Differential substituent effects in 4-X-acetophenones and 4-X-2,6-dimethylacetophenones: basicity constants (pK_{BH^+}) and ^{17}O chemical shifts

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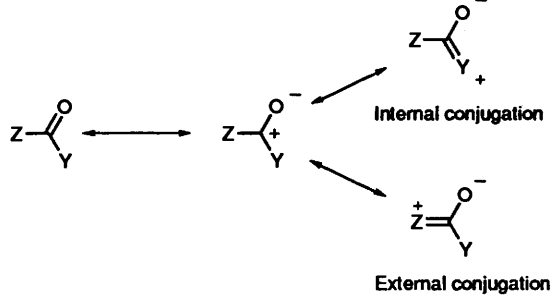
The protonation equilibria of some 4-X-acetophenones (**1c–h, j–l**) and their 2,6-dimethyl derivatives (**2c, d, f–h, l**) have been investigated in sulfuric acid at 298.0 K. Correlations of the pK_{BH^+} values with the *para*-substituent constants evidence a markedly different sensitivity of the base strength of **1** and **2** to substituent effects [$\rho^+(\mathbf{1}) = 1.20 \pm 0.09$, $\rho(\mathbf{2}) = 5.3 \pm 0.5$]. Solvation plays a major role in determining an attenuation (in **1**) or an exaltation (in **2**) of the substituent effect as suggested by the excellent correlation with gas phase basicities for the series **1** and by the behaviour of m^* whose values are essentially constant for **1c–h, j–l** (0.57 ± 0.03) but increase, in the series **2**, as the base strength decreases (m^* 0.48 for X = OMe, 1.08 for X = NO_2). In **2** the steric inhibition of through-conjugation between the 4-X substituent and the carbonyl group also contributes to the observed trends. The ^{17}O NMR chemical shifts for **1a–l** and **2a–d, f–i, l** in $CDCl_3$ have also been collected: in **1** they appear to be related to the pK_{BH^+} values and then to the carbonyl oxygen electron densities, whereas in **2** they are strongly influenced by the spatial location of the oxygen atom and/or of the relevant *p*-orbitals.

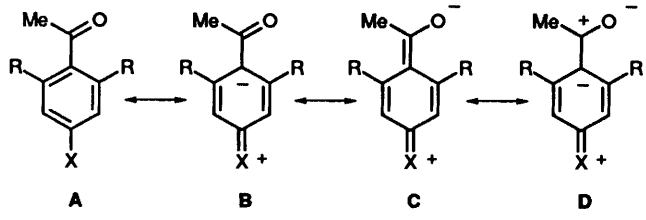
Depending on the nature of Y, the –COY functionality can display, as far as the π-electron distribution is concerned, behaviour ranging from a strong internal conjugation (*i.e.* essentially restricted to within the –COY moiety itself) to a likewise effective interaction with *e.g.* unsaturated Z groups such as an aromatic system (external conjugation) (Scheme 1).



Scheme 1

As evidenced by a number of studies testifying the ongoing interest in the field,[1,2] the balance between the two kinds of conjugation (which obviously rests on the nature of both Y and Z) can be investigated by means of calculations and/or monitored through the evaluation of the substituent effects on some chemical or spectroscopic properties of suitable series of compounds whose Z moiety is characterized by the presence of groups with different polar and resonance contributions.

Recently, we have systematically compared the ^{13}C NMR behaviour of the C=O carbon atom of some aromatic ketones,[1f] esters[1e,f] and amides[1e] (Z = 4-X-C_6H_4; Y = Me, OMe, NH_2) with that of their 2,6-dimethyl analogues (Z = 4-X-2,6-$Me_2C_6H_2$), where the coplanarity between COY and the aryl moiety and thus any substantial conjugation between them are expected to be limited (steric inhibition of resonance). The remarkable differences in the observed chemical shifts of the carbonyl-carbon atom in the two series of acetophenones thus suggest[1f] that through-conjugation (Scheme 2, contributor **C**) predominates in 4-X-acetophenones (R = H) whereas polarization of the carbonyl π-electrons (Scheme 2, charge-alternation



R = H, Me

Scheme 2

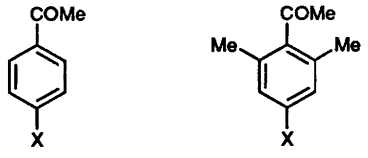
contributor **D**) prevails in 4-X-2,6-dimethylacetophenones (R = Me). On the contrary, as evidenced by the dual substituent parameter analysis of the results, the nature of the substituent effect on the ^{13}C NMR behaviour of the carboxyl-carbon atom of methyl benzoates[1e,f] and benzamides[1e] is not significantly affected by the 2,6-dimethyl substitution, leading to the conclusion that π-polarization represents in such cases the main resonance interaction between *para*-substituents and COY. The importance of π-polarization has been more recently enlightened also by our comparative studies on the protonation equilibria of 4-X-substituted benzamides[1d] and benzoic acids[1a] with those for the corresponding 2,6-dimethyl derivatives.

