14 pp.). For details of the Supplementary Publications scheme see 'Instructions for Authors' (1989), *J. Chem. Soc., Perkin Trans. 2*, in the January issue.

Table 3. Statistical data[a] pertaining to equations (2) and (5): dissociation constants of benzoic acids and rates of alkaline hydrolysis of ethyl arylacetates and benzyl acetates.

Set no.	Solvent	n	$\rho \pm s_\rho$	s	R	Int.	F	$h \pm s_h$	Substituents
$ArCO_2H$									
1a	10E	15[b]	1.089 ± 0.010	0.013	0.9995	−0.004	12 682		*b*
b			1.083 ± 0.009	0.012	0.9996	−0.004	7 884	−0.009 ± 0.004	
2a	50E	24	1.571 ± 0.035	0.059	0.9946	−0.069	2 017		1–24
b			1.484 ± 0.019	0.028	0.9989	−0.030	4 675	−0.051 ± 0.006	
c		14	1.627 ± 0.071	0.065	0.9889	−0.090	531		outside[c]
d			1.484 ± 0.036	0.028	0.9981	−0.033	1 442	−0.049 ± 0.007	
e		10	1.504 ± 0.030	0.036	0.9985	−0.021	2 626		inside[d]
f			1.466 ± 0.030	0.030	0.9991	−0.031	1 972	−0.089 ± 0.040	
g		6	1.475 ± 0.024	0.025	0.9995	0.013	4 253		*e*
h			1.478 ± 0.030	0.028	0.9995	0.022	1 629	0.022 ± 0.088	
3a	75E	24	1.719 ± 0.026	0.043	0.9976	−0.040	4 526		1–24
b			1.689 ± 0.028	0.040	0.9980	−0.027	2 614	−0.017 ± 0.008	
c		14	1.732 ± 0.043	0.040	0.9963	−0.047	1 616		outside[c]
d			1.686 ± 0.047	0.036	0.9972	−0.028	963	−0.016 ± 0.009	
e		10	1.699 ± 0.042	0.051	0.9977	−0.026	1 716		inside[d]
f			1.662 ± 0.048	0.048	0.9982	−0.036	944	−0.087 ± 0.065	
4a	85E	24	1.753 ± 0.028	0.047	0.9973	−0.041	4 007		1–24
b			1.756 ± 0.033	0.048	0.9973	−0.043	1 915	0.002 ± 0.010	
5a	22TB	24	1.481 ± 0.074	0.125	0.9733	−0.146	396		1–24
b			1.289 ± 0.035	0.050	0.9960	−0.060	1 304	−0.112 ± 0.010	
c		14	1.559 ± 0.162	0.149	0.9411	−0.190	93		outside[c]
d			1.227 ± 0.075	0.058	0.9921	−0.057	342	−0.115 ± 0.014	
e		10	1.344 ± 0.027	0.033	0.9985	−0.039	2 581		inside[d]
f			1.327 ± 0.033	0.033	0.9986	−0.044	1 266	−0.041 ± 0.047	
g		6	1.353 ± 0.014	0.015	0.9998	−0.039	10 374		*e*
h			1.347 ± 0.016	0.015	0.9999	−0.058	5 089	−0.044 ± 0.046	
6a	32TB	24	1.652 ± 0.101	0.170	0.9612	−0.194	267		1–24
b			1.375 ± 0.026	0.037	0.9983	−0.071	3 034	−0.161 ± 0.008	
c		14	1.774 ± 0.213	0.196	0.9235	−0.260	70		outside[c]
d			1.309 ± 0.042	0.033	0.9981	−0.074	1 449	−0.160 ± 0.008	
e		10	1.449 ± 0.047	0.057	0.9961	−0.039	1 019		inside[d]
f			1.372 ± 0.034	0.034	0.9988	−0.059	1 486	−0.181 ± 0.045	
g		6	1.413 ± 0.028	0.029	0.9993	0.010	3 089		*e*
h			1.397 ± 0.028	0.026	0.9996	−0.038	1 925	−0.114 ± 0.081	
i		2	1.31			−0.35			3, 15
7a	10E	13[f]	1.099 ± 0.014	0.013	0.9991	−0.005	6 063		*f*
b			1.090 ± 0.014	0.012	0.9993	−0.002	3 668	−0.008 ± 0.004	
8a	30E	15	1.427 ± 0.058	0.062	0.9894	−0.062	606		1–15
b			1.299 ± 0.029	0.026	0.9983	−0.015	1 731	−0.048 ± 0.006	
9a	50E	15	1.607 ± 0.066	0.070	0.9891	−0.074	585		1–15
b			1.453 ± 0.024	0.021	0.9991	−0.017	3 406	−0.058 ± 0.005	
10a	75E	15	1.734 ± 0.035	0.038	0.9973	−0.042	2 391		1–15
b			1.667 ± 0.028	0.024	0.9989	−0.017	2 835	−0.025 ± 0.006	
11a	85E	15	1.738 ± 0.033	0.035	0.9977	−0.034	2 848		1–15
b			1.719 ± 0.040	0.035	0.9979	−0.027	1 395	−0.007 ± 0.008	
12a	10TB	14[g]	1.116 ± 0.019	0.019	0.9983	−0.025	3 542		*g*
b			1.099 ± 0.019	0.017	0.9987	−0.019	2 132	−0.010 ± 0.006	
13a	22TB	15	1.574 ± 0.145	0.154	0.9492	−0.170	118		1–15
b			1.243 ± 0.060	0.053	0.9946	−0.047	556	−0.124 ± 0.012	
14a	32TB	15	1.771 ± 0.192	0.204	0.9312	−0.228	85		1–15
b			1.312 ± 0.041	0.036	0.9981	−0.058	1 567	−0.172 ± 0.009	
15a	40TB	15	1.811 ± 0.168	0.178	0.9484	−0.206	116		1–15
b			1.414 ± 0.046	0.040	0.9976	−0.059	1 270	−0.149 ± 0.010	
16a	50TB	15	1.830 ± 0.149	0.158	0.9594	−0.169	150		1–15
b			1.478 ± 0.043	0.038	0.9979	−0.039	1 424	−0.132 ± 0.009	
17a	60TB	15	1.863 ± 0.129	0.137	0.9703	−0.126	209		1–15
b			1.557 ± 0.030	0.026	0.9990	−0.013	2 968	−0.115 ± 0.006	
18a	75TB	15	1.921 ± 0.093	0.098	0.9853	−0.065	431		1–15
b			1.710 ± 0.040	0.035	0.9983	0.013	1 747	−0.079 ± 0.008	
19a	90TB	15	1.988 ± 0.056	0.059	0.9949	−0.048	1 266		1–15
b			1.886 ± 0.046	0.040	0.9978	−0.010	1 370	−0.038 ± 0.010	
20a	30MCS	6	1.544 ± 0.093	0.067	0.9929	−0.093	278		1, 4, 5, 10, 12, 15
b			1.377 ± 0.053	0.028	0.9991	−0.004	819	−0.049 ± 0.011	
21a	80MCS	6	1.823 ± 0.025	0.018	0.9996	−0.020	5 473		1, 4, 5, 10, 12, 15
b			1.789 ± 0.027	0.014	0.9998	−0.001	4 520	−0.010 ± 0.005	
22a	65DMSO	6	1.766 ± 0.032	0.023	0.9994	0.012	3 119		1, 4, 5, 10, 12, 15
b			1.770 ± 0.051	0.027	0.9994	0.010	1 174	0.001 ± 0.010	

