Basicity (pK_{BH^+}) and Acidity Constants (pK_a^*) of some 3-X-, 4-X-, and 2,6-Dimethyl-4-X-benzoic Acids

Paolo De Maria,[a] Antonella Fontana,[b] Domenico Spinelli,[b] Carlo Dell'Erba,[c] Marino Novi,[c] Giovanni Petrillo[c] and Fernando Sancassan[c]

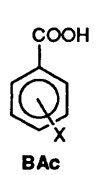
[a] *Dipartimento di Chimica Organica, Università di Palermo, Via Archirafi 20, Palermo 90123, Italy*
[b] *Dipartimento di Chimica Organica 'A. Mangini', Università di Bologna, Via S. Donato 15, Bologna 40127, Italy*
[c] *Istituto di Chimica Organica and CNR Centro di Studio per la Chimica dei Composti Cicloalifatici ed Aromatici, Corso Europa 26, Genova 16132, Italy*

The behaviour of some benzoic acids both as bases (pK_{BH^+}) and acids (pK_a^*) has been compared with that of their 2,6-dimethyl derivatives. In particular the protonation equilibria, while assigning (through the value of the m^* parameter of the excess-acidity method) a significant role to solvation as a stabilising effect on the cations, seem to further assess a major contribution of π-polarisation to the resonance effect of *para*-substituents, although some through-conjugation with electron-donating groups cannot be excluded, possibly enforced by the strong requirement for stabilisation of the positive charge in the protonated forms.

The protonation equilibria in concentrated solutions of mineral acids, of typical carbonyl compounds such as aromatic ketones,[1] amides[2] and esters[1b,1c,3a] have been the subject of a number of studies; on the contrary, only scanty data are available for benzoic acids and benzoyl halides. While the lack of data for aroyl halides is very understandable in view of their high rates of hydrolysis (and the consequent instability of these compounds in aqueous solutions), accurate pK_{BH^+} values for benzoic acids (BAc) can be calculated by standard treatments[4] from protonation data obtained in concentrated sulfuric acid solutions. To our knowledge, though, there is only one paper[5] reporting reliable protonation constants for some 3- and 4-substituted BAc. Earlier pK_{BH^+} values[6] are incorrect, being based on the wrong assumption that benzoic acids follow the H_0 acidity function: it has been actually shown[7] that they closely follow the H_A function and that previous values are some three units too negative.[6,8]

A part of our recent work has been basically devoted to defining better the electronic distribution in aromatic carbonyl compounds such as acetophenones (ArCOMe),[9] benzamides ($ArCONH_2$),[2a,10] or benzoates ($ArCO_2R$: R = methyl[9b] or aryl),[11] with particular attention to the extent of conjugation between the carbonyl group and the aromatic ring. Accordingly, we herein pursue the double aim of filling an evident gap in the knowledge of protonation equilibria of weak bases and (as such equilibria do reflect the electronic environment of the protonating site) of broadening the range of carbonyl derivatives subjected to the above mentioned electron-distribution analysis: thus, previously unreported pK_{BH^+} values (from protonation data in aqueous sulfuric acid at 298 K) for a series of 2,6-dimethyl-4-X-benzoic acids (DMBAc **1–4**, **6**, **11**) are herein compared with the analogous values for 3-X-(BAc **1'**, **3**, **4'–7'**, **9'–11'**) and 4-X-benzoic acids (BAc **1–4**, **6**, **8**, **9**, **11**) deriving from protonation data redetermined, for homogeneity, under identical conditions.

Moreover, acid dissociation constants, pK_a^*, for the same series of acids have been potentiometrically determined in 50 wt% aqueous methanol at 298 K, the use of the mixed solvent being required by the very low solubility of DMBAc in pure water. It should be noted that, although pK_a values of some 3- and 4-substituted BAc in the same solvent have been recently reported[12] by Gumbley and Stewart, pH measurements made use of a pH-meter standardised with aqueous buffers. Herein, standardisation with available[13] buffers in 50 wt% aqueous methanol allows us to obtain pK_a^* values which directly refer to this particular solvent system as the standard state.



BAc

DMBAc

1: X = 4–OMe **6**: X = 4–Br **1'**: X = 3–OMe **7'**: X = 3–I
2: X = 4–Me **8**: X = 4–Ac **4'**: X = 3–F **9'**: X = 3–CF_3
3: X = 4–H **9**: X = 4–CF_3 **5'**: X = 3–Cl **10'**: X = 3–CN
4: X = 4–F **11**: X = 4–NO_2 **6'**: X = 3–Br **11'**: X = 3–NO_2

Experimental

M.p.s were taken on a Büchi 535 apparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 spectrometer; tetramethylsilane was used as internal standard and chemical shifts are reported as δ values. *J*-Values are given in Hz.

Synthesis and Purification of Compounds.—All BAc, 2,6-dimethylbenzoic acid (DMBAc **3**), and 2,4,6-trimethylbenzoic acid (DMBAc **2**) were commercial samples, purified by crystallisation to match literature physical constants.