In order to broaden our knowledge on the electron-density distribution (and its variation induced by substituents) in ArCOY we report herein on protonation (pK_{BH^+}) and ^{17}O

Table 1 Protonation results[a] for 4-X-acetophenones (**1**)[b] and 2,6-dimethyl-4-X-acetophenones (**2**)[c]

	1		2		
X	$-pK_{BH^+}$[b,d,e]	m^*[d]	$-pK_{BH^+}$[c–e]	m^*[d]	$pK_{BH^+}\mathbf{1} - pK_{BH^+}\mathbf{2}$
OMe (**c**)	3.16 ± 0.03	0.54 ± 0.01	3.96 ± 0.05	0.48 ± 0.01	0.80
Me (**d**)	3.68 ± 0.01	0.61 ± 0.01	4.50 ± 0.08	0.56 ± 0.01	0.82
Ph (**e**)	3.96 ± 0.05	0.55 ± 0.01	—	—	—
H (**f**)	4.08 ± 0.24	0.65 ± 0.05	4.85 ± 0.15	0.62 ± 0.02	0.77
			(4.68 ± 0.17)[f]	(0.55 ± 0.03)[f]	(0.60)
F (**g**)	4.15 ± 0.11	0.57 ± 0.02	6.08 ± 0.10	0.76 ± 0.02	1.93
Br (**h**)	4.56 ± 0.05	0.60 ± 0.01	6.93 ± 0.10	0.83 ± 0.01	2.37
	(4.43 ± 0.20)[h]	(0.72 ± 0.04)[h]			(2.50)[i]
CF_3 (**j**)	4.75 ± 0.30	0.56 ± 0.05	—	—	—
CN (**k**)	4.59 ± 0.07	0.50 ± 0.01	—	—	—
NO_2 (**l**)	5.02 ± 0.22	0.58 ± 0.03	9.53 ± 0.42	1.08 ± 0.05	4.51

[a] At 298.0 K in aq. sulfuric acid. [b] By UV spectroscopy, if not otherwise stated. [c] By ^{1}H NMR spectroscopy, if not otherwise stated. [d] pK_{BH^+} Values were calculated by using sets of 8 to 19 log I values determined in the range -1 to $+1$; good correlations were observed in the plots of ($\log I - \log C_{H^+}$) *vs.* X, as indicated by the obtained correlation coefficients (0.990 to 0.999) and standard deviations. [e] For the correlations to be discussed (see text) the UV pK_{BH^+} value for **1h** (4.56) and the ^{1}H NMR pK_{BH^+} value for **2f** (4.85) have been used. [f] By UV. [g] Difference between homogeneous (UV) values. [h] By ^{1}H NMR. [i] Difference between homogeneous (^{1}H NMR) values.



1 **2**

a X = NMe_2 **b** X = NH_2 **c** X = OMe **d** X = Me **e** X = Ph **f** X = H **g** X = F **h** X = Br **i** X = COMe **j** X = CF_3 **k** X = CN **l** X = NO_2

NMR data of some 4-X-acetophenones (**1**)†,[3] and 4-X-2,6-dimethylacetophenones (**2**): the main target of the present study being to monitor how the aforesaid different transmission modes of the substituent effects to the carbonyl group (through-conjugation or π-polarization) affect both its basicity and the electron density on the oxygen atom. Secondly, the comparison of the substituent effects on the carbonyl oxygen as such and on its protonated form (as measured by ^{17}O chemical-shift and pK_{BH^+} data, respectively) will hopefully help to ascertain, with particular regard to the 2,6-dimethyl derivatives, whether the balance between through-conjugation and π-polarization is in any way affected by the involvement of a positively charged probe group [$-C(R)OH^+$], whose quest for electrons from the aryl moiety is obviously expected to be much stronger.

