Protonation of some substituted phenylthiophen-2-ylmethanones in sulfuric acid

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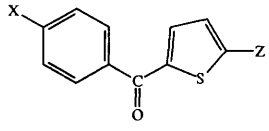
Within the framework of research carried out on the behaviour of ArCOY compounds the title reaction has been investigated in order to gain information on the influence of Ar and of Y on the interaction between Y and CO and between Ar and CO, respectively, when Ar = 4-substituted phenyl and Y = 5-substituted thiophen-2-yl. The pK_{BH^+} values collected in this work have been analysed by linear free energy relationship and the calculated ρ values (0.98 and 2.15 for substitution in the phenyl group and thiophen-2-yl ring, respectively), as well as the mean value (0.97) of m^*, have been compared with those of 5-substituted-2-acetylthiophenes 2 and 4-substituted acetophenones 3. From the above comparisons we conclude that solvation has a role, as important as that of the electronic density on the basic centre, in determining the degree of protonation of weak bases even if they are structurally similar.

The transmission of substituent effects through an aromatic or heteroaromatic ring and its influence on reactivities as well as on physical properties continues to be an appealing research field in physical organic chemistry. In such studies, of great significance is a knowledge of substituent–aromatic (or heteroaromatic) ring-probe interactions, which depend both on the properties of the rings and on the electronic structure and steric requirements of the probe.

The carbonyl moiety is certainly one of the most commonly used and versatile probes for studying such interactions. Thus ^{13}C and ^{17}O NMR chemical shifts,[1] the stretching frequencies[2] as well as the reactivities[3] of carbonyl aromatic compounds have been widely investigated. In aromatic or heteroaromatic carbonyl derivatives, ArCOY, the electron density on the CO group and the interactions between aromatic ring and carbonyl group depend strongly on the nature and conjugative ability of the Y group. Formyl (Y = H)[1e] and acetyl (Y = Me)[1e,4] groups containing Y groups with a low degree of internal (*i.e.*, restricted within the COY moiety itself) conjugation are able to conjugate with the aromatic ring. On the contrary, carboxamido (Y = NH_2),[1e,5] *N*-chlorocarboxamido (Y = NHCl),[6] alkoxycarbonyl (Y = OR)[1e,4,5] and carboxy (Y = OH)[1e,7] groups contain Y groups with a high degree of internal conjugation and which interact with the aromatic ring mainly through a π-polarization mechanism.

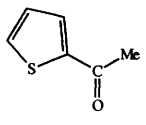
In order to enlarge our knowledge of the behaviour of COY moieties in which the electronic interactions between the carbonyl group and Y are large and also to investigate the influence of Ar and Y, respectively, on the interactions between Y and CO and between Ar and CO, we have determined the acid–base equilibrium constants (pK_{BH^+}) of a series of substituted phenylthiophen-2-ylmethanones **1**. In this system the electronic interaction thiophen-2-yl–probe (carbonyl) can affect the interactions phenyl–probe (carbonyl) and *vice versa*. The substituents present in both rings range from the strongly electron-donating methoxy group to the strongly electron-withdrawing nitro group.

The data so far obtained can be used to make a comparison with literature data concerning 5-substituted 2-acetylthiophenes **2**[8] and 4-substituted acetophenones **3**;[1f] these two series of compounds are particularly interesting because in both cases the methyl, *i.e.* the second group linked to the carbonyl, is not able to strongly interact with carbonyl. Thus, data on **2** and **3** can monitor very well the ability of an aryl or heteroaryl group to conjugate with carbonyl.



1

1ah: X = NO_2; Z = H
1bh: X = Cl; Z = H
1ch: X = Br; Z = H
1dh: X = Me; Z = H
1eh: X = OMe; Z = H
1hh: X = Z = H
1ha: X = H; Z = NO_2
1hb: X = H; Z = Cl
1hc: X = H; Z = Br
1hd: X = H; Z = Me
1he: X = H; Z = OMe



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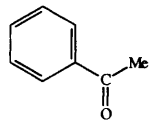

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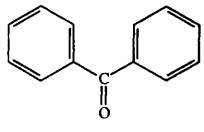

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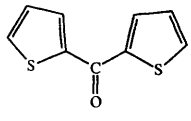


5

For the sake of comparison we have also collected data for the diphenylmethanone **4** and dithiophen-2-ylmethanone **5**. The reaction chosen in this study for monitoring substituent effects is a classical and formally simple reaction, namely protonation of the carbonyl group. Weak organic bases are normally protonated in concentrated solutions of strong acids where relative basicities are strongly affected by both internal (electronic) and external (solvation) effects. The protonation equilibria of **1**, **4** and **5** have been studied in aqueous sulfuric acid solutions at 298 K. Ionization values were determined

