Protonation of some 4-Substituted Benzamides and 2,6-Dimethylbenzamides

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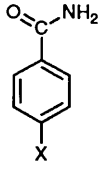
The protonation of the title compounds has been studied in aqueous sulphuric acid at 25 °C. Relevant pK_{BH^+} values have been calculated according to both modified Hammett and excess-acidity methods. The data obtained show that the *para* substituents exert practically the same electronic effects in the two series of amides in spite of the much larger torsion of the carbamoyl group out of the aromatic plane in the 2,6-dimethyl derivatives. The observed behaviour can be related to the internal conjugation of the carbamoyl group which strongly reduces that between the same group and the ring.

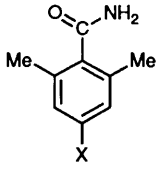
Much work on acid-base properties of amides has been performed in order to investigate the electronic and/or steric effects brought about by structural variations. In particular, based on such studies, it now seems accepted that protonation takes place at the carbamoyl oxygen,[1-3] although the idea of protonation at nitrogen has until recently found some support.[4]

From the information gained, however, it is apparent that some findings clearly contrast with predictions based on the long-recognized electronic effects of the groups linked to the amide function. For example, acetamide is more basic than benzamide by 0.81 pK_{BH^+} units,[1] in spite of a possible resonance delocalization of the positive charge into the phenyl moiety of the benzamide cation. We have shown[5a] recently, in the course of ^{13}C NMR studies on aromatic carboxylic acid derivatives,[5] that the carbonyl-carbon chemical shifts of 2,6-dimethylbenzamides (DMBA) are linearly correlated with those of



BA

X = MeO, Me, H, F, Br, Ac, NO_2

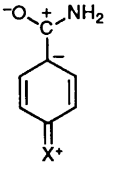


DMBA

X = MeO, Me, H, F, Br, NO_2

benzamides (BA) in DMSO, although available literature data suggest that 2,6-dimethyl substitution causes a marked increase in the torsion angle between the carbamoyl group and the ring.[6] This result, together with those of the Dual Substituent Parameter analysis of the experimental data, highlight the fact that, in 2,6-unsubstituted benzamides too, the carbonyl-carbon chemical shift does not reflect conjugative interactions with *para* substituents: this would correspond, for an electron-donor *para* substituent, to an enhanced weight of the resonance contributor A rather than the fully delocalised form. We suggested that this effect, previously defined by Brownlee *et al.*[7] as a secondary resonance effect, should actually be considered as the principal component of the resonance effect of the carbomoyl,[5a,c] as well as of the alkoxycarbonyl[5b,c,e] and cyano[5b,c] groups.

It has been pointed out[5a] that in DMSO the results could be affected by different degrees and/or models of solvation of the carbamoyl group in BA and DMBA.



A

With the aim of further contributing to the understanding of the matter, we have carried out a comparative study of the substituent effect on the basicities of BA and their 2,6-dimethyl derivatives DMBA in aqueous solutions of H_2SO_4 at 25 °C. In particular, this medium should also guarantee similar solvation models for the two conjugated-acid series. In fact, an investigation[3a] of the substituent effect on the basicities of a significant series of 4-X-benzamides has already been reported, but the reliability of the data is questionable[8,9] on the grounds that the original H_A scale and pK_{BH^+} of indicators used in its construction were *ca.* 0.3 units too negative.

Experimental

Materials.—BA and DMBA were prepared as previously reported.[5a]

pK_{BH^+} *Measurements.*—The essential features of our procedure have been described previously.[10,11] The choice of λ for the determinations, in the region of $\lambda_{max}(BH^+)$, has been made following the criteria described[12] by Yates, Stevens and Katritzky (see the relevant spectroscopic data collected in Table 2).