Experimental

Materials

Acetophenones **1b–l** were commercial samples, distilled or crystallized to match reported physical constants. The synthetic procedure for 2,6-dimethylacetophenones **2b–d**, **f–i** and **l** has been reported elsewhere.[1f]

4-(*N*,*N*-Dimethylamino)acetophenone (**1a**) and the 2,6-dimethyl derivative (**2a**) were synthesized following a reported general procedure[4] *via* methylation (Me_2SO_4) of the corresponding amino derivatives. **1a** (45%), mp 101.5–102.7 °C (lit.,[4] 105–106 °C). **2a** (34%), mp 32.0–32.8 °C; δ_H(200 MHz; $CDCl_3$, Me_4Si) 2.3 (6 H, s), 2.4 (3 H, s), 2.9 (6 H, s) and 6.4 (2 H, s). The NMR spectrum is identical with that reported for a liquid sample, obtained through an alternative route.[5]

pK_{BH^+} Measurements

The pK_{BH^+} values (Table 1) for both series of acetophenones have been calculated by means of the excess-acidity method [eqn. (1)],‡,[6] the agreement with true thermodynamic values

$$\log I - \log C_{H^+} = pK_{BH^+} + m^*X \qquad (1)$$

from earlier investigations for 4-X-acetophenones[3a,b,g] being, in general, very good.

Ionization values ($I = C_{BH^+}/C_B$) for **1c–h**, **j–l** were determined at 298.0 ± 0.5 K in aqueous sulfuric acid solutions by a spectroscopic UV technique whose essential features have been described previously.[1a] As far as it concerns the possible involvement of medium effects in the experimental determinations herein, it should be pointed out that UV spectra of acetophenones show no noticeable medium effect and a simple graphic method[7] was used to account for any such effect. Furthermore, the substantial agreement among the m^* and pK_{BH^+} values calculated by adopting different corrective methods for the medium effect is in turn indicative that the latter is not large on acetophenone UV spectra.

The same UV technique adopted for **1** did not allow the evaluation of I for the whole series of 2,6-dimethyl derivatives (**2c**, **d**, **f–h**, **l**); for these compounds, therefore, the ^{1}H NMR technique was adopted and trimethylammonium ion (0.05 mol dm^{-3}) was used as internal standard to minimize solvent effects on chemical shifts;[8] Fig. 1 shows three representative sigmoid curves obtained by plotting $\Delta\nu$ (*i.e.* $\nu - \nu_{ref}$) *vs.* $-H_0$. When the ν_{BH^+} value was not experimentally accessible it was determined by extrapolation; the ν_{BH^+} value chosen for any curve was one that gave the best correlation coefficient of the plot of eqn. (1).

It is known that the two techniques above (UV and ^{1}H NMR spectroscopy) furnish similar results ($\Delta pK_{BH^+} < 0.5$) for most organic bases,[3b,9] significant exceptions having been observed

† Protonation[3a–d] and ^{17}O NMR studies[3e,f] of some substituted acetophenones have been reported already in the literature: nonetheless, in order to have a set of homogeneous experimental data, we have redetermined herein both ionization values and ^{17}O chemical shifts for all the previously investigated acetophenones.

‡ According to the fact that neither **1**[3b] nor **2** behave as Hammett bases, slopes of log I *vs.* $-H_0$ plots different from unity (generally *ca.* 0.6) have been found.

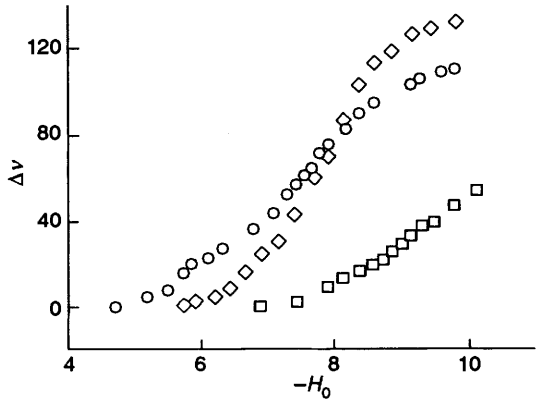


Fig. 1 Plot of Δν *vs.* $-H_0$ for **2c** (○), **2g** (◇) and **2l** (□). The curves start from the same Δν value after suitable vertical shifts.

only for aliphatic ketones:[10] herein, in order to verify the consistency of the two techniques, the ionization values of compounds **1h** and **2f** were determined by both of them and the agreement was found to be satisfactory (Table 1).