Table 3 (*continued*).

Set no.	Solvent	*n*	$\rho \pm s_\rho$	*s*	*R*	Int.	*F*	$h \pm s_h$	Substituents
$ArCH_2CO_2Et + OH^-$									
23a	85% E w/w	5[h]	1.252 ± 0.027	0.018	0.9993	−0.014	2 130		1, 5, 10, 13, 15
b			1.237 ± 0.042	0.021	0.9994	−0.005	817	−0.005 ± 0.008	
24a	56% A w/w	7[i]	1.114 ± 0.178	0.133	0.9418	−0.124	39		1, 2, 5, 10, 12, 13, 15
b			0.849 ± 0.051	0.031	0.9975	0.023	393	−0.100 ± 0.011	
$ArCH_2CO_2Et + OH^-$									
25a	56% A w/w	4[j]	0.719 ± 0.082	0.051	0.9873	−0.044	77		1, 2, 10, 15
b			0.686 ± 0.032	0.019	0.9991	−0.012	282	−0.067 ± 0.018	

[a] Set no., number identifying set of *n* data points. Sets are in pairs: *e.g.*, set 2a gives data for 24 data points in 50E with equation (2); set 2b relates to the same 24 data points with equation (5) and thus includes *h* and its standard deviation s_h; s_ρ, standard deviation of ρ; *s*, standard deviation of the experimental points; *R*, correlation coefficient; int., intercept with ordinate ($\sigma = 0$, or $\sigma = \pi = 0$); *F*, *F* test; actual substituents used, mostly identified by their number in Table 1; see note *a* of Table 1. The use of ($\pi + 0.3$) improves the predominantly (slightly) negative intercepts. [b] $n = 15$ because 8 of the 23 measured pK_a values in 10E have been used to derive aqueous σ values. [c] Outside, substituents with $0.27 < \pi < -0.73$ (see Figure 3). [d] Inside, substituents with $0.27 > \pi > -0.73$ (see Figure 3). [e] Substituents with $-0.26 > \pi > -0.66$, *i.e.*, CMe_2OH, CHO, COMe, CN, NO_2, 3,5-di-NO_2. [f] 1–15 omitting 3-Bu^t and 3,5-di-Bu^t (*cf.* note *b*). [g] 1–15 omitting 3,5-di-Bu^t (*cf.* notes *b* and *f*). [h] J. G. Watkinson, W. Watson, and B. L. Yates, *J. Chem. Soc.*, 1963, 5437; R. O. C. Norman and D. J. Byron, see note *c* of Table III of ref. 3. [i] R. O. C. Norman, G. K. Radda, D. A. Brimacombe, P. D. Ralph, and E. M. Smith, *J. Chem. Soc.*, 1961, 3247; R. O. C. Norman and P. D. Ralph, *J. Chem. Soc.*, 1963, 5431; R. O. C. Norman and D. J. Byron, see note *c* of Table III of ref. 3. [j] E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1938, 1801; E. Tommila, *Ann. Acad. Sci. Fenn., Ser. A*, 1942, **59**, 4.