4-Methoxy-2,6-dimethylbenzoic acid (DMBAc **1**), synthesized as reported[14] from 4-bromo-3,5-dimethylanisole,[15] had m.p. 145.4–146.7 °C (from toluene/40–60 °C light petroleum) (lit.,[14] 144.5–145.0 °C).

4-Fluoro-2,6-dimethyl- (DMBAc **4**), 4-bromo-2,6-dimethyl- (DMBAc **6**), and 2,6-dimethyl-4-nitrobenzoic acid (DMBAc **11**) were synthesised by hydrolysis[16] of the corresponding amides.[10] The acid DMBAc **4** (40%) had m.p. 143.7–144.5 °C (from toluene) (Found: C, 64.2; H, 5.3. $C_9H_9FO_2$ requires C, 64.3; H, 5.4%); δ_H 2.44 (6 H, s) and 6.78 (2 H, d, J_{HF} 9.2) (the CO_2H proton gives no detectable signal, probably owing to fast exchange with trace water). The acid DMBAc **6** (81%) had m.p. 194.7–196.0 °C (from toluene/80–100 °C ligroine) (lit.,[17]

198–199 °C). The acid DMBAc **11** (90%) had m.p. 179.4–180.6 °C (from toluene) (lit.,[16] 179–181 °C).

pK_{BH^+} *Measurements.*—The essential features of the adopted procedure for spectrophotometric determinations have been described previously.[18] The criteria for the choice of λ, in the region of $\lambda_{max}(BH^+)$, as well as the correction for the factors that may affect the spectra, other than the protonation process, have also been already discussed.[2]

The uncertainty in the spectrophotometric determination of ionisation ratios, ($I = C_{BH^+}/C_B$), for the 4-nitroderivatives is very high since the spectral UV behaviour of the protonated and unprotonated form of these acids is both qualitatively (λ_{max}) and quantitatively (extinction coefficients) similar (see Table 1). Therefore the protonation of 4-nitrobenzoic and 2,6-dimethyl-4-nitrobenzoic acid has been studied by ^{13}C NMR spectroscopy, following the technique described by Scorrano *et al.*[1b,3,19] The ionisation ratio is given by eqn. (1) and changes in chemical shift [relative to tetramethylammonium ion (TEMA)] of the carboxyl carbon atom were monitored as a

$$I = (\delta - \delta_B)/(\delta_{BH^+} - \delta) \quad (1)$$

function of acidity. Values of the (relative) chemical shift of the unprotonated (δ_B) and protonated form (δ_{BH^+}) of the investigated acids are reported in Table 1. Solutions about 0.02 mol dm^{-3} in substrate and 0.01 mol dm^{-3} in TEMA were employed and spectra run at 298 K on a Varian Gemini 300 NMR instrument with broad-band decoupling. Field-frequency lock was achieved by adding D_2O to the solutions; no lock was needed in concentrated H_2SO_4 solution, owing to the high stability of the cryomagnet. The consistency of the two techniques (UV and ^{13}C NMR spectroscopy) was tested on the parent compounds (BAc **3** and DMBAc **3**) and was found satisfactory (see Table 2). Fuming sulfuric acid was necessary in order to achieve complete protonation of the two nitroacids. Unfortunately, published H_A values (from 2.5% H_2SO_4 to 90% H_2SO_4[20] and from 85% H_2SO_4 up to 17% fuming H_2SO_4)[21] do not overlap in the common region: therefore pK_{BH^+} values for these two acids were calculated simply by means of the EA method [eqn. (3)].

We also attempted to determine pK_{BH^+} for 3-cyanobenzoic acid (BAc **10'**) and 4-acetylbenzoic acid (BAc **8**). However, in solutions of concentrated H_2SO_4, ^{13}C NMR spectroscopy qualitatively evidenced extensive H_2SO_4 addition to the cyano group of the former and protonation also at the acetyl group of the latter compound. Thus, in 98.2 wt% H_2SO_4, the ^{13}C NMR spectrum of 4-acetylbenzoic acid shows the signal for the protonated acetyl group (δ 165.12 relative to that of TEMA).

pK_a^* *Measurements.*—pK_a^* Values were determined by potentiometric measurements (Radiometer PHM 84 pH-meter) with a glass electrode and a LiCl saturated calomel electrode as the reference. The electrodes were standardised with acetate and hydrogenphosphate buffers of known[13] pH* in 50 wt% aqueous methanol. Substrate solutions *ca.* 2.5×10^{-3} mol dm^{-3} were titrated with carbonate-free 0.1 mol dm^{-3} sodium hydroxide. The 'back titration' procedure, recommended[22] for most reliable results, was applied in all cases using 0.1 mol dm^{-3} HCl. Ionisation constants (pK_a^*) were calculated as described by Albert and Serjeant;[22] the concentrations of the ionic species were corrected by use of the corresponding activity coefficients determined according to the Davies equation[23a] with Debye–Huckel functions (A 0.802 $mol^{-1/2}$ $dm^{3/2}$ $K^{3/2}$ and B 0.371×10^8 cm^{-1} $mol^{-1/2}$ $K^{1/2}$)[23b] appropriate to this particular solvent system. Each pK_a^* value (Table 3) is the average of at least four titrations, each consisting of fifteen or more data points.