^{17}O NMR Measurements

The ^{17}O NMR spectra for **1a–l** and **2a–d, f–i, l** were recorded on a Varian VXR-300 spectrometer at 40.670 MHz; all spectra were acquired at natural abundance for anhydrous $CDCl_3$ solutions at 298.0 ± 0.5 K. Chemical shifts (δ) were referenced to external 1,4-dioxane.[11] Acquisition parameters: spectral width 30 kHz, 2 K data points, 90° pulse angle (35 μs pulse width), quadrature phase detection, acquisition times $T_{acq} > 5T_2$, 50 000–150 000 scans. Processing parameters: exponential multiplication of the FIDs by a line-broadening (LB) factor of 10–25 Hz and zero-filling up to 16 K,[12] resulting in a digital resolution of 3.7 Hz per point after FT.

Results and discussion

Unhindered acetophenones (1)

As a consequence of the expected opposite base-strengthening or -lowering effects played by electron-releasing or -withdrawing *para*-substituents, respectively, acetophenones **1** experience (Table 1) a basicity decrease of about two pK units on going from the *para*-methoxy (**1c**) to the *para*-nitro (**1l**) derivative. The dependence of pK_{BH^+} on the substituent can most adequately be expressed by means of a linear free energy correlation with σ_p^+ constants[13] [eqn. (2); $\Delta pK_{BH^+} = pK_{BH^+(4\text{-}X)} - pK_{BH^+(4\text{-}H)}$]: the marked deviation of the *para*-cyano derivative (**1k**), which has been excluded from eqn. (2), could be the

$$-\Delta pK_{BH^+(1)} = (0.07 \pm 0.04) + (1.20 \pm 0.09)\sigma_p^+ \quad (n = 8, r = 0.982) \quad (2)$$

consequence of the well known interactions between the cyano group itself and the strong protonating medium.[1a] The requirement for σ_p^+ constants (as well as the calculated ρ^+ value) matches very well previous analyses on comparable sets of acetophenones§[3c] and clearly speaks for an essentially conjugative nature of the interaction between the aromatic ring and the acetyl group[1f] or its protonated form.

The mean value (0.57 ± 0.03) of the m^* parameter of the excess-acidity treatment identifies the nature of **1** as oxygen bases,[14] monitoring, for the conjugate acids, high solvation requirements which are remarkably constant along the whole series of substituents investigated: this very constancy of the interactions with the medium, which itself remains practically unaltered along the series of substituents, guarantees the excellent correlation [eqn. (3)] between the pK_{BH^+} values and the

$$-\Delta pK_{BH^+(1)} = (0.00 \pm 0.01) + (0.17 \pm 0.00) \times [-\Delta pK_{BH^+(1),gas}] \quad (n = 6, r = 0.999_3) \quad (3)$$

available gas phase basicities¶[15] which again is obtained by excluding the *para*-cyano derivative (see above).

Furthermore, the low value of the slope in eqn. (3), which clearly mirrors a much lower substituent effect in solution than in the gas phase, can be in turn well justified on the grounds of the appreciable stabilization of BH^+ through solvation: such an effect is commonly known as a solvent attenuation of the substituent.[15b,16]

The ^{17}O chemical shifts of **1** in $CDCl_3$ (Table 2) range from 501.0 ppm for the 4-dimethylamino (**1a**) to 563.8 ppm for the 4-nitro (**1l**) derivative, showing that electron-withdrawing substituents cause a high-frequency shift (deshielding effect) while electron-releasing substituents shield the oxygen atom, matching a behaviour already observed in CD_3CN for a less extended series of acetophenones.[3f] The effect of the bromo and fluoro substituents is very feeble, deshielding and shielding, respectively.