The values of optical absorbance, *D*, for amides are affected[1,3] by changes in the medium, independently of the changes produced by protonation. These medium effects are of uncertain magnitude and nature and several corrective methods have been proposed.[13-21]

Indeed, it has been observed that in many instances, as solutions of amide-conjugate acids are made more and more acidic, the UV and NMR spectra continue to undergo changes. Although Liler[4] interpreted these changes as a medium effect on the equilibrium shown in Scheme 1, with the *N*-protonated forms being displaced by the *O*-protonated forms in concentrated acids, the more generally accepted[22] cause is attributed to a medium effect on the spectra of the *O*-protonated forms.

Table 1 Acid dissociation constants, pK_{BH^+}, for 4-X-benzamides (BA) and 2,6-dimethyl-4-X-benzamides (DMBA) in aqueous sulphuric acid at 25 °C

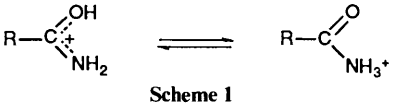
BA	H_A method		EA method		DMBA	H_A method		EA method	
X	pK_{BH^+}	m	pK_{BH^+}	m^*	X	pK_{BA^+}	m	pK_{BH^+}	m^*
OMe	−1.25	1.03	−1.28	0.58	OMe	−1.24	1.05	−1.27	0.58
Me	−1.40	1.00	−1.37	0.54	Me	−1.47	1.02	−1.46	0.55
H	−1.54	1.05	−1.58	0.57	H	−1.65	0.97	−1.62	0.51
F	−1.65	1.00	−1.67	0.56	F	−1.78	1.01	−1.77	0.56
Br	−1.87	0.97	−1.84	0.54	Br	−1.93	0.98	−1.94	0.55
Ac	−2.08	1.04	−2.08	0.53	—	—	—	—	—
NO_2	−2.80[a]	0.69	—	—	NO_2	−2.74[a]	0.70	—	—

[a] $(H_A)_{\frac{1}{2}}$ values: see text.

Table 2 Spectral data (UV) for the free base, B, and its conjugate acid, BH^+, of some 4-X-benzamides (BA) and 2,6-dimethyl-4-X-benzamides (DMBA) in aqueous sulphuric at 25 °C

	BA				DMBA			
	B		BH^+		B		BH^+	
X	λ_{max}/nm	log ε	λ_{max}/nm	log ε[a]	λ_{max}/nm	log ε	λ_{max}/nm	log ε[a]
OMe	197	4.43	191	4.21	198	4.57	197	4.53
	252[b]	4.14[b]	217	4.02	268[c]	3.01	222[c]	3.85
			284[b]	4.29[b]			266	3.50
Me	197	4.46	197	4.24	196	4.56	194	4.42
	237	4.03	258	4.12			216[c]	3.73
							254	3.23
H	194	4.52	196	4.30	192	4.53	191	4.38
	225[d]	3.96[d]	245[d]	4.09[d]	267	2.67	206	3.86
							240	3.08
							272	2.91
F	194	4.52	197	4.20	200	4.43	198	4.30
	227	3.93	250	4.06	227[c]	3.66	245	3.27
Br	199	4.39	195	4.17	199	4.58	199	4.39
	242	4.10	262	4.18	225[c]	3.86	245	3.40
Ac	197	4.25	196	4.32				
	252	4.15	259	4.31				
NO_2	195	4.12	192	4.40	190	4.18	187	4.06
	265	4.04	263	4.22	206	4.07	202	4.11
					275	3.80	267	3.85

[a] Determined in acid solutions having H_A values 2 log units below the point of 50% ionisation ($[B] = [BH^+]$). [b] Literature values, B: λ_{max} 253, log ε 3.23; BH^+: λ_{max} 283, log ε 4.17 (K. Yates and J. C. Riordan, *Can. J. Chem.*, 1965, **43**, 2328). [c] Shoulder. [d] Literature values, B: λ_{max} 225, log ε 3.95; BH^+: λ_{max} 240, log ε 4.07 (K. Yates and H. Way, *Can. J. Chem.*, 1965, **43**, 2131.