Results

The pK_{BH^+} dissociation constants (Table 2) were calculated[2] (with an estimated uncertainty of ±0.05 units) from spectrophotometric and/or ^{13}C NMR data by both the H_A[20] and the excess acidity (EA)[24] methods according to eqns. (2) and (3) respectively. For the two 4-nitroderivatives only the EA method was used, as mentioned in the Experimental section.

$$\log I = -mH_A + pK_{BH^+} \quad (2)$$

$$\log I - \log C_{H^+} = pK_{BH^+} + m^*X \quad (3)$$

All the investigated carboxylic acids closely follow the H_A function, the slope m of log I *vs.* H_A plots being 1.04 ± 0.04. The agreement between pK_{BH^+} values obtained by the two methods (H_A and EA) is very good, differences being within 0.1 units, and average values were used in all correlations. Spectral data (UV and ^{13}C NMR spectroscopy) for the free carboxylic acid (B) and its protonated form (BH^+) of 3-X-, 4-X- and 2,6-dimethyl-4-X-benzoic acids are reported in Table 1.

pK_{BH^+} Values for a series of 3- and 4-substituted benzoic acids can be calculated from literature data[25] of H_2SO_4 concentrations at half protonation, assuming that the whole series follows the H_A function. Such estimated values match our experimental ones well (see Table 2).

The agreement between the present and Zalewski's[5] values can in turn be regarded as satisfactory, when taking into account that the original[26] H_A scale and pK_{BH^+} of indicators used in its construction were *ca.* 0.33 units too negative.[20]

Experimental pK_{BH^+} values for BAc and DMBAc have been correlated with σ and σ^+ substituent constants,[27] and the results are reported in eqns. (4)–(7) in the form ($-\Delta pK_{BH^+}$) *vs.* substituent constant [$(\Delta pK_{BH^+}) = (pK_{BH^+})_X - (pK_{BH^+})_H$]. The fit improvement achieved through the employment of σ^+ constants is mainly attributable to the strong electron-donating *para*-methoxy group, whose deviation from eqns. (4) and (6) is sizeable.

$$(-\Delta pK_{BH^+})_{BAc} = -(0.07 \pm 0.02) + (0.86 \pm 0.05)\sigma \quad (n\ 14, r\ 0.981) \quad (4)$$

$$(-\Delta pK_{BH^+})_{BAc} = (0.03 \pm 0.01) + (0.65 \pm 0.02)\sigma^+ \quad (n\ 14, r\ 0.993) \quad (5)$$

$$(-\Delta pK_{BH^+})_{DMBAc} = -(0.16 \pm 0.05) + (0.77 \pm 0.14)\sigma \quad (n\ 6, r\ 0.940) \quad (6)$$

$$(-\Delta pK_{BH^+})_{DMBAc} = -(0.05 \pm 0.02) + (0.59 \pm 0.04)\sigma^+ \quad (n\ 6, r\ 0.992) \quad (7)$$

Accordingly, a cross-correlation of ($-\Delta pK_{BH^+}$) values for DMBAc against those for the corresponding BAc yielded eqn. (8)

$$(-\Delta pK_{BH^+})_{DMBAc} = -(0.54 \pm 0.29) + (0.92 \pm 0.07)(-\Delta pK_{BH^+})_{BAc} \quad (n\ 6, r\ 0.990) \quad (8)$$

Moreover ($-\Delta pK_{BH^+}$) values for 4-substituted BAc or DMBAc were correlated with the corresponding ($-\Delta pK_{BH^+}$) values for benzamides (BA)[2a] [eqn. (9)] and 2,6-dimethylbenzamides (DMBA)[2a] [eqn. (10)]. A better fitting of the latter correlations was observed when the data relevant to the strong electron-donating *para*-methoxy substituent were excluded from the least-squares treatment [eqns. (9') and (10'); see also

Table 1 Spectral data (UV and ^{13}C NMR spectroscopy) for the free carboxylic acid, B, and the corresponding protonated form, BH^+, of 3-X-benzoic acids (3-X-BAc), 4-X-benzoic acids (4-X-Bac) and 2,6-dimethyl-4-X-benzoic acids (DMBAc)

	3-X-BAc				4-X-BAc						DMBAc					
	B		BH^+		B			BH^+			B			BH^+		
X	λ^a_{max}/-nm	log ε^b	λ^a_{max}/-nm	log ε^c	λ^a_{max}/-nm	log ε^d	δ^e	λ^a_{max}/-nm	log ε^c	δ^e	λ^a_{max}/-nm	log ε^f	δ^e	λ^a_{max}/-nm	log ε^c	δ^e
OMe	208	4.41	214	4.11	208[g]	4.08		222	3.85		216[g]	3.86		239[g]	3.74	
	239	3.91	261	4.03	260	4.17		300	4.25		272	3.06		261	4.04	
	296	3.31	315	3.25										312	3.83	
Me					252	4.10		211[g]	3.87		243[g]	3.42		282	3.95	
								277	4.27							
H					235	3.99	114.69[h]	263	4.23	125.68[i]	233[g]	3.36	118.92[j]	206[g]	3.97	133.00[i]
					270[g]	2.26		305	3.48		271	3.05		268	3.71	
F	231	4.06	256	4.10	236	4.03		207[g]	3.99		230[g]	3.23		206	3.94	
	280	3.26	302	3.07				263	4.20					269	3.72	
Cl	203	4.40	208	4.20												
	236	3.86	214[g]	4.19												
	285	2.55	262	4.04												
			313	3.18												
Br	206	4.49	208[g]	4.19	249	4.08		212[g]	3.76		240[g]	3.72		282	3.85	
	235	3.96	220	4.31				283	4.15							
	287	3.00	262	4.12												
			320	3.47												
I	221	4.26	208	3.04												
	245[g]	3.78	234	4.12												
			262	3.65												
Ac					255	4.24		288	4.25							
					290[g]	3.38										
CF_3	228	4.06	250	4.15	228	3.96		248	4.16							
	272	2.78	292	3.35	278	3.42		312	3.72							
NO_2	221	4.39	232	4.35	265	4.16[k]	111.87[j]	269	4.23[k]	123.71[l]			116.33[j]			126.31[l]
	265	3.91	268[g]	3.86												