The extremely good correlation [eqn. (4)] between the

$$^{17}O\ SCS(1) = (0.2 \pm 0.3) + (25.0 \pm 0.4)\sigma_p^+ \quad (n = 12, r = 0.999) \quad (4)$$

carbonyl-oxygen substituent chemical shifts ($SCS = \delta_{4\text{-}X} - \delta_{4\text{-}H}$) and σ_p^+ constants reassesses,[1f] also for the unprotonated acetyl group, the essentially conjugative nature of resonance interactions with the aromatic moiety (*i.e.* external conjugation); the calculated ρ^+ value is similar to that previously obtained by Dahn and co-workers.[3e]

Furthermore, as a logical consequence of the goodness of fit of both eqns. (2) and (4), the ^{17}O SCS values do correlate with $-\Delta pK_{BH^+}$ [eqn. (5)]: this occurrence undoubtedly supports the

Table 2 ^{17}O NMR substituent chemical shifts ($SCS = \delta_{4\text{-}X} - \delta_{4\text{-}H}$) for 4-X-acetophenones (**1**) and 2,6-dimethyl-4-X-acetophenones (**2**)[a]

X	SCS(1)	SCS(2)	δ(2) − δ(1)
NMe_2 (**a**)	−41.5	−7.3	84.2
NH_2 (**b**)	−33.0	−3.7	79.3
OMe (**c**)	−17.8	−0.1	67.7
Me (**d**)	−8.1	1.2	56.9
Ph (**e**)	−4.5	—	—
H (**f**)	0.0	0.0	50.0
F (**g**)	−3.5	3.9	57.4
Br (**h**)	2.9	4.6	51.7
COMe (**i**)	12.8	4.9	42.1
CF_3 (**j**)	13.7	—	—
CN (**k**)	18.2	—	—
NO_2 (**l**)	21.3	10.7	39.4
δ_H[b]	542.5	592.5	

[a] At 298.0 K in $CDCl_3$ (see Experimental). [b] Chemical shifts (ppm) for the parent systems (X = H).

§ The slope value of eqn. (2) is intermediate between those obtainable from previously reported pK_{BH^+} data.[3a,g]

¶ A somewhat less satisfactory correlation between gas phase and solution basicities of acetophenones has been already reported,[15a] exploiting an older set[3d] of pK_{BH^+} values.

view[3e] that in unhindered acetophenones the ^{17}O chemical shift mainly depends on the electron density on the oxygen atom itself.[1c]

$$^{17}O\ SCS(\mathbf{1}) = -(1.3 \pm 1.2) + (19.9 \pm 2.1)[-\Delta pK_{BH^+(1)}] \quad (n = 8, r = 0.968) \quad (5)$$

2,6-Dimethylacetophenones (2)

Qualitatively, the pK_{BH^+} trend for hindered acetophenones (Table 1) is, as expected, similar to that experienced by **1** (*e.g.* electron-releasing substituents increasing the basic strength), but a comparison between the two series of compounds on more quantitative grounds reveals that the introduction of two methyl groups *ortho* to the carbonyl (*i*) causes a decrease in basicity throughout, despite the generally acknowledged base-strengthening polar effect of alkyl groups, (*ii*) enforces the use of σ_p (instead of σ_p^+) for the best fit of pK_{BH^+} with substituent parameters [eqn. (6)], although (*iii*) greatly enhancing the

$$-\Delta pK_{BH^+(2)} = (0.53 \pm 0.17) + (5.3 \pm 0.5)\sigma_p \quad (n = 6, r = 0.985) \quad (6)$$

basicity dependence on the substituent effect,‖ as evidenced by the size of the susceptibility constant of eqn. (6) [$\rho(\mathbf{2}) = 5.3$, to be compared with $\rho^+(\mathbf{1}) = 1.2$ of eqn. (2)]: thus K_{BH^+} undergoes a variation of six orders of magnitude on going from the *para*-methoxy (**2c**) to the *para*-nitro (**2l**) derivative.

Points (*i*) and (*ii*) above find a straightforward rationale in the well known steric inhibition of conjugation played by two *ortho* methyl groups[1f,17] which, rotating the carbonyl group out of the plane of the aromatic ring, would raise the energy of the conjugate acid (BH^+) with respect to the neutral molecule (where resonance stabilization is expected to be of much less relevance): a gross quantification of the basicity decrease due to such inhibition of conjugation is provided by the ΔpK_{BH^+} value for the two parent compounds [$pK_{BH^+(1f)} - pK_{BH^+(2f)} = 0.8$], amounting to something less than one order of magnitude. Moreover, the experimental evidence is that while, in agreement with the markedly different susceptibility values of eqns. (2) (for **1**) and (6) (for **2**), the basicity gap between the two series of acetophenones steeply increases for electron-withdrawing substituents [$pK_{BH^+(1)} - pK_{BH^+(2)} = 2.5$ for X = Br, 4.5 for X = NO_2], it remains virtually constant for X = H, Me, OMe (*ca.* 0.8 p*K* units). Particularly significant is, in this regard, the not very good $\Delta pK_{BH^+(2)}$ *vs.* $\Delta pK_{BH^+(1)}$ correlation (Fig. 2, $n = 6$, $r = 0.935$), attributable to a change in the essence of the substituent effect on the basicity of **2** with respect to **1**.**

