Proton activating factors and keto–enol-zwitterion tautomerism of 2-, 3- and 4-phenylacetylpyridines

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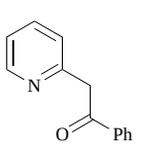
Equilibrium constants for keto–enol tautomerism of 2-, 3- and 4-phenylacetylpyridines in aqueous solution at 25 °C have been measured as pK_T^E = 3.35, 4.2 and 3.1 respectively (K_T^E = [enol]/[ketone], $pK_T^E = -\log K_T^E$). Corresponding values for the *N*-protonated ketones are 1.64, 2.80 and 1.54. These enol contents are consistently higher than those of the isomeric phenacylpyridines, except in the case of the (unprotonated) 2-isomer where the greater enol content of the latter (pK_T^E = 2.0) can be attributed to more effective stabilization by hydrogen-bonding to the pyridyl nitrogen in a six- than five-membered ring. The tautomeric constants were obtained by combining rate constants for enolisation, measured by halogen trapping, with rate constants for relaxation of the enol tautomer (generated by quenching the enolate anion into acid or acidic buffers) to its more stable keto isomer. Approximate tautomeric constants for zwitterion formation (pK_T^Z = 4.6, 7.4 and 6.1 for 2-, 3- and 4-isomers respectively) are inferred from measurements of ionisation constants and keto–enol tautomeric constants for *N*-methylated ketones by taking the *N*-methylated enolate anions as models for the zwitterions and correcting for the substituent effect of the methyl group. The tautomerism is discussed in terms of the relationship $pK_T = \Delta pK_{ab}$ + log PAF which dissects tautomeric constants into contributions from (*a*) a difference in pK_as of non-interacting acidic and basic tautomeric sites (ΔpK_{ab}) and (*b*) a mutual stabilisation of these sites from conjugative, inductive or hydrogen-bonded interactions between them. This stabilisation is described by a proton activating factor (PAF) measuring the effect of protonation at one tautomeric site upon the ionisation constant at the other.

There have been many investigations of the tautomerism of aldehydes and ketones in the past fifteen years,[1–8] including a number of studies of α-heterocyclic ketones.[3–6] Less attention has been given to ketones in which a heterocyclic substituent is bound directly to the carbonyl group,[7,8] however, and, as examples of these, in this paper we report measurements of keto–enol tautomeric constants for 2-, 3- and 4-phenylacetylpyridines ($PhCH_2COPy$). The results are of interest for comparison with previous measurements for the isomeric phenacylpyridines ($PhCOCH_2Py$)[3,4] and as a preliminary to studies of the more complex tautomerism of pyridacyl pyridines ($PyCOCH_2Py$).[9]

Unlike simple ketones *N*-heterocyclic ketones can tautomerise through migration of hydrogen from a carbon to a nitrogen atom as well as from carbon to oxygen. Shown below are all three tautomers of 2-phenacylpyridine (**1**–**3**) and 2-phenylacetylpyridine (**4**–**6**) together with the *N*-protonated tautomers (only) of the corresponding 3- and 4-phenacyl- and phenylacetyl-pyridines (**7**–**10**). For the 2- and 4-phenacylpyridines the



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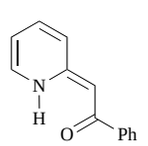

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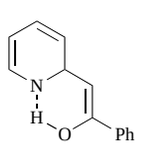

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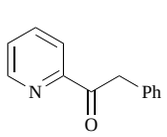

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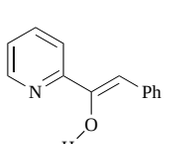

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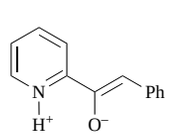

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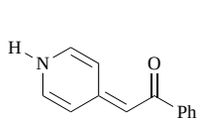
N-protonated tautomers are enaminones (**2** and **7**) and for the 3-phenacylpyridine (**8**) and the phenylacetylpyridines (**6**, **9**, **10**) they are zwitterions.[3] The distinction between these structures rests on the presence or absence of direct resonance, leading to charge neutralisation, between the ionic centres created by the proton shift. This resonance is strongly stabilising for the 2- and 4-phenacylpyridines, and these enaminones are more stable than their respective enols, whereas for 3-phenacylpyridine and the phenylacetylpyridines the enols are more stable than the zwitterions. Resonance and, indeed, electrostatic or inductive interactions between their charge centres are an important influence upon the stabilisation of the tautomers, and in this paper we describe the use of 'proton activating factors' to measure this stabilisation.[10]