[a] λ Range: 220–330 nm. [b] In H_2SO_4 60–68%. [c] In H_2SO_4 95–98%. [d] In H_2SO_4 58–63%. [e] δ is the chemical shift of the carboxyl carbon atom relative to tetramethylammonium ion. [f] In H_2SO_4 62–66%. [g] Shoulder. [h] In H_2SO_4 34%. [i] In H_2SO_4 98.5%. [j] In H_2SO_4 24–30% and CD_3OD 50%. [k] Ref. 6*a*. [l] In 17% fuming H_2SO_4.

Table 2 Acid dissociation constants, pK_{BH^+}, for 3-X- and 4-X-benzoic acids (BAc), 2,6-dimethyl-4-X-benzoic acids (DMBAc) by both UV and NMR techniques at 298 K

	BAc							DMBAc					
	H_A method		EA method					H_A method		EA method			
X	pK_{BH^+} (UV)	m	pK_{BH^+} (UV)	m*	pK_{BH^+} (NMR)	m*	Calculated from ref. 25	pK_{BH^+} (UV)	m	pK_{BH^+} (UV)	m*	pK_{BH^+} (NMR)	m*
3-OMe	−4.44	1.09	−4.46	0.51			−4.56	—	—	—	—		
4-OMe	−3.95	1.02	−3.91	0.52			−4.08	−4.12	1.04	−4.14	0.50		
4-Me	−4.24[a]	1.04	−4.26	0.48			−4.25	−4.48	1.05	−4.42	0.50		
H	−4.39[b,c,d]	1.02	−4.43	0.51	−4.32	0.53	−4.46	−4.61	1.04	−4.66	0.52	−4.72	0.56
3-F	−4.62	1.08	−4.59	0.50			−4.67	—	—	—	—		
4-F	−4.41[e]	0.99	−4.34	0.51			−4.48	−4.63	1.06	−4.52	0.48		
3-Cl	−4.60	1.00	−4.68	0.49			−4.76	—	—	—	—		
3-Br	−4.61[f]	1.02	−4.69	0.52			−4.69	—	—	—	—		
4-Br	−4.47	0.97	−4.49	0.50				−4.68	0.98	−4.58	0.49		
3-I	−4.55	1.09	−4.66	0.50			−4.68	—	—	—	—		
3-CF_3	−4.68	1.05	−4.66	0.50				—	—	—	—		
4-CF_3	−4.77[g]	1.08	−4.82	0.50				—	—	—	—		
3-NO_2	−4.95	1.03	−4.89	0.49			−4.97	—	—	—	—		
4-NO_2					−4.96	0.49						−5.09	0.56

[a] Ref. 5: $pK_{BH^+} = -4.52$. [b] Ref. 1*c*: $pK_{BH^+} = -4.56$. [c] Ref. 5: $pK_{BH^+} = -4.70$. [d] Ref. 7: $pK_{BH^+} = -4.60$. [e] Ref. 5: $pK_{BH^+} = -4.92$. [f] Ref. 5: $pK_{BH^+} = -5.14$. [g] Ref. 5: $pK_{BH^+} = -5.34$.

Fig. 1 for a more direct comparison of the regression lines of eqns. (9) and (9′)].

$$(-\Delta pK_{BH^+})_{BA} = (0.17 \pm 0.08) + (1.56 \pm 0.25)(-\Delta pK_{BH^+})_{BAc} \quad (n\ 6, r\ 0.953) \quad (9)$$

$$(-\Delta pK_{BH^+})_{BA} = (0.07 \pm 0.02) + (2.01 \pm 0.09)(-\Delta pK_{BH^+})_{BAc} \quad (n\ 5, r\ 0.997) \quad (9')$$

$$(-\Delta pK_{BH^+})_{DMBA} = (0.27 \pm 0.08) + (1.56 \pm 0.28)(-\Delta pK_{BH^+})_{DMBAc} \quad (n\ 6, r\ 0.943) \quad (10)$$

Table 3 Dissociation constants, pK_a^*, for 3-X-benzoic acids (3-X-BAc), 4-X-benzoic acids (4-X-Bac) and 2,6-dimethyl-4-X-benzoic acids (DMBAc) in 50 wt% aqueous methanol at 298 K