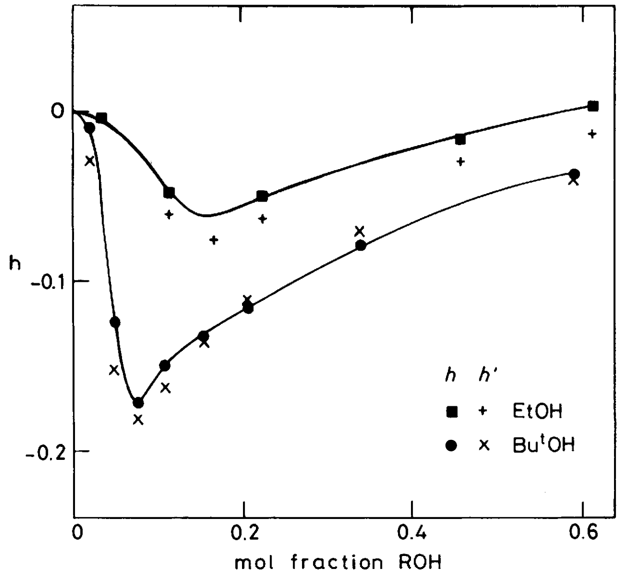

Figure 4. Dependence of h_m and h'_m on solvent composition for E/H_2O and TB/H_2O; h_m is from Table 3, h'_m is obtained from equation (5) by using only $\Delta(3\text{-}NO_2)$ to give $\rho_m = \Delta(3\text{-}NO_2)/0.71$, and Δ(3,5-di-Bu^t) or (for 10E and 10TB) Δ(3-Bu^t) with $\pi = 3.96$ or 1.98 and $\sigma = -0.14$ or -0.07.

Table 4. Benzoic acids:[a] thermodynamic pK_a values of the parent, and substituent effects expressed as $100(pK_a^\circ - pK_a)$, in 30% and 80% methyl Cellosolve and 65% DMSO, at 25 °C.

Substituent	30MCS	80MCS	65DMSO[b]
H	4.84	7.21	−6.06
3-Bu^t	−22	−16	−12
3,5-di-Bu^t	−37	−29	−24
$3\text{-}CEt_3$	−38	−23	−19
$3\text{-}NO_2$	99	126	124
3-OH			−2
3-OMe			19
3-F	48	61	63
3-I	40	63	66
4-Me	−20	−18	−20
4-Bu^t	−21	−15	−20
$4\text{-}CEt_3$	−30	−24	−21
$4\text{-}SiMe_3$			8
$4\text{-}NPh_2$		−33	−32
4-OH	−43	−59	−52
4-OMe	−31	−34	−35

[a] See note *a* Table 1. [b] See also Table 5 and ref. 8.

Table 5. Benzoic acids:[a] thermodynamic pK_a values of the parent, and substituent effects expressed as $100(pK_a^\circ - pK_a)$, in DMSO–water mixtures, at 25 °C.

	Substituents			
% DMSO	H	3-Bu^t	$3\text{-}CEt_3$	$3\text{-}NO_2$
0	4.21	−7		71
10	4.33	−7		77
20	4.50	−7		83
30	4.69	−9		89
40	4.96	−10	−19	97
50	5.28	−11	−18	106
65	6.06	−12	−19	124
80	7.29	−14	−16	141

[a] See note *a* Table 1, and note *b* of Table 4.

NO_2 in combination with its large σ_m value implies that the straight line connecting the data points for H and $3\text{-}NO_2$ gives a good approximation of the 'true' Hammett plot; this justifies the calculation of the σ_m values as for Figures 1 and 2. Further, the data points for two groups with the same π and different σ_m should give ρ_m as $\Delta pK_a/\Delta\sigma$. An example is the pair 3,5-di-Me/3-I with $\pi = 1.07$ and 1.12, and $\sigma_m = -0.13$ and $+0.35$, yielding $\rho_m = 1.31$ in 32TB; the intercept of the line through these points is -0.35, however. It is interesting to note that when using equation (2) for the pairs H/3,5-di-Me and H/3-I, the ρ_m values are 3.4 and 0.5, respectively.

Deviations from the Hammett equation for the pK_a values of $ArCO_2H$ are not restricted to E/H_2O and TB/H_2O; in fact, maximum h_m values of -0.05 to -0.20 are the rule in water–organic solvent mixtures.[6] In order to avoid unnecessary alarm we thought it useful to include here our data for $ArCO_2H$ in two other often used solvent mixtures, MCS/H_2O[7] (Table 4) and $DMSO/H_2O$[8] (Tables 4 and 5).