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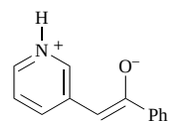

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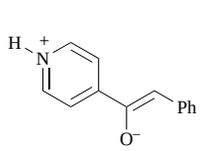

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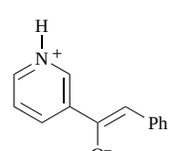

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A further influence on the stabilities of enol and enaminone tautomers is hydrogen-bonding. The hydrogen-bonded enol of 2-phenacylpyridine (**3**) amounts to 1% of an equilibrium mixture of tautomers in aqueous solution at 25 °C compared with less than one part in 10^4 for 4-phenacylpyridine. A point of interest in comparing phenacyl- and phenylacetyl-pyridines therefore is to determine whether the enol of 2-phenylacetylpyridine (**5**), in which the hydrogen bond occurs in a five- rather

than a six-membered ring, is comparably stabilised. It is assumed that in these structures (and **3**) the hydrogen-bonding maintains the configuration of the exocyclic double bond in a *Z*-configuration.[11] Further consideration of *E*–*Z* isomerism of enol or enaminone tautomers is postponed to a later paper.

The 3- and 4-phenylacetylpyridines were studied previously by Bunting and Stefanidis,[12–14] who measured rate and equilibrium constants for ionisation of the ketones to their enolate anions. The ketones are quite acidic (pK_as 13.1 and 12.3 respectively) and are appreciably ionised in dilute aqueous sodium hydroxide. This suggested to us that the enol tautomers might be generated by quenching solutions of their enolate ions in excess acid or acidic buffer. Tautomeric constants could then be measured by combining rate constants for relaxation of the enol to their stable keto tautomers with the corresponding value for enolisation of the ketone, measured in the usual way by trapping the enol as it is formed from the ketone with iodine or bromine.[6] This indeed was the starting point for the present investigation.

Results

2-Phenylacetylpyridine

This compound (**4**) was not studied by Bunting and Stefanidis[12] and so was investigated in more detail than its isomers. Spectrophotometric measurements of ionisation constants in acidic and basic media gave pK_a = 2.30 ± 0.09 and pK_a = 12.02 ± 0.09 for *N*-protonation of the ketone and *C*-protonation of its enolate anion respectively. Stopped flow measurements of rates of enolate ion formation in the range 0.01–0.12 M hydroxide ion gave pK_a = 11.9 from the ratio of slope to intercept of a plot of first-order rate constants against base concentration, in good agreement with the directly measured value. Rate constants for ketonisation were measured by quenching a basic solution of the enolate anion into HCl or acidic buffers and monitoring relaxation of the initially formed enol (**5**) to the thermodynamically more stable keto tautomer by stopped-flow spectrophotometry.

The measured first-order rate constants for tautomerisation in buffer solutions (k_{obs}) reflect contributions from second order rate constants for general acid and/or general base catalysis (k_{GA} and k_{GB}) by acidic (AH) and basic (A^-) components of a buffer and a first-order buffer independent rate constant (k_o) for reaction with H_2O, H^+ or OH^- as shown in eqn. (1).[9] Values of k_{GA} and k_{GB} were obtained from slopes (k) of

$$k_{obs} = k_o + k_{GA}[AH] + k_{GB}[A^-] \quad (1)$$

plots of k_{obs} against the concentration of the base component of the buffer at different (constant) buffer ratios (R = [AH]/[A^-]) which, as shown in eqn. (2), have k_o as intercept. Plotting

$$k_{obs} = k_o + k[A^-] \quad (2)$$

values of k against the buffer ratio then gave k_{GA} and k_{GB} as a further slope and intercept (eqn. 3) based on measurements at three or four buffer ratios.

$$k = k_{GB} + Rk_{GA} \quad (3)$$

Rate constants for the reverse enolisation reaction were measured from reaction of the ketone with bromine and iodine.[6,15] These may also be expressed as in eqn. (1) and separated into values of k_o, k_{GA} and k_{GB} using eqns. (2) and (3). Occasionally, for either ketonisation or enolisation, equations had to be modified to take account of partial protonation of the reactant or reversibility of the tautomerisation reaction.[3,6]

