

Protonation equilibria of some *ortho*-substituted and annelated aryl and thiophen-2-yl and -3-yl ketones

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Renato Noto,^{*a} Francesca D'Anna,^a Michelangelo Gruttadauria,^a Paolo Lo Meo^a and Domenico Spinelli^b

^a Dipartimento di Chimica Organica "E. Paternò", Università di Palermo, Viale delle Scienze, Parco d'Orleans II, I-90128 Palermo, Italy

^b Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, Via S. Donato 15, I-40127 Bologna, Italy

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For some phenyl- (**1–8**) and thiophen-2-yl (**9–11**) and thiophen-3-yl (**12–14**) ketones quantum-mechanical (PM3) calculations have been performed, and for compounds **2**, **3**, **5–8**, **10–14** protonation equilibria have been determined. Phenyl ketones have similar values for the m^* parameter and show good linear correlation between the proton affinities calculated in the gas phase and the measured pK_{BH^+} values, which in turn parallel the trend for the calculated carbonyl–phenyl ring dihedral angle. It appears that the differences in basicity are governed essentially by "internal" factors (carbonyl–ring conjugation), while the base–conjugate acid differential solvation is not significantly affected by structural changes. In contrast thiophen-2-yl and -3-yl ketones show a complex behaviour, with strong variations in m^* values, and no linear correlation between proton affinities and pK_{BH^+} . Factors related to the solvent shell organization probably assume an important role here.

Introduction

The carbonyl moiety has been widely used as one of the most effective and common probes with which to investigate the transmission of substituent effects through conjugate systems and to evaluate their influence on chemical and physical properties. To investigate these properties chemical reactivities¹ and protonation equilibria,² as well as IR stretching frequencies³ or ¹³C and ¹⁷O NMR chemical shifts⁴ have been studied. In particular we have extensively studied the protonation equilibria of aromatic and heteroaromatic carbonyl derivatives Ar–COY (aldehydes, ketones, carboxylic acids, amides, *etc.*),⁵ so that the characteristics of the interactions between substituent, conjugated bridge, probe and Y group can be considered at present to be quite well understood.

In the last few years we have focussed our interest on the transmission of substituent effects by studying alkyl aryl and alkyl thienyl ketones^{4f,6} as well as aryl thienyl⁷ or diaryl and dithienyl ketones.⁸ The above studies have been carried out using spectroscopic techniques (¹³C and ¹⁷O NMR) and protonation equilibria studies both in solution and in the gas phase. In particular we have found that the basicity of aromatic ketones, similarly to those of other weak organic bases, are strongly affected by two kinds of factors: internal (electronic effects) and external (solvation effects). Recently, we also investigated the effect of steric crowding around the carbonyl moiety by measuring the basicity of several alkyl 2,6-dialkylphenyl ketones⁹ with alkyl groups with different steric characteristics: the results obtained suggested that steric inhibition of solvation was the common prevailing factor affecting the carbonyl basicity at least in the absence of strong conjugative interactions.

With the aim of gaining further knowledge of the interplay of the effects involved in determining the basicity of the carbonyl group, we report here data relevant to the protonation equilibria for phenyl, thiophen-2-yl and 3-yl ketones **1–14** (Fig. 1). We have chosen these compounds in such a way that in the presence of similar electronic characteristics, different

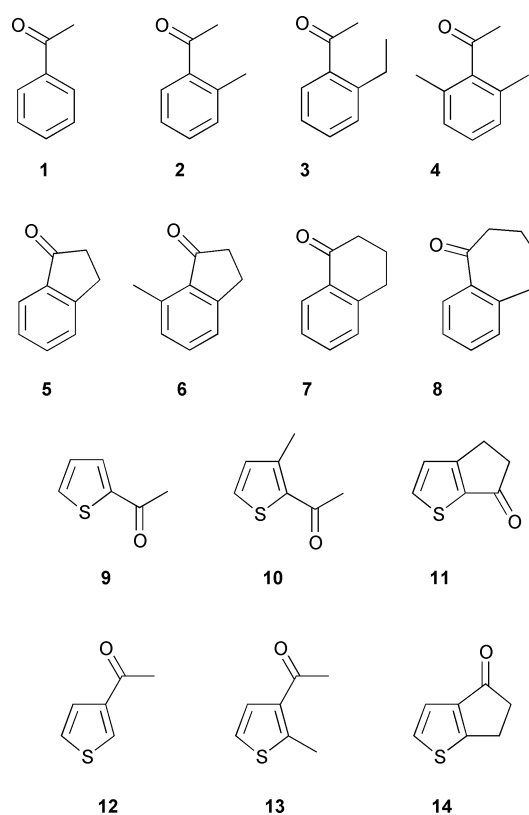


Fig. 1 Ketones 1–14.