The sets 20–22 of Table 3 give the statistical data and show that 80MCS and 65DMSO have been fortunate choices with

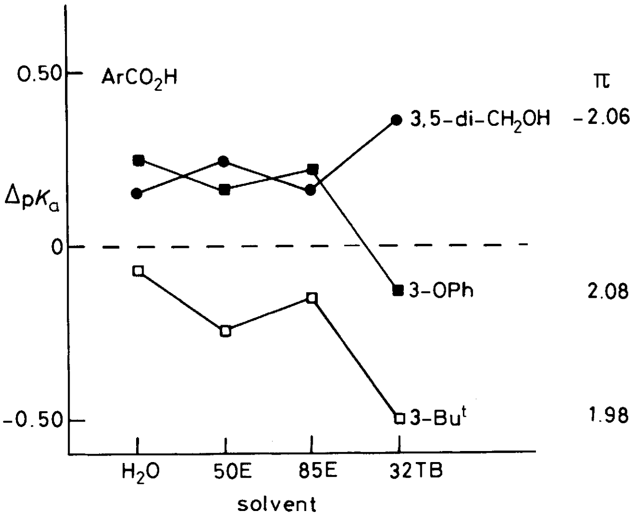

Figure 5. Showing 'parallel' and 'mirrored' behaviour of groups with large positive and large negative π values.

respect to adherence to equation (2); h_m is virtually zero. MCS/H_2O probably resembles E/H_2O, as suggested by $h_m = -0.05$ in 30MCS. The mixture DMSO/H_2O is of special interest in that the constancy of $\Delta(3\text{-}Bu^t)/\Delta(3\text{-}NO_2)$ in Table 5 indicates that $h_m = 0$ for the entire range 0–80MCS, with possibly some deviation for 3-CEt_3 ($h_m \leq -0.02$). The values for 4-Bu^t are, like those in 75E and 85E, in agreement with our low σ_p value in Table 1; their average is -0.09 ± 0.01 ($n = 4$; see also below).

The sets 23 and 24 of Table 3 relating to work by Watson and co-workers and Norman and co-workers on alkaline ester hydrolysis refer back to the large difference of σ of 3,5-di-Bu^t in 85.4% E (w/w) and 56% A (56% acetone–water, w/w) mentioned in the introduction. The normal value of $\sigma = -0.14$ in 85% E goes with a vanishingly small h_m. The strongly negative $\sigma = -0.53$ in 56% A goes with a considerable $h_m = -0.10$ and equation (5) shows a corresponding strong improvement over equation (2); the $h\pi$ term forms about 80% of the substituent effect.

Set 25, regarding alkaline hydrolysis of a (small) number of benzyl acetates in 56% A is included in Table 3 to give credit to work by Tommila. Equation (2) does not give entirely satisfactory results, and some thirty years ago we considered this to be possibly due to impurities in the compounds, all four being high-boiling liquids. The improvement by equation (5) confirms the reliability of the experiments and supports the equation.

In equations (5) and (6) we distinguished between h_m and h_p. Inspection of Tables 1 and 2 suggests that the anomalies are somewhat smaller for *para*- than for *meta*-substitution. Thus $\Delta(4\text{-}Bu^t) = -0.40$ and $\Delta(3\text{-}Bu^t) = -0.50$ in 32TB. Subtracting the ρσ contributions gives -0.25 and -0.40 for the $h\pi$ terms, *i.e.*, $h_p = 0.63\, h_m$. A statistical measure comes from fitting equation (8) to the 31 data points for H and 15 substituents tabulated in both *meta*- and *para*- position; the pair 32TB/50E was chosen because the ρ values are almost equal. This approach yields the (relative) $h_m = -0.126 \pm 0.011$ and $h_p = -0.096 \pm 0.012$ from which $h_p = 0.76\, h_m$.*

$$\Delta(32TB) = \rho\Delta(50E) + h_m\pi + h_p\pi \qquad (8)$$

Tables 1 and 2 contain several data which further illustrate equation (5) and deserve comment.

(*a*) Table 1 gives examples of other *meta*-substituents showing $h\pi$ anomalies; 3-Ph and 3-OPh (both with a change in sign of Δ between 85E and 32TB) and 3- and 4-$SiMe_3$. The 3-OH group shows other influences to be operative as well.[9]

(*b*) Groups with the same standard σ value but different π should have Δ values which differ more the larger h_m. The 3-alkyl groups give a perfect demonstration (Figures 1 and 2). An example with large σ values provides the pair 3-NO_2/3,5-Cl_2 with $\sigma_m = 0.71$; in 50E $\Delta = 1.07$ and 1.02, in 32TB $\Delta = 0.99$ and 0.69, respectively.

(*c*) Figure 5 shows the parallel behaviour of Δ for groups with different σ_m and large and equal positive π (3-OPh and 3-Bu^t) and the mirrored behaviour of Δ for a group with an equally large but negative π [3,5-$(CH_2OH)_2$].

(*d*) The series 4-NH_2, 4-NHPh, 4-NPh_2 in 32TB shows $\Delta = -0.64, -0.81, -0.70$, an unexpected and irregular order in view of the inductive effect of Ph and steric inhibition of resonance. Working backwards and calculating $\sigma_p = (\Delta - 0.76\, h_m\pi)/\rho_m$ we obtain $\sigma_p = -0.57, -0.47, -0.19$; these values are acceptable and agree well with the corresponding values calculated from 50E: $-0.57, -0.42, -0.25$, and from 75E: $-0.54, -0.40, -0.19$, respectively; the averages are -0.56, 0.43, and -0.21.