X	3-X-BAc pK_a^*	4-X-BAc pK_a^*	DMBAc pK_a^*
OMe	5.55 ± 0.04	6.02 ± 0.03	5.27 ± 0.06
Me	—	5.96 ± 0.03	5.25 ± 0.02
H	5.67 ± 0.03	5.67 ± 0.03	5.06 ± 0.02
F	5.29 ± 0.02	5.56 ± 0.05	4.87 ± 0.05
Cl	5.24 ± 0.03	—	—
Br	5.25 ± 0.03	5.36 ± 0.04	4.70 ± 0.03
I	5.30 ± 0.03	—	—
Ac	—	5.19 ± 0.01	—
CF_3	5.16 ± 0.04	5.10 ± 0.03	—
CN	4.92 ± 0.03	—	—
NO_2	4.85 ± 0.02	4.76 ± 0.02	3.93 ± 0.01

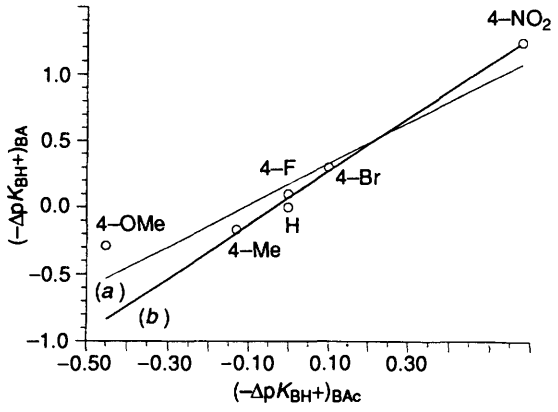


Fig. 1 Correlations of $(-\Delta pK_{BH^+})$ for benzamides (BA) *vs.* $(-\Delta pK_{BH^+})$ for corresponding benzoic acids (BAc). Line (*a*) eqn. (9), *n* 6; line (*b*) eqn. (9′), *n* 5 (the 4-OMe substituent is neglected).

$$(-\Delta pK_{BH^+})_{DMBA} = (0.23 \pm 0.07) + (1.96 \pm 0.33)(-\Delta pK_{BH^+})_{DMBAc} \quad (n\ 5, r\ 0.961) \quad (10')$$

As far as the pK_a^* dissociation constants are concerned, values for BAc and DMBAc in 50 wt% aqueous methanol at 298 K are reported in Table 3. Such values correlate well with substituent σ constants according to eqns. (11) and (12) $[(\Delta pK_a^*) = (pK_a^*)_X - (pK_a^*)_H]$.

$$(-\Delta pK_a^*)_{BAc} = -(0.02 \pm 0.02) + (1.18 \pm 0.04)\sigma \quad (n\ 16, r\ 0.993) \quad (11)$$

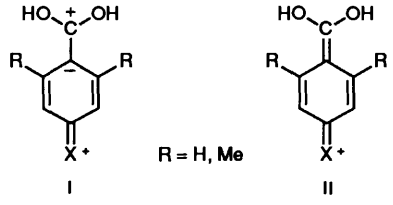
$$(-\Delta pK_a^*)_{DMBAc} = (0.07 \pm 0.03) + (1.30 \pm 0.08)\sigma \quad (n\ 6, r\ 0.992) \quad (12)$$

Consistently a cross-correlation for the two series of acids gave a very good fit [eqn. (13)].

$$(-\Delta pK_a^*)_{DMBAc} = (0.09 \pm 0.03) + (1.07 \pm 0.07)(-\Delta pK_a^*)_{BAc} \quad (n\ 6, r\ 0.991) \quad (13)$$

Discussion

Basicity Constants pK_{BH^+}.—The observed good correlation of $(-\Delta pK_{BH^+})$ for BAc with σ^+ values [eqn. (5)] could at first sight be assumed[6a] as an indicator of extensive conjugation between the protonated carboxyl group and the benzene ring. However, the bulk of the results herein suggests that some caution should be taken in drawing conclusions in this regard. Of particular relevance is, in this respect, the similarity in the behaviour of BAc and DMBAc, as shown *e.g.* by the occurrence that (*a*) the $(-\Delta pK_{BH^+})$ values of the two series best correlate with the same Hammett constants (σ^+) and (*b*) the relevant susceptibilities (ρ^+) are not significantly different for the two series, as also evidenced by the slope of the cross-correlation of eqn. (8) being very close to unity. If it is assumed that the two methyl groups, by effectively opposing the coplanarity of the carboxyl function and of the benzene ring,* leave little role, if any, to conjugative interactions between the two moieties in both unprotonated and protonated DMBAc, the similar response to the *para*-substituent effect in BAc should exclude major contributions of conjugation also to the basicity of unhindered benzoic acids.† In this frame it is conceivable that π-polarisation (canonical structure **I**, in the case of electron-donating 4-X groups) rather than through-conjugation (canonical structure **II**) is the major stabilising factor for the protonated forms of both unhindered and hindered acids.