Table 1 Acid dissociation constants, $-pK_{BH^+}$, for compounds **1**, **4** and **5** determined by UV in aqueous sulfuric acid at 298 K

Substrate	$-pK_{BH^+}$	m^*	r
1ah	6.00 ± 0.26	0.97 ± 0.05	0.986
1bh	5.41 ± 0.08[a]	0.97 ± 0.02	0.997
1ch	5.31 ± 0.13[b]	0.96 ± 0.03	0.994
1dh	4.91 ± 0.08[c]	0.97 ± 0.02	0.997
1eh	4.45 ± 0.07[d]	0.95 ± 0.02	0.998
1hh	5.18 ± 0.08[e]	1.00 ± 0.02	0.998
1ha	6.95 ± 0.31	0.90 ± 0.05	0.988
1hb	5.57 ± 0.09	0.98 ± 0.02	0.998
1hc	5.45 ± 0.13	0.99 ± 0.03	0.997
1hd	4.53 ± 0.09	1.05 ± 0.02	0.996
1he	3.53 ± 0.07	1.23 ± 0.03	0.997
4	4.80 ± 0.08[f]	0.80 ± 0.02	0.997
5	5.41 ± 0.08[g]	1.08 ± 0.02	0.998

[a] Lit.,[11] 5.80. [b] Lit.,[11] 5.70. [c] Lit.,[11] 4.87. [d] Lit.,[11] 4.75. [e] Lit.,[11] 5.50. [f] Lit.,[12] 4.97 (m^* 0.70). [g] Lit.,[11] 5.01.

spectrophotometrically and used to calculate the pK_{BH^+} values by means of the excess-acidity method [eqn. (1)].[9]

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

It must be remembered that the value of the m^* parameter identifies the nature of the base (*i.e.*, the site of protonation) and furnishes information about the degree of relative solvation of the conjugated acid–base pair.[1f,9,10]

The pK_{BH^+} and m^* values of some compounds analysed in this work have already been reported,[11,12] but except for **4** the solvation parameter (m^*) values have not been calculated. In order to have a self-consistent and complete series of data for protonation equilibria of compounds **1**, **4** and **5**, we believed it appropriate to repeat the measurements.

Results and discussion

In Table 1 are reported the pK_{BH^+} and m^* values for the protonation equilibria of compounds **1**, **4** and **5**. Also reported are some pK_{BH^+} values from the literature. As can be seen, no significant difference ($\Delta pK_{BH^+} \leqslant 0.4$) exists between our own and the literature data.

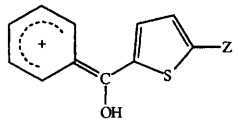
The substituted phenylthiophen-2-ylmethanones **1** show very similar m^* values close to 1.0. Only for **1he** has a significantly higher m^* value (1.23) been calculated: this behaviour can be related to the extensive extra-conjugation between the methoxy and carbonyl (or protonated carbonyl) groups *via* the thiophene ring which helps charge dispersion in **1heH**$^+$, lowering its solvation requirements. Bearing in mind that the m^* value is a parameter which depends on the degree of relative solvation of the conjugate acid–base pair[10] (**1H**$^+$ − **1**), similar m^* values indicate that similar variations in the solute–solvent interactions occur in all compounds studied on going from the base to the conjugated acid. The mean value (0.97 ± 0.03) of m^* calculated for compounds **1** is comparable to that for 2-acetylthiophenes **2** (0.85 ± 0.05)[8] and is substantially higher than that for acetophenones **3** (0.57 ± 0.03).[1f]

Since substituted phenylthiophen-2-ylmethanones **1** have essentially the same steric hindrance around the carbonyl group, different basicities of isomers (*i.e.*, in pairs of compounds containing the same substituent in one or in the other ring; see *e.g.*, the couple **1ah** and **1ha**: $|\Delta pK_{BH^+}|$ *ca.* 1) must be attributed to quantitatively different transmission of substituent effects through the two aromatic rings.