(*e*) Additivity is mostly acceptable for 3,5-disubstitution. The deviations with 3,5-di-Bu^t are only apparent through the position of the minimum at 26TB; for 3,5-di-OH additivity applies, though equations (2) and (5) are not well obeyed. An interesting exception is 3-CH_2OH-5-Br which was chosen because the sum of the π values is almost zero ($-1.03 + 0.86$). In practice additivity of Δ is not well obeyed in the mixed solvents and the group behaves roughly as though π is *ca.* 0.9 in the range 20–60TB. The literature contains other examples in which the combination of a positive and a negative π yields an experimental π which is more positive than the π-sum,[5b] *e.g.*, 1-CH_2OH-3-Cl (π-sum 1.64, log *P* 1.94) and 1-CH_2OH-3-NO_2 (π-sum 0.65, log *P* 1.21). Such deviations are evidently not covered by equation (5).

Discussion

The practical implications of our results are clear. The most direct is that solvent mixtures in the ranges 20E–60E and 15TB–90TB introduce more or less serious complications with respect to the Hammett equation. Such solvents are not a good choice with which to derive standard (aqueous) σ values as Δ/ρ.

If in water–organic solvent mixtures simple Hammett behaviour is desired, *e.g.* for mechanistic studies, it is advisable either to use *meta*-substituents having a fairly narrow range of π values like the 'insides' in sets 6e and 6g, or to choose solvent mixtures like 10E, 75E, 85E, 80MCS, or 65DMSO; possibly a combination of these alternatives would be even better.

If a specific solvent mixture has to be used a large set of data for substituents with proper ranges of σ and π should verify equations (4)–(6) and give a reliable *h*, and thus separate the $h\pi$ terms and ρσ terms. For the purpose of orientation a short cut can be considered in which, for example, only data for H, 3-NO_2 (large σ, small π) and 3-Bu^t (small σ, large π) are used. Solving the two equations (5) for ρ and *h* gives, in our cases, values which are very close to those in Table 3, and also to those obtained by taking ρ from $\Delta(3\text{-}NO_2)/0.71$ and solving equation (5) for $\Delta(3\text{-}Bu^t)$ (Figure 4).

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* The correlation ($n = 31$) has $\rho = 0.944 \pm 0.016$; $s = 0.033$; $R = 0.9978$; intercept $= -0.026$; and $F = 2\,067$. [The equation $\Delta(32TB) = \rho\Delta(50E)$ gives $s = 0.083$; $R = 0.9855$; intercept $= -0.106$; and $F = 982$]. Treatment of the pairs 32TB/10E and 32TB/75E as in equation (8) gives $h_p = 0.63\, h_m$ ($n = 25$) and $h_p = 0.81\, h_m$ ($n = 31$), respectively. The average of the three values is 0.73. When treating the *meta* and *para* sets separately ($n = 16$) the pairs 32TB/50E yield (relative) values $h_m = -0.131 \pm 0.011$ and $h_p = -0.097 \pm 0.007$, whence $h_p = 0.74\, h_m$.

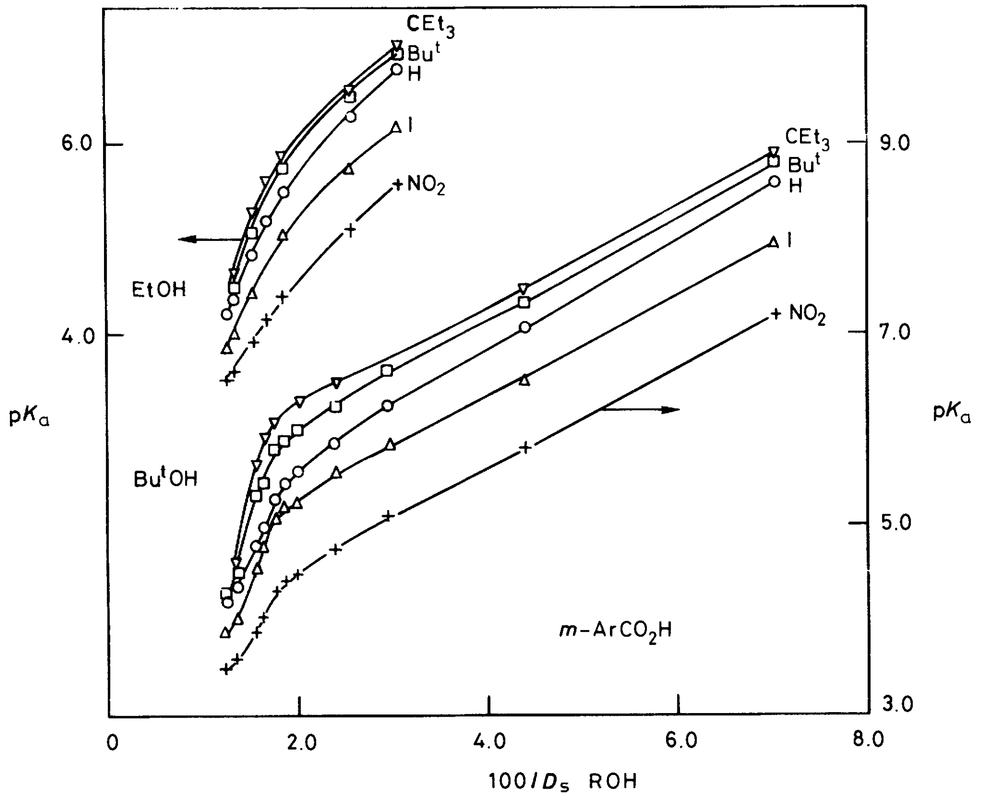

Figure 6. Thermodynamic pK_a values as a function of the reciprocal of the bulk relative permittivity, $1/D_s$.