Scheme 1

A recent analysis of 'medium effects' in the protonation reactions of amides has been reported[23] in terms of the EA method, claiming to permit accurate calculations of pK_{BH^+} and m^* values in the presence of these effects. Three limiting cases have been isolated and it turned out that compounds of the type examined in the present work (apart perhaps from the *p*-nitro derivatives) fall into Case 1 (*i.e.* compounds which protonate in relatively weak acid, with medium effects on the base form, B, not observable and having $\Delta m^* \leqslant 0.1$). This series of amides[23] exhibits a medium effect on the protonated form, BH^+, which is virtually linear with acidity functions over the range 20–90% H_2SO_4. In these instances a simple graphical correction[17] is adequate and has therefore been adopted in the present work for all the compounds investigated. As a check we found that our pK_{BH^+} value for benzamide (−1.58, m^* 0.57) compares very well with that produced by the above-mentioned analysis[23] (−1.54, m^* 0.54), which in turn exactly matches the value obtained by the H_A method.

Results and Discussion

Dissociation constants were calculated from spectrophotometric data ($I = C_{BH^+}/C_B$) by both the H_A[9] and the excess-acidity (EA)[24] methods, according to eqns. (1) and (2), respectively. In eqn. (2), C_{H^+} is the proton concentration, while X represents the excess-acidity value.[24]

$$\log I = -mH_A + pK_{BH^+} \quad (1)$$

$$\log I - \log C_{H^+} = pK_{BH^+} + m^*X \quad (2)$$

The results are reported in Table 1. Apart from the *para*-nitro derivatives, all the investigated BA species closely follow the H_A function, the slopes (m) of log I *vs.* H_A plots being 1.01 ± 0.02. The deviant behaviour of 4-nitrobenzamide is not unprecedented and is attributable[3a] to the uncertainty in the spectrophotometric determination of I, caused by both qualitatively and quantitatively similar absorptions of B and BH^+. Here, for both 4-nitro- and 2,6-dimethyl-4-nitrobenzamide, which show comparable deviations (m 0.69 and 0.70, respectively), $(H_A)_{\frac{1}{2}}$ values, rather than pK_{BH^+}, are reported in Table 1, while the EA method has not been applied. The agreement among pK_{BH^+} values obtained by the two methods (H_A and EA) is very good, differences being not higher than 0.04

pK_{BH^+} units and within our experimental uncertainty of ±0.05 pK_{BH^+} units: this is not a trivial result, as there is evidence[25] for this not being necessarily the case. In those instances in which disagreement between the two methods is observed, the question arises[25] as to which method gives the more accurate estimate of the real thermodynamic quantity.

An examination of the data in Table 1 also reveals that the corresponding BA and DMBA exhibit very similar pK_{BH^+} values, the differences being $\leqslant 0.1$ pK_{BH^+} units. Conversely, 2,6-dimethyl substitution produces a decrease in basicity of some 0.7 pK_{BH^+} units in the protonation reaction of anilines[26] but in contrast causes an increase in basicity of some 0.4 pK_{BH^+} units in the protonation of *N*,*N*-dimethylanilines in protic solvents. The former effect has been attributed[26] essentially to steric inhibition of solvation, the latter to steric inhibition of resonance.

The fact that a base-strengthening electronic effect of the two *ortho* methyl groups in going from BA to DMBA was not observed could be attributed to a counterbalancing steric inhibition of solvation in the corresponding conjugate acids. Unfortunately slope parameters, m^*, of eqn. (2) do not offer a real clue to this interpretation. It is well known[2b,24] that amides display characteristic m^* values in the range 0.5—0.6. These values, which are low if compared to those of nitrogen bases such as primary anilines (showing m^* values of 1.00[2b,24]), are believed[2b] to be primarily evidence of strong hydrogen-bonding of the *O*-protonated BH^+ with H_2O. The m^* values for BA and DMBA (Table 1) fall well within the expected range, with no appreciable differences between the two series of compounds. This is in turn not completely unexpected as benzamide and *N*-alkylbenzamides, whose similar basicities have been likewise attributed[1] to steric inhibition of solvation counteracting the alkyl inductive effect, exhibit (for primary alkyl groups) essentially the same m^* values too. This situation[1] will hopefully be clarified when more extensive benzamide gas-phase basicity data become available.