If we look at the pK_{BH^+} and m^* values of **1hh** (−5.18 and 1.00, respectively), 2-acetylthiophene (−4.20 and 0.92, respectively)[8] and acetophenone (−4.08 and 0.65, respectively),[1f] we see that substitution of the methyl group of 2-acetylthiophene by a phenyl ring causes a decrease in basicity of about one pK unit. This can be ascribed essentially to differences in the electronic effects of the methyl and phenyl groups, since the two conjugate acid–base pairs show comparable solvation variations as indicated by the similar m^* values. This seems to exclude the possibility that the difference in basicity observed can be ascribed to different steric hindrances offered by the methyl and phenyl groups in the protonation of the carbonyl group, as the steric constants of the two groups (E_s −1.24 and −1.015 to −3.82, respectively)[13] might lead us to suppose. Substitution of the methyl group of the acetophenone with the thiophen-2-yl ring causes once again a decrease in basicity of about one pK unit, but in this case the decrease is ascribable to differences both in electronic effects of the methyl group and thienyl ring and in solvation variations for the two substrates. In particular, if one supposes that acetophenone and **1hh** are similarly solvated, the different m^* values observed could derive from a reduced solvation of **1hhH**$^+$ with respect to the protonated acetophenone. This reduced solvation of **1hhH**$^+$ could arise from differences in resonance stabilisation due to an increase in conjugation on going from the protonated acetophenone to **1hhH**$^+$: this would cause a greater delocalization of the positive charge in **1hhH**$^+$ than in protonated acetophenone. An alternative explanation in terms of hindrance to solvation by steric effects is made unlikely by the similar solvation requirements of the methyl and phenyl groups (demonstrated above) which might also be expected to extend to the thiophen-2-yl group, by comparison (reported later) of measurements of ρ for protonation of the two reaction families.

The substituents affect the basicity of the carbonyl group as expected, *i.e.* electron-withdrawing and electron-repelling substituents reduce and increase the basicity, respectively. The pK_{BH^+} values were analysed by means of the Hammett equation and the best correlations ($\rho_X^+ = 0.98 \pm 0.02, i = 0.03 \pm 0.01$, $n = 6$, $r = 0.996$ for **1ah–eh**, **1hh** and $\rho_Z^+ = 2.15 \pm 0.03$, $i = 0.04 \pm 0.01$, $n = 6$, $r = 0.998$ for **1ha–he**, **1hh**) were obtained by using σ_p^+ substituent constants.[14] The ρ values calculated show once more that the thiophene ring transmits the substituent effect better than the benzene ring.

The ρ value ($\rho_Z^+ = 2.15$) calculated for compounds **1ha–he**, **1hh** (*i.e.*, for compounds bearing a substituent on the thiophene ring) is similar to that for 5-substituted 2-acetylthiophenes[8] ($\rho^+ = 2.12 \pm 0.28, i = 0.30 \pm 0.14, n = 6, r = 0.966$).† These results seem to indicate that methyl and phenyl groups affect the transmission of substituent effects into the thenoyl moiety in the same manner. This is somewhat surprising since it could be expected that the conjugation of the phenyl ring with the carbonyl group would be able to cause an attenuation (a sort of levelling effect, which would decrease the ρ value) in the transmission of substituent effects. Instead, the above result shows that a resonance structure such as **6** has little importance in describing the resonance of compounds **1ha–he**, **1hh**, also if Z is a strongly electron-withdrawing substituent.



6

Conformational studies on phenylthiophen-2-ylmethanones have shown[15] that the phenyl ring is turned out of the plane defined by the coplanar thienyl ring and carbonyl group: this

† The susceptibility constants for the protonation of 5-substituted 2-acetylthiophenes and of 4-substituted acetophenones (see later) have been recalculated from literature values considering only the substituents present in compounds **1** to make the comparisons self-consistent.

geometry can be related to the greater ability of the thienyl ring to conjugate with the carbonyl group ($\rho_Z^+ > \rho_X^+$). Since the twist angle is less than 90°, however, and the energy barrier to rotation is low some conjugation between the phenyl ring and the carbonyl group could be expected.

The ρ value ($\rho_X^+ = 0.98$) calculated for compounds **1ah–eh**, **1hh** (*i.e.*, for compounds bearing a substituent in the phenyl ring) is smaller than that ($\rho^+ = 1.22 \pm 0.04$, $i = 0.05 \pm 0.07$, $n = 5$, $r = 0.981$) for 4-substituted acetophenones.[1f] This seems to indicate that the unsubstituted thiophen-2-yl ring competes with the phenyl ring in conjugation with the carbonyl group thus exerting a levelling effect. However, considering that the two series of substituted phenylthiophen-2-ylmethanones have very similar m^* values, it is probable that also in compounds **1ah–eh**, **1hh**, independent of the substituent in the phenyl ring, thiophen-2-yl–carbonyl conjugation competes with the phenyl–carbonyl conjugation. The decrease in ρ values on going from 4-substituted acetophenones[1f] to compounds **1ah–eh**, **1hh** seems to exclude the hypothesis of an increase in steric hindrance to solvation due to the thienyl group. Indeed, in this case desolvation of **1ahH**$^+$–**ehH**$^+$, **1hhH**$^+$ should increase conjugation between the phenyl ring and carbonyl moiety, stabilizing the positive charge, and consequently an increase in ρ value should be observed. In fact, an increase in steric hindrance to solvation on going from 4-substituted acetophenones to **1ah–eh**, **1hh** could have been expected as a consequence of the different orientation of the phenyl group (coplanar in 4-substituted acetophenones and out of the plane of the carbonyl group for compounds **1**) rather than the higher steric requirements in **1ah–eh**, **1hh**. However, this hypothesis conflicts both with the use of σ_p^+ substituent constants in the correlation of pK_{BH^+} data for **1ah–eh**, **1hh** and with m^* values for **1ah–eh**, **1hh** similar to those of 5-substituted acetylthiophenes.[8]