Once equations (4)–(6) are found to be satisfactory, aqueous values of σ can be found by working backwards as illustrated above for the 4-amino groups. Of course, small values of $[\Delta - h\pi]$ may make the results somewhat doubtful, but such σ values should be better than those from equations (1)–(3). As a numerical example we give the results for the seven values for 4-Bu^t in TB/H$_2$O. The values of Δ/ρ_m vary from -0.11 to -0.30; the values of $(\Delta - 0.76\ h_m\pi)/\rho_m$ vary from -0.05 to -0.11 with an average of -0.08 ± 0.02. The same average is obtained when using all fourteen available data.*

As regards rationalization of the above deviations from the Hammett equation there would seem to be no alternative but to relate them to the well-known anomalies of thermodynamic properties of the mixed solvents and the concomitant anomalies of reactivities in these solvents.[10,11] Extremes such as in 5–10 mol% TB/H$_2$O have been observed often and are usually ascribed to clathrate- or clathrate-like structures of water sheaths surrounding the organic solvent molecules, structures which increase 'the resistance offered by the solvent'[11] to the solvent reorganization occurring when a solute is added.

Anomalies of this type are already found in the pK_a values as a function of solvent composition expressed as either vol%, mol%, or $1/D_s$ (Figure 6). We interpret these curves as showing an upward bulge which is at a maximum at about 32TB; in this region the acid strength is anomalously low due to the ion requiring a larger reorganization of the solvent structure than the acid. The relation to equation (4) is strongly suggested by the observation that for benzoic acid the function $[pK_a + ah_m]$ with $a \approx 2$ harmonizes with a smooth curve without inflections† resembling the smooth pK_a curves of formic acid[12] and acetic acid[12] in TB/H$_2$O, or, significantly, acetic acid *and* benzoic acid in DMSO/H$_2$O.[13] Equation (5) then states that for, *e.g.*, 3-Bu^t-benzoic acid the function $[pK_a + \rho_m\sigma_m + 1.98\ h_m]$ approximates the pK_a curve of benzoic acid, *i.e.*, that the bulge of $[pK_a + \rho_m\sigma_m]$ is more prominent than that for the pK_a of benzoic acid; the function $[pK_a + \rho_m\sigma_m + (1.98 + a)h_m]$ then approximates a smooth curve. If a substituent with negative π value (CH$_2$OH) is present, the bulge in $[pK_a + \rho_m\sigma_m]$ is less pronounced than that for the pK_a of benzoic acid (see below).

When accepting the smoothness of these functions as a criterion of normalcy, the lack of bulge with formic acid indicates that the sensitivity to the order of the mixed solvent begins when the acid (and its anion) is made less hydrophilic by a ligand with positive π, as in benzoic acid or in the aliphatic acids[12b] which show a bulge with the longer chains: cyclohexanecarboxylic acid behaves like benzoic acid. Thus, benzoic acid begins to lose in the competition for water (or t-butyl alcohol) which is least available when the order of the solvent is at a maximum. Perhaps this concept of the 'partition' of water between t-butyl alcohol and the solute gives a clue to the success of the use of π as an additional parameter: the real partition defining π is determined by the same or similar factors. When the hydrophilicity of the acid is further decreased (Bu^t) a further adverse effect on acid strength results. A benzoic acid with a substituent with negative π (CH$_2$OH) experiences the same sort of competition but suffers less than the parent.

Figure 7 indicates that ρ_m of ArCO$_2$H shows the same anomaly in TB/H$_2$O. In this case the function $[\rho_m + h_m]$ shows an approximately smooth curve; once more there is no trace of a

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* The usually quoted σ(4-Bu^t) = -0.197 stems from benzoic acids in water by J. W. Baker, J. F. J. Dippy, and J. E. Page, *J. Chem. Soc.*, 1937, 1774. This figure is of doubtful value since the reported range of concentrations is only 0.20–0.17 × 10^{-3} mol dm^{-3} instead of the usual three- or four-fold variation in concentration. Again, such solutions are almost saturated: J. B. Shoesmith and A. Mackie, *J. Chem. Soc.*, 1936, 300 give a solubility of 0.29 × 10^{-3} mol dm^{-3} at 25 °C.

† For $a = 1$ an upward bulge remains; for $a = 4$ a downward bulge appears at 22TB; $a = 2$ is possibly somewhat better than $a = 3$. It will be noted that the smoothness is determined by the pK_a values in 22 and 32TB (*cf.* Figure 7 relating to the ρ_m values).

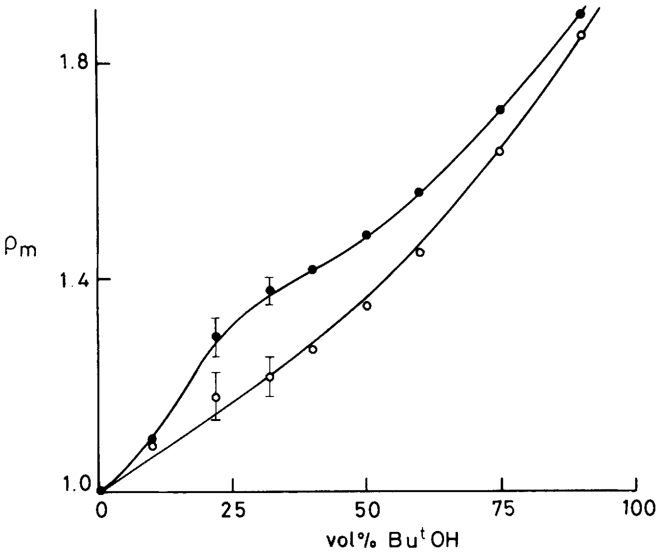

Figure 7. Values of ρ_m from equation (5) (●) and $[\rho_m + h_m]$ (○) in TB/H_2O. For 22 and 32TB the ρ_m values are from sets 5b and 6b (n = 24); see text.