Interestingly, however, the fact that the calculated m^* values for benzamide herein (0.57) and elsewhere[1] (0.54) are very similar to that for acetamide (0.55)[1] suggests a non-significant resonance delocalization of the positive charge into the phenyl moiety of the benzamide cation, since such charge delocalization should result in a lower interaction with the solvent and consequently an appreciably higher[2b] m^* value. The negligible resonance interactions of the carbamoyl group with the aromatic ring suggest, as a most important consequence, that the extent of the coplanarity of the two moieties does not influence the nature of substituent effects on the strength of the conjugate acids. Accordingly, in spite of the sizeable torsion of the carbamoyl group out of the aromatic plane in DMBA,[6] $(pK_{BH^+})_{DMBA}$ values, determined by the H_A method, give a good linear correlation† with the corresponding $(pK_{BH^+})_{BA}$ values (slope 0.93 ± 0.05, *r* 0.993, *n* 6, CL > 99.9%). The above results suggest that pK_{BH^+} values in BA and DMBA are governed by similar electronic factors. The pK_{BH^+} values of both series of amides consistently gave satisfactory correlations‡ with Hammett σ_p constants[27] [eqns. (3) and (4), respectively], although the significance of the latter equation could be somewhat limited by the narrower σ_p range.

$$(pK_{BH^+})_{BA} = -(1.14 \pm 0.05)\sigma_p - (1.57 \pm 0.01) \quad (3)$$
$$(r\ 0.995,\ n\ 6,\ CL > 99.9\%)$$

$$(pK_{BH^+})_{DMBA} = -(1.40 \pm 0.09)\sigma_p - (1.65 \pm 0.02) \quad (4)$$
$$(r\ 0.994,\ n\ 5,\ CL > 99.9\%)$$

The susceptibility constant, ρ, for benzamides (−1.14) is somewhat different from that calculated previously (−0.92),[3a] by using incorrect[8,9] pK_{BH^+} values. Significantly poorer correlations, on the other hand, are observed by using σ_p^+ values[27] (*r* 0.947 and 0.952, respectively), a result which has already been taken as evidence[28] of the lack of conjugation between the protonated carbamoyl group and the aryl moiety: this was rationalized[2c] by admitting that the presence of a full positive charge in the protonated form, by increasing the stabilisation through H-bonding with water molecules, limits the importance of the conjugative delocalization of the positive charge itself onto the aromatic ring. The similar behaviour observed for DMBA could be in turn explained by the steric inhibition to conjugation caused by the two *ortho* methyl groups.

Conversely, also on the grounds of our above-mentioned ^{13}C NMR results[5a] on benzamides and 2,6-dimethylbenzamides in $(CD_3)_2SO$, we believe that the results herein should find a different rationalization. In our opinion, the similar behaviour of BA and DMBA can be explained essentially on the basis of the importance of the internal conjugation of the unprotonated and protonated carbamoyl group in limiting that between the same groups and the ring.§

In the case of the structurally similar methyl 4-X-benzoates, an analogous rationale for the lack of importance of conjugative interactions between the methoxycarbonyl group and the ring[5b] was put forward by comparison with the behaviour of 4-X-acetophenones and of several series of aryl benzoates having different extents of electron delocalization within the ester moiety.[5e]

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† The $(H_A)_i$ values of the two *p*-nitro derivatives have been included in this correlation because, although thermodynamically not significant, they are reciprocally consistent.

‡ In correlations 3 and 4 the pK_{BH^+} data determined by the H_A method have been used; the same conclusions would be attained by using pK_{BH^+} values obtained through the EA method in view of the similarity of the two data sets (Table 1).

§ The importance of the electron-releasing power of the NMe_2 group in limiting the conjugation of $CONMe_2$ with an aromatic ring has been previously stressed.[29]

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