Enol Content of α-Pyridyl- and Pyridinio-acetophenones
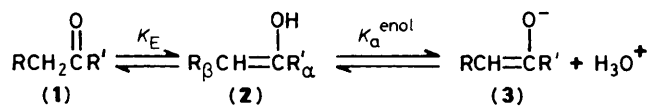
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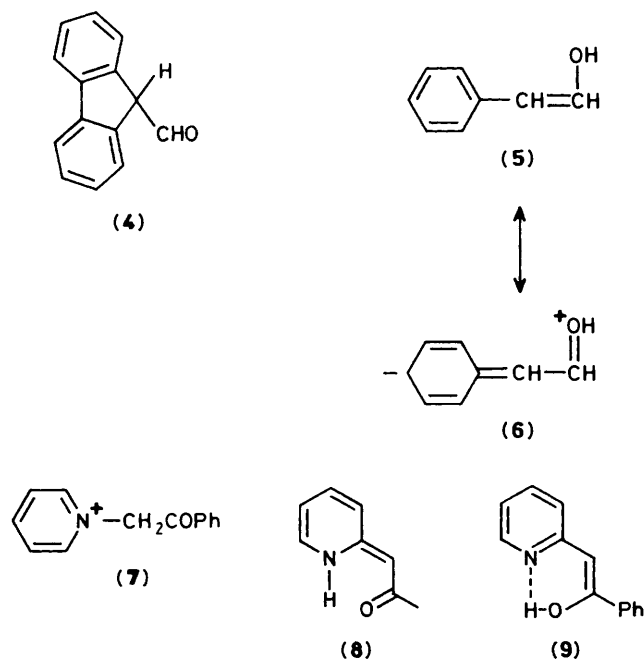
A comparison of the effects of phenyl, pyridyl, and pyridinio substituents upon keto–enol tautomerisation and enol ionisation equilibria of acetophenone shows that polar effects upon bond hybridisation and resonance interaction with 'neutral' double bonds are important influences upon enol stability.

In the past five years the availablity of measurements of keto–enol tautomerisation constants of a number of simple aldehydes and ketones, including acetaldehyde, acetone, and acetophenone,[1—4] has made possible an examination of substituent effects upon these equilibria.[1,5,6] Steric effects have been discussed in detail by Rappoport,[5,6] and the purpose of this communication is to consider electronic effects. These are interesting because keto–enol equilibria involve only neutral molecules whereas electronic effects normally reflect resonance or inductive stabilisation of ionic charges.

Enols can be substituted at α- or β-carbon atoms [see (2)]. At either position the main effect of the substituent is upon the double bond of the enol. At the α-position however the effect is complicated by a compensating interaction with the carbonyl group of the keto tautomer,[1,6] and for aryl and alkyl groups this leads to opposite effects of substituents upon the equilibrium at the the two positions. Thus the enol content of acetaldehyde ($pK_E = 6.23$ in aqueous solution)[4] is greater than that of acetophenone ($pK_E = 7.96$) but much less than that of diphenylacetaldehyde[7] ($pK_E = 0.98$) or 9-formyl-fluorene[8] (4) ($pK_E = -1.7$).

The effect of β-aryl substituents is remarkable in that the double bond of the enol appears to be stabilised by more than would be expected of an ionic charge. Thus the β-fluorenyl group increases the enol content of acetaldehyde by much more (10^8 as compared with 10^3) than it does the ionisation of the enol to its enolate anion [(2) ⇌ (3)]; similar behaviour has been noted by Kresge for diphenylacetaldehyde.[7]

Here we compare effects of strongly electron-withdrawing β-aryl groups, exemplified by pyridyl and pyridinio groups, upon keto–enol and enol ionisation equilibria. Intuitively, electron withdrawal should stabilise both enol and enolate ion by resonance [(5) ⟷ (6)] and disfavour the keto tautomer inductively. Consistently, ρ for the enolisation of arylacet-aldehydes in Me_2SO is positive (0.76) and σ^- is required to correlate the p-nitro group:[9] larger effects would be expected for ionisation of the enols.
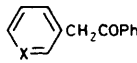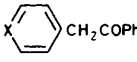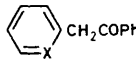
The effects of phenyl and 1-pyridinio (7) substituents at the methyl carbon atom of acetophenone are compared in Table 1, and those of 2-, 3-, and 4-pyridyl and pyridinio substituents (both NH^+ and NMe^+) in Table 2: the effect of a fluorenyl group is also shown. Tautomeric constants (K_E) in aqueous solution come from combining rate constants for enolisation and ketonisation which were determined respectively by halogen trapping and relaxation of the enol generated by quenching the enolate anion ($pK_a{}^{keto} < 14$) in acid. For (2-pyridyl)acetophenone, for which the enamine tautomer (8) is more stable than the enol (9),[10] spectrophotometric measurements in non-polar solvents, in which the enol *is* stable, were extrapolated to water. For the 2-, 3-, and 4-pyridinio systems measurement of pK_as for C- and O-protonation of N-methyl and N-H enaminones [e.g. (8)] were combined as $K_E = K_a{}^O/K_a{}^C$, with $K_a{}^O$ for O-protonation