bulge in $DMSO/H_2O$ [Δ(3-NO_2)]. Yet, some doubt as to the existence of the bulge in TB/H_2O remains. Figure 7 was constructed from our best ρ_m values, *i.e.*, using for 22TB and 32TB the sets with $n = 24$ (5b, 6b) with $\rho_m = 1.289 \pm 0.035$ and 1.375 ± 0.026. When using the sets 12–19 consistently (n = 15 or 14), with $\rho_m = 1.243 \pm 0.060$ for 22TB and $\rho_m = 1.312 \pm 0.041$ for 32TB, the presence of a bulge appears questionable. These data conform surprisingly well to linearity: $\rho_m(x\text{TB}) = 1 + (0.0096 \pm 0.0002)x$ where x is our volume percentage; with $s = 0.02$, $R = 0.998$ ($n = 9$).* On the other hand, the errors in ρ_m are such that there is no disagreement with Figure 7, and the 'inside' sets 5f and 6f as well as 5h and 6h give higher ρ_m values in 22TB and 32TB which indicate the presence of a bulge. However this may be, any anomaly in ρ_m does not exceed 10%.

The above approach raises some interesting questions. Equations (4)–(6) define $h \equiv 0$ for $ArCO_2H$ in water. Since Figure 6 shows these acids to be sensitive to the structural peculiarities of the solvent, and since water is taken to be structured, the standard aqueous σ values may be suspected of having a component which reflects that order. This component seems to be small at best in view of the observation that the Hammett equation is followed so closely in such varying solvents as 85E, 65DMSO, and benzene[3] which clearly must have a *different* and probably smaller degree of order. This possibly means that water is relatively flexible with respect to the three-dimensional reorganization required by the solute.

A related question is whether, by introducing substituents with increasingly negative π values, the upward bulge can be transformed into a downward bulge. We have no such examples: 3,5-$(CH_2OH)_2$-benzoic acid still shows a small upward bulge in TB/H_2O for $[pK_a + \rho\sigma]$, although with the assumed $\pi = -2.06$ of 3,5-$(CH_2OH)_2$ the estimated anomaly of benzoic acid ($a \approx 2$) should be compensated. One possibility is that downward bulges do not exist because there are no solvent mixtures which provide water with greater ease than does water. If so, a levelling-off of the effect of negative π substituents has to be expected. In this connection it is noteworthy that in 32TB the mono-substituted acids with positive π-substituents (-0.01 to $+2$) give a larger $h_m = -0.183 \pm 0.018$ ($n = 11$) than those with negative π-substituents ($+0.01$ to -2), $h_m = -0.116 \pm 0.026$ ($n = 11$).

As to the inequality $h_m \neq h_p$ we found for $ArCO_2H$, our treatment is of no avail ($\pi_m = \pi_p$). Distance as one factor is suggested by the low h' value for $ArCH_2CH_2CO_2H$ (see below), but an estimation of the solvation of each separate entity, which is probably required for an explanation, is far beyond our Hammett-type equations.

The deviations from the Hammett equation are not restricted to the pK_a values of $ArCO_2H$. In the present paper we have already given some examples of ester hydrolysis (sets 23–25). From an earlier paper[3] we quote the highly negative σ values in 50E for 3-Bu^t and 3,5-di-Bu^t in the series $ArCH_2CO_2H$ and $ArCH_2CH_2CO_2H$, corresponding to h' values of -0.06 and -0.03, respectively. We wish to add one fundamental extension here: the dissociation constants of ammonium acids, where the charged particle is the acid and, therefore, positive values of h are found; these have a magnitude comparable to those for the carboxylic acids.[6] As a dramatic consequence, plotting ΔpK_a of $ArCH_2NH_3^+$ *versus* ΔpK_a of $ArCH_2CO_2H$ in the same solvent, for ten of our usual substituents (1, 2, 4–6, 10, and 12–15 of Table 1), yields correlation coefficients $R = 0.893$ for 50E and $R = 0.381$ for 32TB. Plotting the corresponding $[\Delta - h\pi]$ values gives $R = 0.998$ for 50E and $R = 0.981$ for 32TB. The latter value is quite acceptable in view of the magnitude of the $h\pi$ terms, up to 0.5 pK units. The direct comparison of $ArNH_3^+$ and $ArCO_2H$ or ArOH gives similar results. A convincing single illustration is the substituent effect of 4-Bu^t in piperidinium ion which is acid-strengthening by 0.23 pK units in 50E and 0.54 pK units in 32TB.