It is noteworthy, though, that, in spite of the generally acknowledged polar effect of methyl groups, each DMBAc is slightly (some 0.2 units) *less basic* than the corresponding BAc, an outcome which could actually suggest a somewhat more effective charge stabilisation in the protonated BAc, possibly involving the through-conjugation component hampered in the dimethylated counterparts.

In order to discern the different contribution of polar and resonance effects of the substituents on the observed trend of pK_{BH^+} values, a Dual Substituent Parameter (DSP) treatment[31] of the $(-\Delta pK_{BH^+})$ values for 4-X-substituted BAc and DMBAc was undertaken. Such DSP analysis, again giving the best fit with σ_R^+ parameters [eqns. (14) and (15)], confirms, as the essential feature, the similarity in the behaviour of the two series of acids. Thus, while minor differences show up as far as the polar susceptibility constants are concerned, the resonance susceptibilities are much alike for BAc and DMBAc giving further support to the above mentioned assumption of a π-polarisation stabilising component in the protonated acids.

$$(-\Delta pK_{BH^+})_{BAc} = (0.74 \pm 0.04)\sigma_I + (0.64 \pm 0.03)\sigma_R^+ \quad (n\ 7, r\ 0.990) \quad (14)$$

$$(-\Delta pK_{BH^+})_{DMBAc} = (0.50 \pm 0.04)\sigma_I + (0.65 \pm 0.03)\sigma_R^+ \quad (n\ 6, r\ 0.987) \quad (15)$$

As suggested[6b] in order to explain the basicity observed for a series of 2-alkylbenzoic acids compared to that of benzoic acid

* The torsion of the carboxyl group out of the aromatic plane in DMBAc is undoubtedly sizeable: for 2,6-dimethylbenzoic acid twist angles of 70° (from spectroscopic data),[28] 53° (from X-ray diffraction studies)[29] or 27° (from molecular mechanics calculations)[30] have been estimated.

† The reasoning herein neglects the possibility that, in the case of DMBAc, the enhanced requirements for charge delocalisation induced by protonation could enforce conjugative interactions between the protonated carboxyl group and the aromatic nucleus through a decreased torsion angle. We are presently attempting to shed light on this point by means of theoretical calculations both on geometry and on charge distribution in the molecules involved.

itself, steric inhibition to solvation of the protonated form of DMBAc should also be taken into account as a contributing factor to the above mentioned decreased basicity of DMBAc with respect to BAc. In this regard it should be anyway pointed out that the m^* parameters of eqn. (3) (see Table 2), which are thought to reflect primarily the susceptibility of the protonated substrate to stabilisation by solvation (especially through hydrogen bonding),[1b] are not sensitive enough to monitor the presumably small solvation differences between the two series involved in the present analysis (mean m^* values from Table 2 are 0.50 ± 0.01 for BAc and 0.52 ± 0.03 for DMBAc). Nonetheless, the just quoted figures, being typical of aromatic acyl derivatives such as acetophenones (0.50–0.60),[1b,9a] benzamides (0.55),[2a] thiophene-2-carboxanilides (0.54)[2b] can be taken (together with the fact that both BAc and DMBAc closely follow the H_A acidity function) as compelling evidence for a carbonyl protonation rather than a hydroxyl protonation of the carboxyl group.[6] The importance of the solvation of the conjugate acids of our compounds as a stabilising effect clearly emerges when comparing the present m^* values with the significantly higher ones of benzoate esters such as methyl (m^* 0.81)[1b] or ethyl benzoate (m^* 0.73).[1c] Undoubtedly the positive charge in protonated carboxylic acids can effectively be spread by resonance in a highly symmetrical form. Moreover the protonated carboxylic acid (**III**) has one more hydrogen-

III **IV**

Scheme 1

bonding site than does the ester (**IV**). Consistently, a comparison of the pK_{BH^+} values of benzamide (−1.56),[2a] benzoic acid (−4.38) and methyl benzoate (−7.05),[3a] while assigning the role of the strongest base to the amide, shows that the carboxylic acid is significantly *more basic* than the ester, despite the electron repulsion commonly played by the methyl group.

In view of a comparison with different aromatic acyl derivatives aimed at drawing a sensible map of the electronic behaviour of ArCOY compounds, a result which deserves a closer insight is represented by the experimental better correlation of $(-\Delta pK_{BH^+})$ for both BAc and DMBAc with σ^+ [eqns. (5) and (7)] rather than with σ [eqns. (4) and (6)]. This outcome is, in fact, seemingly in contrast with our recent findings[2a] on 4-X-benzamides (BA) and 2,5-dimethyl-4-X-benzamides (DMBA) for which the lack of appreciable external conjugation of the carbamoyl group with the aromatic ring (justifiable[2a] on the grounds of an effectively competing internal conjugation within the carbamoyl group itself) hinged on the very fit of $(-\Delta pK_{BH^+})$ with σ rather than with σ^+ *para*-substituent constants. A somewhat different behaviour between benzoic acids and benzamides also emerges when considering that the protonation of the latter (ρ_{BA} 1.14; ρ_{DMBA} 1.40)[2a] is considerably more sensitive to the *para*-substituent effect than that of the former (ρ_{BAc} 0.86, ρ^+_{BAc} 0.65; ρ_{DMBAc} 0.77, ρ^+_{DMBAc} 0.59). In such comparison between benzoic acids and benzamides the observed dissimilar sensitivity as well as the better correlation with different Hammett constants can find a rationale, at the light of the already mentioned π-polarisation as the major stabilising effect, when considering that the free and protonated carboxyl group are both more electron demanding and less polarisable than the relevant carbamoyl counterparts.