The overall picture of substituent effects in **2** is rather complicated by the occurrence that the m^* value (Table 1) surprisingly[14] increases from 0.48 (for the 4-OMe derivative **2c**) to 1.08 (for the 4-NO_2 compound **2l**), in spite of the constancy of the protonation site and of the expected substantial invariance of steric crowding on the protonation site itself. Fig. 3 shows plots of ($\log I - \log C_{H^+}$) *vs.* *X* based on NMR measurements for **2c**, **g**, l. The different m^* values lead to a crossing of the straight lines relative to **2c** and **2g**, corresponding to an inversion in the relative basicities at *X ca.* 7.5: in water the former is a stronger base, while the reverse holds above 87% sulfuric acid. Moreover, the fairly good linearity of the plot of m^* *vs.* σ_p [eqn. (7)]

$$m^*(\mathbf{2}) = (0.66 \pm 0.02) + (0.56 \pm 0.06)\sigma_p \quad (n = 6, r = 0.978) \quad (7)$$

testifies a tight correlation between the substituent effect and the differential B *vs.* BH^+ solvation, where electron-releasing groups increase solvation, electron-withdrawing ones significantly decrease it.

The dependence†† of $-\Delta pK_{BH^+(2)}$ on m^* [obviously expected on the grounds of both eqns. (6) and (7)] is in turn clearly evidenced by the excellent correlation shown in Fig. 4: what must be stressed here is the positive slope of such correlation, *i.e.* a result which is qualitatively opposite to that commonly found in the field,[14] where a stronger solvation (*i.e.* the shift towards lower m^* values) is generally required when BH^+ is less stabilized by the substituent electronic effects. Such behaviour, which is, to our knowledge, unprecedented, and might be defined as 'reversed solvent exaltation' of substituent effects, could be again accounted for on the grounds of the preclusion of effective conjugation between the aromatic ring and the carbonyl group in hindered acetophenones. Thus, the effect of 4-X substituents on C-1 in **2** would affect the electron density on the oxygen atom and hence its basicity insofar as, by means of π-polarization: (*i*) electron-donating substituents increase basicity and provide

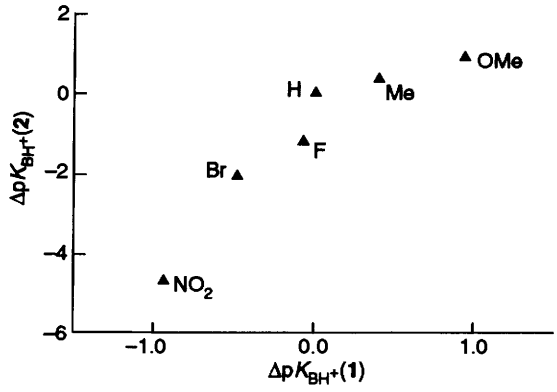


Fig. 2 Cross-correlation between basicity constants of **1** and **2**: $\Delta pK_{BH^+(2)} = -(1.0 \pm 0.3) + (2.9 \pm 0.6)\Delta pK_{BH^+(1)}$ ($n = 6$, $r = 0.935$)

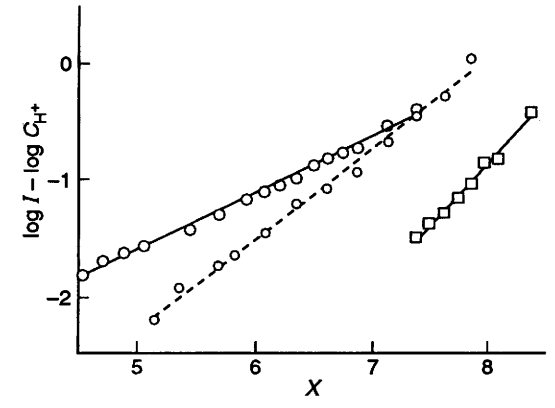


Fig. 3 Plot of ($\log I - \log C_{H^+}$) *vs.* *X* for **2c** (○), **2g** (○) and **2l** (□)

‖ The cooperation of effects (*ii*) and (*iii*) herein is rather surprising, as enhanced substituent constants (*e.g.* σ^+) generally lead to increased susceptibility constants.