Elements of the described anomalies can be found in the literature. We draw attention to the upward bulge in the pK_a value of benzoic acid[12] and cyclohexanecarboxylic acid[12b] in TB/H_2O, observed by Morel and others; the lack of it for CH_3CO_2H[12] in TB/H_2O and for CH_3CO_2H *and* $PhCO_2H$ in $DMSO/H_2O$ has already been mentioned.[13] Dollet and Juillard[14] measured the enthalpies of solution of the potassium salts of the four *para*-halogen-substituted benzoic acids and found anomalies in TB/H_2O in the order F $\ll$ Cl < Br < I with extrema at *ca.* 5 mol%; they ascribed these to hydrophobic size effects.

Rochester *et al.*[15] studied the pK_a values in TB/H_2O of phenol and four derivatives: 4-Bu^t, 4-Br, 4-NO_2, and 4-CHO. From their results we observe the following: (*a*) the pK_a values of the phenols show an upward bulge similar to that of the benzoic acids in Figure 6; (*b*) the effect of 4-Bu^t increases from -0.24 pK_a units in water, to a maximum of -0.60 pK_a units in 7 mol% TB/H_2O; (*c*) the effect of 4-Br decreases from 0.65 pK_a units in water, to a minimum of 0.42 pK_a units in 10 mol% TB/H_2O; and (*d*) the discussion of pK_a anomalies on the basis of the Hammett equation, ascribing the deviations to varying ρ values only, is not in line with our treatment and not in harmony with our results.

It is appropriate here to refer to the recent work of Fan and Jiang[16] on the alkaline hydrolysis at 45 °C of *meta*- and *para*-substituted aryl octanoates, denoted 8-Y, and aryl hexadecanoates, 16-Y, in 55–70% DMSO (v/v). For the 16-Y series in 55% DMSO they found a highly convincing failure of the Hammett equation as illustrated by the order of reactivities 3-Cl < H < 3-NO_2. Like us,[17] they introduced the hydrophobic constant as an additional parameter, writing equation (9), where f is Rekker's hydrophobic fragmental constant.

$$\log K = \rho\sigma + hf + C$$

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* In E/H_2O linearity is also approximated: $\rho_m(x\text{E}) = 1 + (0.0086 \pm 0.0003)x$ with $s = 0.02$, $R = 0.998$ ($n = 6$). Extrapolation to 100E gives 1.87 which agrees well with $\rho_m = 1.85 \pm 0.09$, $R = 0.988$ on the basis of pK_a data from M. Ludwig, V. Baron, K. Kalfus, O. Pytela, and M. Večeřa, *Collect. Czech. Chem. Commun.*, 1986, **51**, 2135 (n = 13 of our set of 24).

† Some notes on this treatment are given in the supplementary material.

Impressive results were obtained with h as large as -0.78 ± 0.05 ($n = 11$, $F = 222$) in 55% DMSO, and $h = -0.50$, -0.41, and -0.33 in 60, 65, and 70% DMSO, respectively.[†] The observed behaviour was 'ascribed to aggregation and coiling.' The 8-Y series was considered to follow equation (2); the rates for H, 3-Cl, and 3-NO_2, however, yield h values between -0.1 and -0.2.

The relation to our work is probably less than suggested by the likeness of the chosen correlation equations. Whereas our h appears as a measure of solvent structure, their h probably reflects solute structure in a solvent mixture with little structure. In this connection we recall that for $ArCO_2H$ dissociation $h = 0$ in 0–80 DMSO (Table 5) and that our ρ values vary very smoothly in DMSO/H_2O and fairly regularly or regularly even in TB/H_2O (Figure 7), whereas their ρ value drops abruptly from 1.11, 1.14, and 1.12 in 70, 65, and 50% DMSO to 0.34 in 55% DMSO. As for interpretation, we believe that for our pK_a values aggregation of the solutes is not of importance;[*] coiling is, of course, not relevant to the benzoic acids.

Further thermodynamic data are needed to obtain a more complete, less naive interpretation of the observed anomalies. We hope that the present work will provide some useful leads.

Experimental

Materials.—Those details on the preparation and physical data of the carboxylic acids which are not given in ref. 4 are specified in Table 6 in the supplementary material. Solvents; water, CO_2-free conductivity water; ethanol, CO_2-free (Baker Analyzed); t-butyl alcohol (Chemically Pure) was dried over anhydrous potassium carbonate and distilled; methyl Cellosolve (Merck p.a.) was treated with calcium oxide and barium oxide, and then distilled, the first 25% being discarded (Simon *et al.*[7]), b.p. 122–123 °C; DMSO (Aldrich, 99+%) was dried over a molecular sieve 3A and distilled *in vacuo*, b.p. 93–94 °C/35 mm.

Dissociation Constants.—The thermodynamic pK_a values at 25 °C were determined as described[18] and exemplified[2,18] previously. Physical data of the solvents (density, relative permittivity, solvent correction of the pH reading, and pK_w) are listed in Table 7 in the supplementary material, which also includes further notes on the measurements.

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[*] Potentiometry at 5×10^{-3} mol dm^{-3} and spectroscopy at 5×10^{-5} mol dm^{-3} with aniline, 3-Bu^t-aniline, and 3,5-di-Bu^t-aniline in 32TB, gave virtually the same pK_a values (λ *ca.* 280 nm; I for acetate buffers 2×10^{-3} mol dm^{-3}); *cf.* notes *q* and *r* of Table 1 and notes *b* and *c* of Table 2.

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