† Our ΔpK_a 0.61 between benzoic and 2,6-dimethylbenzoic acids is close to the value of 0.85 found in pure water.[28]

Acidity Constants (pK_a^*).—Inspection of the results presented in Table 3 shows that DMBAc are some 0.7 units *more acidic*† than the corresponding benzoic acids, well matching their herein already reported lower basicity. The well known *ortho*-effect[28,32] operating in the dissociation of these acids seems thus to be fully confirmed herein. However, while such an effect was traditionally attributed to steric inhibition of delocalisation[32] which would reduce stabilisation of the undissociated acid in DMBAc, the present results, excluding any major conjugative effect, rather point to the involvement of specific solvation.[7,33–36]

The susceptibility constant (ρ) for the ionisation of our 3- and 4-substituted benzoic acids in 50 wt% methanol is 1.18 ± 0.04 [eqn. (11)] a value which well matches the previously reported ones of 1.28[12] and 1.09,[37] and which lies, as expected,[34] in between those in water (1.00) and in pure methanol (1.54).[38] As the susceptibility constant for the ionisation of DMBAc is 1.30 ± 0.08 [see eqn. (12)], it can be concluded that the sensitivity of $(-\Delta pK_a^*)$ to the substituent is very similar for the two classes of benzoic acids. The same conclusions can also be derived from the value close to unity of the slope of the cross-correlation of eqn. (13).

Finally, the $(-\Delta pK_{BH^+})$ *vs.* $(-\Delta pK_a^*)$ correlations [eqns. (16) and (17) for BAc and DMBAc, respectively, obviously restricted to the *para*-substituted acids] are not entirely

$$(-\Delta pK_{BH^+})_{BAc} = -(0.06 \pm 0.04) + (0.73 \pm 0.09)(-\Delta pK_a^*)_{BAc} \quad (n\ 7, r\ 0.963) \quad (16)$$

$$(-\Delta pK_{BH^+})_{DMBAc} = -(0.19 \pm 0.07) + (0.56 \pm 0.14)(-\Delta pK_a^*)_{DMBAc} \quad (n\ 6, r\ 0.897) \quad (17)$$

satisfactory as expected on the grounds of the occurrence that, for the two series of acids, $(-\Delta pK_{BH^+})$ and $(-\Delta pK_a^*)$ best correlate with different substituent constants; this can be in turn rather straightforwardly rationalised *via* the resonance stabilising effect that electron-donating groups might exert on the protonated carboxylic group (but not, of course, on the carboxylate anion), thus justifying the requirement for the σ^+ or the σ scale for the best fit of $(-\Delta pK_{BH^+})$ and $(-\Delta pK_a^*)$ data, respectively.

Acknowledgements

We thank CNR and MURST for financial support.

References

1 (*a*) R. A. Cox, C. R. Smith and K. Yates, *Can. J. Chem.*, 1979, **57**, 2952; (*b*) A. Bagno, G. Scorrano and R. A. More O'Ferrall, *Rev. Chem. Intermed.*, 1978, **7**, 313; (*c*) J. T. Edward and S. C. Wong, *J. Am. Chem. Soc.*, 1977, **99**, 4229. However the reliability of the reported pK_{BH^+} values for acetophenones has been recently questioned (see J. Toullec, *Tetrahedron Lett.*, 1988, **29**, 5541).

2 (*a*) P. De Maria, C. L. Barbieri, D. Spinelli, C. Dell'Erba, M. Novi, G. Petrillo and F. Sancassan, *J. Chem. Soc., Perkin Trans. 2*, 1991, 373 and refs. cited therein; (*b*) P. De Maria, V. Frenna, C. L. Barbieri, S. Frascari and D. Spinelli, *J. Chem. Research* (*S*), 1991, 268; (*M*), 2557 and refs. cited therein.

3 (*a*) A. Bagno, G. Scorrano and V. Lucchini, *Gazz. Chim. Ital.*, 1987, **117**, 475; (*b*) A. Bagno, V. Lucchini and G. Scorrano, *Bull. Soc. Chim. Fr.*, 1987, 563.

4 C. H. Rochester, *Acidity Functions*, Academic Press, London, 1970.

5 R. I. Zalewski, *Bull. Acad. Pol. Sci., Ser. Sci. Chem.*, 1972, **20**, 853.

6 (*a*) R. Stewart and K. Yates, *J. Am. Chem. Soc.*, 1960, **82**, 4059; (*b*) R. Stewart and M. Granger, *Can. J. Chem.*, 1961, **39**, 2508.