** The overall parallelism between the effect of H, Me and OMe on pK_{BH^+} in **1** and **2** could in principle be regarded as a breakdown in the correlation between basicities and substituent effects in the latter series, indicating a qualitative similarity of the electronic effects played by electron-releasing groups in the two series: anyway, such an alternative explanation of the experimental data does not find support, in our opinion, in the bulk of the results further discussed in the text.

†† A similar trend of both m^* and pK_{BH^+} values was observed[10] for alkanones. In fact, on going from 3,3-dimethylbutan-2-one to 2,2,4,4-tetramethylpentan-3-one m^* varies from 0.37 to 0.85 and the acidity correspondingly increases from $pK_{BH^+} = -3.37$ to -7.24. Such trend is only due to steric inhibition to solvation, which affects both m^* values and basicity constants.

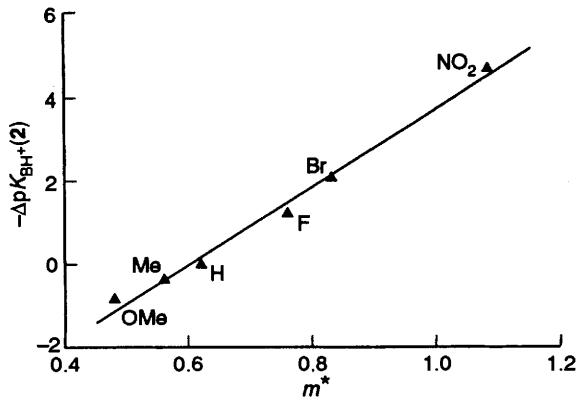
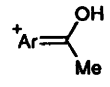


Fig. 4 Basicity dependence on m^* for 4-X-2,6-dimethylacetophenones: $-\Delta pK_{BH^+(2)} = -(5.6 \pm 0.3) + (9.4 \pm 0.5)m^*$ ($n = 6, r = 0.995$)

stabilization for $\mathbf{2H}^+$, the constancy of m^* for X = MeO, Me and H reflecting insignificant changes of medium effects over a pK_{BH^+} variation of less than one order of magnitude; (*ii*) electron-withdrawing substituents, conversely, decrease basicity and destabilize $\mathbf{2H}^+$ more strongly than in **1** and in $\mathbf{1H}^+$ and thus enforce the use of more and more concentrated H_2SO_4 solutions: this should in turn prevent effective solvation of $\mathbf{2H}^+$ (increasing m^*, as observed) as a consequence of a change in the medium itself. On the contrary, as far as unhindered acetophenones (**1**) are concerned, the occurrence of free conjugative interactions determines the electron withdrawal by the strongly electron-acceptor protonated carbonyl group whichever the substituent X, making **E** the common array along the whole series and therefore minimizing differences in the solvation of $\mathbf{1H}^+$: accordingly, the observed constancy of m^* throughout can be easily accounted for.



E

Inspection of the ^{17}O NMR data reported in Table 2 reveals that in each dimethylacetophenone the carbonyl oxygen is deshielded with respect to the corresponding acetophenone, the chemical shift difference amounting to 50 ppm for the parent compounds. This finding, hardly related to any conceivable electronic effect of the two methyl groups,‡‡ could be consistent with a markedly reduced through-conjugation between the carbonyl and the aryl moieties in **2f** with respect to **1f**.

In addition, substituent effects are markedly smaller in **2** than in **1**, their ranges amounting to 18 and 63 ppm respectively; in particular, in the series **2** only the two strongest electron-donating substituents appear to cause a sizeable shielding of the carbonyl oxygen; moreover the chemical shift difference between corresponding terms of the two series is larger for X = NMe_2 than for X = NO_2, as the former group undergoes a reduction of its conjugative interaction with the carbonyl on going from **1** to **2** while the latter cannot conjugate with the carbonyl in either series of compounds. All these findings appear to support a marked reduction of conjugative interactions between the X-substituent and the carbonyl oxygen in **2** with respect to **1**.