conjugation between the carbonyl moiety and the aryl or the hetaryl ring occurs because of their steric nature: as a matter of fact the extent of conjugation largely depends on the dihedral angle between the carbonyl group and the aromatic system, as pointed out for other compounds by several authors.^{4g,h}

Compounds **1–14** are weak organic bases which are protonated only in concentrated solutions of strong acids. The

Table 1 Basicity parameters for ketones 1–14 in aqueous sulfuric acid mixtures

	$-pK_{\text{BH}^+}$	m^*		$-pK_{\text{BH}^+}$	m^*
1 ^a	4.08	0.65	8	3.97 ± 0.03	0.61 ± 0.02
2 ^b	4.10 ± 0.06	0.64 ± 0.02	9 ^d	4.20	0.92
3	4.13 ± 0.02	0.63 ± 0.02	10	3.01 ± 0.03	0.69 ± 0.02
4 ^a	4.85	0.62	11	2.54 ± 0.03	0.51 ± 0.02
5	3.65 ± 0.07	0.58 ± 0.02	12	3.52 ± 0.04	0.57 ± 0.02
6	3.23 ± 0.07	0.59 ± 0.02	13	2.77 ± 0.03	0.51 ± 0.02
7 ^c	3.72 ± 0.07	0.64 ± 0.02	14	2.33 ± 0.05	0.36 ± 0.02

^a See ref. 13. ^b Lit.,¹⁰ 6.13. ^c Lit.,¹¹ 6.09. ^d See ref. 6.

protonation equilibria of 2¹⁰ and 7¹¹ have already been studied by other authors using different methods to calculate pK_{BH^+} values so that they do not allow significant comparison. In this work the protonation equilibria of these ketones and of compounds 3, 5, 6, 8, 10–14 have been studied in aqueous sulfuric acid at 298 K. Ionization values ($I = C_{\text{BH}^+}/C_{\text{B}}$) have been determined spectrophotometrically and used to calculate the pK_{BH^+} values using eqn. (1) (excess acidity method)¹²

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

whose slope (m^*) usually gives information about the nature of the base involved (*i.e.*, its value depends on the site of protonation) as well as about the degree of solvation of the acid–base pair.^{4f,12,13}

In order to gain further and independent information about the degree of conjugation some semiempirical (PM3)¹⁴ quantum-mechanical calculations have been carried out: thus the energies of the optimized species, the values of the dihedral angle between the carbonyl group and the phenyl (or thienyl) ring have been calculated and the proton affinities in the gas phase (P.A.) have been determined by eqn. (2)

$$\text{P.A.} = \Delta H_{\text{B}}^{\text{f}} - \Delta H_{\text{BH}^+}^{\text{f}} + 1537.1 \text{ kJ mol}^{-1} \quad (2)$$

where 1537.1 kJ mol⁻¹ is the literature value¹⁵ suggested for the heat of formation of H⁺ in the gas phase.

Results and discussion

Data on the protonation equilibria and results of semiempirical (PM3) quantum-mechanical calculations of ketones 1–14 are collected in Tables 1 and 2, respectively.

Behaviour of aryl ketones 1–8

Notwithstanding the important variations in their chemical structures aryl ketones 1–8 have similar m^* values (0.62 ± 0.02). Bearing in mind that the m^* value is a parameter that depends on the site of protonation (in the cases examined the ketonic oxygen) and on the degree of relative solvation of the acid–base pair involved, similar m^* values indicate that there are similar variations in the solute–solvent interactions in all the phenyl compounds studied on going from the base to its conjugated acid. However, if one reasonably supposes that ketones are similarly solvated then the m^* values indicate a similar extent of solvation of protonated ketones.^{13,16}

In contrast the pK_{BH^+} values for 1–8 indicate that they are sensitive to structural variations. In fact, there is a difference of 1.6 pK units on going from the most basic ketone (6) to the least basic one (4). Considering acetophenone 1 as the reference compound, the introduction of an *ortho*-methyl (2) or -ethyl (3) group does not cause a significant variation in pK_{BH^+} , thus indicating that the electron-releasing substituent effect (base-strengthening) and the opposing steric inhibition of conjugation (base-weakening) caused by the *ortho*-alkyl groups are