7 R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, 1968, **46**, 2469.

8 Z. Geltz, H. Kokocinska, R. I. Zalewski and T. M. Krigowski, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1069.

9 (*a*) D. Dattolo, M. Gruttadauria, R. Noto, C. Dell'Erba, G. Petrillo, F. Sancassan, L. Lamartina and D. Spinelli, *Misure di* pK_{BH^+} *di*

Acetofenoni e di 2-Acetiltiofeni, Cofem 92, Galzignano (Italia) 5-8/7/1992; D. Dattolo, P. De Maria, R. Noto, A. Fontana, D. Spinelli, C. Dell'Erba, M. Novi and G. Petrillo, *Acid Dissociation Constants, pK_{BH^+}, of Some Protonated Benzoic Acids, Acetophenones and their 2,6-Dimethyl Derivatives*, 11th Conference on Physical Organic Chemistry, Ithaca (NY) 2-7/8/1992; (*b*) C. Dell'Erba, F. Sancassan, M. Novi, G. Petrillo, A. Mugnoli, D. Spinelli, G. Consiglio and P. Gatti, *J. Org. Chem.*, 1988, **53**, 3564 and refs. cited therein.

10 C. Dell'Erba, A. Mele, M. Novi, G. Petrillo, F. Sancassan and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1990, 2055.

11 C. Dell'Erba, F. Sancassan, G. Leandri, M. Novi, G. Petrillo, A. Mele, D. Spinelli and G. Consiglio, *Gazz. Chim. Ital.*, 1989, **119**, 643.

12 S. Gumbley and R. Stewart, *J. Chem. Soc., Perkin Trans. 2*, 1984, 529.

13 D. D. Perrin and B. Dempsey, *Buffers for pH and Metal Ion Control*, Chapman and Hall, London, 1974, ch. 6.

14 R. C. Fuson, J. Corse and P. B. Welldon, *J. Am. Chem. Soc.*, 1941, **63**, 2645.

15 J. D. Edwards and J. L. Cashaw, *J. Am. Chem. Soc.*, 1956, **78**, 3821.

16 O. O. Laaketehdas, BP 896 720/1962 (*Chem. Abstr.*, 1962, **57**, 11113i).

17 R. C. Fuson, S. L. Scott and R. V. Lindsey, *J. Am. Chem. Soc.*, 1941, **63**, 1679.

18 (*a*) P. De Maria, G. Consiglio, C. Arnone and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1983, 481; (*b*) P. De Maria, R. Noto, G. Consiglio and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1989, 791.

19 E. M. Arnett and G. Scorrano, *Adv. Phys. Org. Chem.*, 1976, **13**, 83.

20 J. T. Edward and S. C. Wong, *Can. J. Chem.*, 1977, **55**, 2492.

21 G. D. Frederick and C. D. Poutter, *J. Am. Chem. Soc.*, 1975, **97**, 1797.

22 A. Albert and E. P. Serjeant, *The Determination of Ionisation Constants*, Chapman and Hall, London, 1971, ch. 3.

23 (*a*) C. W. Davies, *Ion Association*, Butterworths, London, 1962; (*b*) M. Paabo, R. A. Robinson and R. G. Bates, *J. Chem. Eng. Data*, 1964, **9**, 374.

24 R. A. Cox and K. Yates, *J. Am. Chem. Soc.*, 1978, **100**, 3861.

25 R. Stewart, *The Proton: Applications to Organic Chemistry*, Academic Press, New York and London, 1985, ch. 3, 118–119.

26 K. Yates, J. B. Stevens and A. R. Katritzky, *Can. J. Chem.*, 1964, **42**, 1957.

27 O. Exner, *Correlation Analysis of Chemical Data*, Plenum Press, New York and London, 1988.

28 J. M. Wilson, N. E. Gore, J. E. Sawbridge and F. Cardenas-Cruz, *J. Chem. Soc. B*, 1967, 852.

29 V. Benghiat and L. Leiserowitz, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1778.

30 M. Charton and B. I. Charton, *3rd European Symposium on Organic Reactivity*, Göteborg, July 7–12 1991, p. 84.

31 S. Ehrenson, R. T. C. Brownlee and R. W. Taft, *Prog. Phys. Org. Chem.*, 1973, **10**, 1; D. J. Craik and R. T. C. Brownlee, *Prog. Phys. Org. Chem.*, 1983, **14**, 1; J. Bromilow, R. T. C. Brownlee, D. J. Craik, P. R. Fiske, J. E. Rowe and M. Sadek, *J. Chem. Soc., Perkin Trans. 2*, 1981, 753.

32 J. F. J. Dippy, S. R. C. Hughes and J. W. Laxton, *J. Chem. Soc.*, 1954, 1470.

33 J. Steigman and D. Sussman, *J. Am. Chem. Soc.*, 1967, **89**, 6406.

34 M. Charton and B. I. Charton, *J. Org. Chem.*, 1968, **33**, 3872.

35 M. Hojo, M. Utaka and Z. Yoshida, *Tetrahedron*, 1971, **27**, 2713.

36 D. Spinelli, R. Noto and G. Consiglio, *J. Chem. Soc., Perkin Trans. 2*, 1976, 747.

37 H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.

38 W. L. Bright and H. T. Briscoe, *J. Phys. Chem.*, 1933, **37**, 787.

Paper 2/06559B
Received 9*th December* 1992
Accepted 22*nd December* 1992