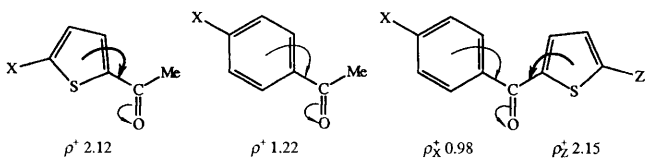
Inspection of the pK_{BH^+} data and m^* values of compounds **4** and **5** provides other interesting data about the relative effects of the phenyl and thiophen-2-yl rings on the protonation equilibra of the carbonyl group. Substitution of the phenyl ring in **1hh** with a thiophen-2-yl ring causes a very small decrease in basicity, probably due to differences in the acid reinforcing character of the two rings, this being higher for thiophen-2-yl than for phenyl as is also indicated by the difference in strengths observed for 2-thiophenecarboxylic acid ($pK_a = 3.51$)[16] and benzoic acid ($pK_a = 4.20$).[17] The m^* values for the two compounds (1.00 for **1hh** and 1.08 for **5**) show that solute–solvent interactions in the protonation equilibria of the two compounds are similar. Substitution of the thiophen-2-yl ring in **1hh** with a phenyl ring causes a small increase in basicity. However, in this case the variation must be ascribed both to electronic (as above) and to solvation factors as shown by the difference in m^* values (1.00 for **1hh** and 0.80 for **4**).

Conclusions

The protonation equilibria of compounds **1**–**5** seem to be hardly affected by the conformational or steric requirements of the rings linked to the carbonyl group.

The data collected in this work increase our knowledge about the behaviour, as far as the π-electron distribution is concerned, of COY functionality. The two groups of phenylthiophen-2-ylmethanones investigated, *i.e.* substituted in the thienyl ring or in the phenyl ring, show different degrees of internal conjugation. Thus, one of the two groups (thiophen-2-yl) can preferentially interact with the carbonyl group and consequently the second group (phenyl) is less effective: then different susceptibility constants in the two series are observed (ρ_Z^+ $0.98 \ll \rho_X^+$ 2.15).

A more general picture of the results is evident on comparing the susceptibility constants calculated for phenylthiophen-2-ylmethanones with our previous data on 5-substituted 2-acetylthiophenes and 4-substituted acetophenones, considering in all series the same set of substituents (MeO, Me, H, Cl, Br and NO_2). Because of the competition of the thiophen-2-yl group the lowest susceptibility constant was calculated for the **1ah–eh**, **1hh** series ($\rho_X^+ = 0.98$), a larger susceptibility constant was calculated for 4-substituted acetophenones ($\rho^+ = 1.22$), while for 5-substituted 2-acetylthiophenes and for the **1ha–he**, **1hh** series the largest (similar) values were calculated ($\rho^+ = 2.12$ and $\rho_X^+ = 2.15$, respectively).



Experimental

Materials

Compounds **1**, **4** and **5** were prepared according to the general method previously reported[18] and the melting points agreed with those given in the literature.

pK_{BH^+} Measurements

The pK_{BH^+} and m^* values reported in Table 1 are, respectively, the intercept and slope, evaluated by least-squares treatment for the straight lines from eqn. (1).[9] Ionization values ($I = C_{BH^+}/C_B$) were determined at 298 ± 0.5 K in aqueous sulfuric acid by spectroscopic UV techniques whose essential features have been previously described.[1f] The UV absorption spectra of equimolar solutions of any base **1**, **4** and **5** at different sulfuric acid concentrations were also affected by medium effects, thus no isosbestic point was detected. Medium effects on absorption curves were corrected by means of the characteristic vector analysis (CVA) method.[12] The absorption curves were reproduced at 99% accuracy with only two vectors, the first, associated with the protonation process, accounting for about 95% of the total variability.

The C_{H^+} and X values used in eqn. (1) were calculated by interpolation of literature data.[10]

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