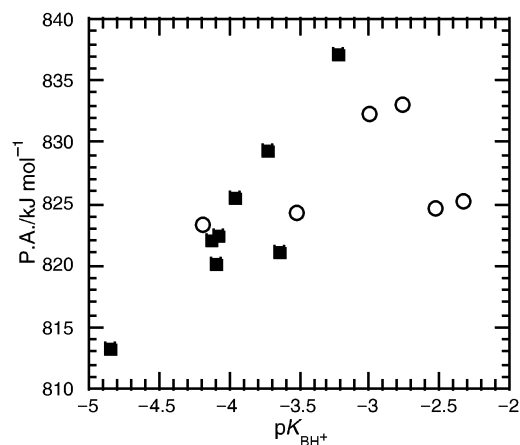


Fig. 2 P.A. vs. pK_{BH^+} plot for phenyl ketones 1–8 (■) and thienyl ketones 9–14 (○). Linear correlation for ketones 1–8 gives: P.A. = $(877 \pm 11) + (13 \pm 3) pK_{\text{BH}^+}$ ($n = 8$, $r = 0.886$); excluding the datum for 5: P.A. = $(885 \pm 6) + (15 \pm 1) pK_{\text{BH}^+}$ ($n = 7$, $r = 0.979$).

similar thus cancelling each other out. In contrast the introduction of a second *ortho*-methyl group (as in 4) causes a significant decrease of the basicity because of the dramatic out-of-the-plane rotation of the carbonyl group with respect to the aromatic ring which prevents the resonance stabilization of the protonated species.¹⁷

Data obtained from semiempirical calculations on the stability and geometry of the ketones studied and their conjugated acids seem a helpful instrument for understanding our data. If we look at compounds 2, 3, 5, 7 and 8 we have a clear indication of the importance of conjugation in determining the pK_{BH^+} values. Moreover, of the annelated ketones (5, 7 and 8) 5, in which the phenyl group is annelated to a five-membered ring, is the most basic compound probably because the carbonyl group is forced to be coplanar with the phenyl ring. The basicity decreases on annelation to six- and seven-membered rings or with unannelated ketones 2 and 3 because of the increase in dihedral angle values (see Table 2). Concerning annelated ketones the situation parallels the trend in pK_{BH^+} values observed for non-annelated 5-, 6- and 7-membered cycloalkanes.† So it is reasonable to suppose that the differences in basicity between 5, 7 and 8 depend essentially on geometric factors as pointed out for cycloalkanes.¹⁸

The difference in the pK_{BH^+} values of ketones 5 and 6 reflects the electronic effect (base-strengthening) of an *ortho*-methyl group: a similar effect was observed with the introduction of a *para*-methyl group into acetophenone.^{5a} Once again the difference in basicity ($\Delta pK_{\text{BH}^+} = 1.62$) between ketones 4 and 6 mirrors the importance of conjugation in determining the extent of protonation.

As compounds 1–8 show similar variations in solvation on going from the base to the protonated form (*i.e.*, similar m^* values, see above), there is a satisfactory correlation (Fig. 2) between proton affinities and calculated pK_{BH^+} values. Surprisingly the point corresponding to ketone 5 deviates from the straight line, therefore the correlation is very much improved by excluding this point.

Behaviour of thienyl ketones 9–14

The protonation equilibria of ketones 9–14 show quite different behaviour compared with aryl ketones: *e.g.*, significant variations in both m^* and pK_{BH^+} values have been observed.

We have already compared the protonation data of 9 with those of 1,⁶ pointing out that the larger value of m^* for 9 than

† The pK_{BH^+} values of cyclopentanone, cyclohexanone and cycloheptanone are -2.59 , -2.76 and -2.85 , respectively.¹⁸ A roughly uniform decrease in basicity ($\Delta pK_{\text{BH}^+} = 1.04 \pm 0.04$), depending on the electronic effect of the benzo annelated ring, has been observed.

Table 2 Calculated (PM3) heats of formation, dihedral angles between the carbonyl group and aromatic moiety, and proton affinities for ketones **1**–**14**

	$\Delta H_{\text{B}}^{\text{f}}/\text{kJ mol}^{-1}$	Dihedral CO–Ar angle ^{a/p}		$\Delta H_{\text{BH}^+}^{\text{f}}/\text{kJ mol}^{-1}$	Dihedral CO–Ar angle ^{a/p}	Proton affinity/ kJ mol ⁻¹
1	-77.65	29	1·H⁺	637.07	0	822.38
2	-113.65	72	2·H⁺	603.37	0	820.08
3	-135.08	85	3·H⁺	579.93	32	822.09
4	-145.21	90	4·H⁺	578.55	38	813.34
5	-75.43	0	5·H⁺	640.63	0	821.04
6	-107.92	0	6·H⁺	592.03	0	837.16
7	-102.18	7	7·H⁺	605.63	1	829.29
8	-110.30	63	8·H⁺	601.28	4	825.52
9	-37.46	167	9·H⁺	676.29	180	823.34
10	-76.02	66	10·H⁺	628.74	179	832.34
11	-20.47	0	11·H⁺	691.82	0	824.81
12	-46.55	180	12·H⁺	665.74	180	824.39
13	-78.36	119	13·H⁺	625.68	180	833.06
14	-19.72	180	14·H⁺	692.91	180	825.23

^a For thienyl ketones **9**–**14** the values 0 and 180° refer to conformers *s-trans* and *s-cis* respectively.

for **1** (0.92 and 0.65, respectively) and the similar values of pK_{BH^+} for the two ketones (4.20 and 4.08, respectively) could be related to the extensive conjugative nature of heteroaromatic derivatives, a factor that balances the high electron-withdrawing effect of the thiophene ring.