$$\underset{(1)}{RCH_2CR'} \overset{O}{\overset{\|}{}} \overset{K_E}{\rightleftharpoons} \underset{(2)}{R_\beta CH{=}CR'_\alpha} \overset{OH}{\overset{|}{}} \overset{K_a{}^{enol}}{\rightleftharpoons} \underset{(3)}{RCH{=}CR'} \overset{O^-}{\overset{|}{}} + H_3O^+$$

$$K_E = [(2)]/[(1)] \quad pK_E = -\log K_E$$

(4)

(5)

(6)

(7)

(8)   (9)

Table 1. Keto–enol equilibrium constants (pK_E) and enol acidities ($pK_a{}^{enol}$) of phenyl- and 1-pyridinio-acetophenones.

	pK_E	$pK_a{}^{enol}$	$\Delta pK_E{}^a$	$\Delta pK_a{}^{enol}{}^a$
MeCOPh	7.96	10.35		
PhCH$_2$COPh	5.15[b]	11.0[c]	2.81	−0.7
Me$_2$N⟨⟩$\overset{+}{N}$CH$_2$COPh	5.56	7.65	2.40	2.70
⟨⟩$\overset{+}{N}$CH$_2$COPh	6.12	4.8	1.84	5.55
FlCHCOPh[d]	1.91	7.53	6.05	2.82

[a] Difference from value for acetophenone. [b] A. J. Kresge, manuscript in preparation. [c] Based on pK_E and a value of $pK_a = 16.1$ for the ketene extrapolated from measurements in non-aqueous solvents.[13] [d] M. Harcourt and R. A. More O'Ferrall, unpublished results (FlCH$_2$ denotes fluorene).

Table 2. Keto–enol equilibrium constants and enol acidities of 2-, 3-, and 4-pyridyl- and pyridinio-acetophenones.

	pK_E			pK_a^{enol}		
	X = NMe+	NH+	N	NMe+	NH+	N
(2-pyridyl) CH₂COPh	4.23	3.89	4.82	6.75	6.41	8.83
(3-pyridyl) CH₂COPh		2.86	(4.2)[a]		4.19	(8.5)[a]
(4-pyridyl) CH₂COPh	2.4	3.35	2.0	3.5	2.60	11.27

[a] Estimated from assignment of $pK_a = 6.4$ for N-protonation of the enol, based on $pK_a = 6.0$ for the enol of 3-pyridylacetophenone and assuming the ratio of 3- and 4-enol substituent effects to be the same as that for the 3- and 4-enolate anions.

determined kinetically, *e.g.* from a pH–rate profile for the thermodynamically favoured C-protonation (K_a^C).[11]

From Table 1 it can be seen that, unexpectedly, the stabilising effect of a 1-pyridinio group on the enol is *smaller* than that of a phenyl group [$pK_E = 6.12$ for (7) as compared with 5.15 for phenylacetophenone] while that of the 4-dimethylaminopyridinio group ($pK_E = 5.56$) falls between the two. By contrast 2-, 3-, and 4-pyridyl and pyridinio substituents are more stabilising ($pK_E = 3.4$—4.3) than the phenyl group. [The enol of (2-pyridyl)acetophenone is unusually stable, presumably because of hydrogen bonding; see (9).]

The low enol content of (1-pyridinio)acetophenone seems best explained by an unfavourable effect of this highly electronegative substituent upon the increase in s character of the bond to the substituent between keto (sp³) and enol (sp²) tautomers. Apparently this effect is dominant when N⁺ is directly bound to the double bond, but for more remote substitution (N⁺ or N) it is more than compensated by resonance.

In contrast to their rather small effects upon enol stability, the nitrogen atoms of the pyridyl and pyridinio substituents significantly increase ionisation of enols to their enolate ions. This behaviour is expected, but again differs from that of β-aryl substituents *per se* and, in this respect, underlines the importance of the latter in stabilising non-polar carbon–carbon double bonds by resonance. This importance is perhaps underemphasised in simple valence bond treatments which stress that resonance stabilisation is greater for ions and radicals than for neutral molecules because in the latter resonance entails an unfavourable separation of charge or radical centres.[12]

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