However, this approach could lead to an overestimation of the role of steric inhibition of conjugation in **2**, because any discussion about the carbonyl oxygen chemical shift should take into account that on going from **1** to **2** the carbonyl oxygen changes its position with respect to the aromatic ring. Particular points to be stressed are the following: (*i*) it has been reported[18] that in 4-substituted benzyl alcohols the behaviour of the ^{17}O chemical shifts reveals a reverse resonance effect of substituents as a possible consequence of the fact that the oxygen atom, β to the aryl ring, is located out of its plane;[19] the same topological effect causing a reverse effect of 4-X substituents in benzyl alcohols could cause (or contribute to cause) an attenuation of normal substituent effects in **2**. (*ii*) In the sterically hindered **2** a compression of the oxygen p-orbitals[20] caused by the two *ortho*-methyl groups, could coincide to increase the ^{17}O chemical shifts. (*iii*) The torsion angle between the acetyl and aryl moieties could not be constant through all the series **2**, causing small variations in ^{17}O data.§§[,21]

For the possible concurrency of all these effects, care has to be taken in comparing the carbonyl oxygen chemical shifts of the two studied series of compounds. However, the reasonable correlation of the ^{17}O SCS of **2** with σ_p substituent constants [eqn. (8)] appears to indicate that all the main operative effects

$$^{17}O\ SCS(\mathbf{2}) = (1.6 \pm 0.5) + (10.8 \pm 1.2)\sigma_p \quad (n = 9, r = 0.961) \quad (8)$$

are either direct or indirect consequences of the electronic effect of substituents, although only some of them can be related to the electron density on the oxygen atom.

As the ^{17}O SCS values correlate with σ_p, they necessarily correlate also with ΔpK_{BH^+} values [eqn. (9)].

$$^{17}O\ SCS(\mathbf{2}) = (1.2 \pm 0.4) + (2.0 \pm 0.2)[-\Delta pK_{BH^+(2)}] \quad (n = 6, r = 0.983) \quad (9)$$

The correlation parameters of eqns. (5) and (9) mirror the intriguing finding that when comparing the two methoxyl derivatives **1c** and **2c** a large chemical shift variation (84 ppm) is accompanied by a moderate ΔpK_{BH^+} change (−0.8 units), while for the two nitro compounds a smaller chemical shift variation (39 ppm) corresponds to a large ΔpK_{BH^+} difference (−4.51 units).¶¶ Anyway, these results can be explained reasonably by taking into account that in the series **2** an exalted, solvation-promoted substituent effect on pK_{BH^+} is matched by an over-attenuation of the substituent effect on ^{17}O chemical shifts for topological reasons.

Conclusions

At variance with that previously observed for amides[1d] and benzoic acids,[1a] in the 4-X-acetophenone system the 2,6-dimethyl substitution brings about remarkable variations in the electronic array of the probe group, as measured by either protonation equilibria or carbonyl-oxygen ^{17}O chemical shifts. The analysis of pK_{BH^+} and the relevant m^* values, while restating for **2** the already acknowledged[1f] steric inhibition of through-conjugation between the *para*-substituent and the carbonyl group, at first sight stresses the role of solvation in determining an attenuation (for **1**) and an exaltation (for **2**) of substituent effects on base strength. In our opinion, a more marked basicity variation along the series **2** causes the more

‡‡ It is relevant to note that in the series **1** a 4-methyl group causes an expected shielding (8 ppm) with respect to hydrogen, well in line with its polar effects on the carbonyl moiety.

§§ MM2 Calculations actually forecast minor variations of the torsion angle between the acetyl and the aromatic moieties along the whole series **2** (52.5 ± 0.4); nonetheless some effect of such variations could manifest itself by inducing scattering of points or deviations from linearity (see text).

¶¶ The different behaviour of ^{17}O chemical shift in **1** and **2** is also indicated by the relatively poor correlation between SCS(**1**) and SCS(**2**) ($n = 9, r = 0.947$, slope = 0.24 ± 0.03).

basic ketones to be protonated in mixtures still rich in water, the less basic ones in an almost water-free medium; this causes a macroscopic medium change, which can greatly affect the m^* values. Thus, the large basicity range observed for **2** is the result of the cooperation of both strong substituent effects and induced medium effects. This well matches the hypothesis of Bunnett and Olsen[22] that hydration changes could not be the only relevant factor in determining the significance and the absolute value of φ and hence of m^* ($m^* = 1 - \varphi$). Probably in water-rich mixtures the importance of hydration changes masks the other effects, that can become relevant in water-poor mixtures. ^{17}O Chemical shifts appear to be useful indicators of the carbonyl-oxygen electron density only in the series **1**, while in the hindered **2**, owing to the location of the oxygen atom out of the ring plane, they seem to be governed by a blend of several factors.

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