Ketone **12** is more basic than the isomer **9** according to the lower electron-withdrawing effect of the thiophen-3-yl group with respect to thiophen-2-yl. Moreover, because in the thiophene ring a group, acetyl in this case, conjugates less efficiently at the 3-position than at the 2-position, a greater variation in solvation of the conjugated acid–base pair has been observed (m^* values, 0.57 and 0.92, respectively).

The introduction of a methyl group in the *ortho*-like position of both **9** and **12** causes an increase in basicity at variance with what is observed on going from **1** to **2**, where the pK_{BH^+} values remained constant. Once again the more favourable steric disposition associated with 5-membered rings allows the alkyl groups to exert their electronic effects (base-strengthening). For the thiophen-2-yl derivative on going from **9** to **10** a clear increase in solvation has also been observed.

Interestingly a similar increase in basicity can be monitored by comparing the pK_{BH^+} values of methylthienyl ketones with the corresponding 5-membered annelated ketones (e.g., **10** with **11** or **13** with **14**), thus confirming the increased basicity observed in phenyl ketones (i.e., on going from **2** to **5**): in all three cases the same ΔpK_{BH^+} values have been calculated (0.45 ± 0.01). It has also been evidenced that in the thiophene series annelation causes variations in solvation too, as testified by the significant variations observed in m^* values.

Unlike the phenyl derivatives, thienyl ketones did not give any correlation between pK_{BH^+} values and calculated proton affinities, indicating that the differential solvation of the involved species changes significantly along the two series of ketones and that entropic contributions can be related to the different organisation of the solvent shell around the species thus affecting the acid–base properties.

In the thiophene series the position of the carbonyl group and its distance from the ring sulfur atom as a function of the carbonyl–ring dihedral angle probably play an important role in determining some aspects of substrate solvation. For example, simulations show that the hydrogen bond between the carbonyl group and the water molecule is weaker by about 4 kJ mol⁻¹ when the approach is from the site of the sulfur atom (“wrong” side). In this case the carbonyl and the water molecule define an angle of 140°, significantly greater than the ideal value of 120°; in contrast, the approach from the “right” side gives an angle of 115°.

In conclusion we can say that the proximity of the carbonyl group to the sulfur atom strongly affects the effective solvation of the species. We would also expect that this effect should be more important in the solvation of the ketone rather than of its protonated counterpart because in the latter case the structural effects upon the solvent molecules exerted by the positively charged C=OH⁺ group should largely overwhelm the effect of the sulfur atom. In other words we can explain the variations in m^* as a specific effect on solvation which is weak in **9** (nearly free internal rotation) and strong in **11** (forbidden internal rotation).

Experimental

Materials

Compounds **2**, **5**, **7**, **8** and **12** were commercial products purified by the usual techniques. Compounds **3**,¹⁹ **6**,²⁰ **10**,²¹ **11**,²² **13**²³ and **14**²⁴ were prepared according to literature procedures.

pK_{BH^+} measurements

The pK_{BH^+} and m^* values reported in Table 1 are the intercepts and slopes (obtained by least-squares treatment) of the straight lines derived from eqn. (1), respectively. Ionization ratios ($I = C_{\text{BH}^+}/C_{\text{B}}$) were determined at 298.1 ± 0.5 K in aqueous sulfuric acid by spectroscopic UV techniques, whose features have been previously described.⁷ Because absorption spectra are affected by medium effects (isosbestic points have not been observed), corrections were made by means of the CVA (Characteristic Vector Analysis) method.²⁵ The absorption curves were reproduced to 99% accuracy with only two vectors, the first (accounting for 93–95% of the total variability) associated with the protonation process. The C_{H^+} and X values used in eqn. (1) were calculated by interpolation from literature data.¹²

PM3 calculations

Semiempirical calculations, as full geometry optimizations, were performed at the PM3 level of theory by means of the MOPAC93 program available in the CS Chem3D Pro™ package (version 3.5) for Macintosh, distributed by Cambridge Soft Corporation.

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