Values of k, k_o, k_{GA} and k_{GB} for ketonisation and halogenation of 2-phenylacetylpyridines in lutidine (2,6-dimethylpyridine) and acetic acid buffers are listed in Table 1 and Table 2

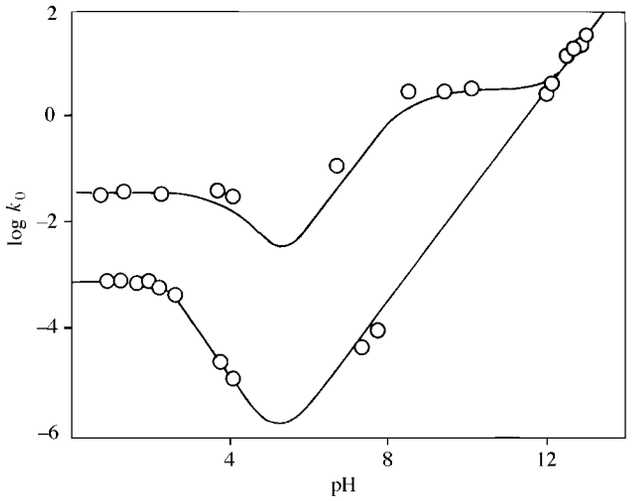


Fig. 1 Log k–pH profile for enolisation of 2-phenylacetylpyridine (lower line) and ketonisation of its enol (upper line)

respectively. Values of k_o from measurements in solutions of sodium hydroxide or hydrochloric acid are given in Table 3. Measurements for borate buffers, which showed practically no buffer catalysis at low buffer concentrations, are also included in Table 3.

The equilibrium constant for keto–enol tautomerism K_T may be obtained from a ratio of rate constants for enolisation and ketonisation of **4** measured under the same conditions at a pH where both enol and ketone (rather than their conjugate acids or bases) are reactants. The most complete set of such measurements relates to lutidine and acetate buffers. For the lutidine buffers, in which catalysis by buffer base only is observed, K_T may be evaluated from eqn. (4) in which the superscripts E and

$$K_T = k_{GB}^{E}/k_{GB}^{K} \quad (4)$$

K refer to enolisation and ketonisation respectively. Substituting values of k_{GB}^{E} and k_{GB}^{K} from Tables 1 and 2 gives $K_T = 5.3 \times 10^{-4}$. This compares with $K_T = 4.0 \times 10^{-4}$ based on k_{GA}^{E} and k_{GB}^{K} for acetate buffers. Taking the average of these values gives $K_T = 4.7 \times 10^{-4}$ and pK_T = 3.33.

Strictly speaking k_{GB}^{K} in the denominator of eqn. (4) should be corrected for a contribution from the rate constant for enolisation, since k_{GB}^{K} is measured for an equilibrium relaxation and represents a sum of rate constants for ketonisation and enolisation. In practice k_{GB}^{E} is too small for this correction to be required. However, a further correction arises because K_T is really an 'effective' equilibrium constant reflecting the combined formation of enol (EH) and zwitterion (ZH) tautomers from the ketone (KH). This means that K_T = ([EH] + [ZH])/[KH] = $K_T^E + K_T^Z$, where K_T^E = [EH]/[KH] and K_T^Z = [ZH]/[KH] are the tautomeric constants for formation of enol and zwitterion alone. Evaluation of K_T^Z, which allows correction of K_T to K_T^E is described below.

The buffer independent rate constants for both enolisation and ketonisation are conveniently displayed as pH-profiles by plotting log k_o against pH as in Fig. 1. In this Figure, the lower plot represents enolisation and the upper plot (the faster) ketonisation. Both reactions show acid- and base-catalysed pathways at low and high pHs respectively. At a sufficiently low pH the acid catalysis becomes saturated, as expected of *N*-protonation of ketone and enol reactants. For enolisation the inflection in the pH-profile is consistent with the measured pK_a for *N*-protonation of the ketone. At high pH base-catalysis of ketonisation is also saturated, reflecting ionisation of the enol to its enolate anion. The two profiles intersect at the pK_a for the basic ionisation of the keto tautomer (pH = 12.0).

The limiting pH-independent rate constants in acidic solutions from the two pH-profiles represent enolisation ($k_{H_2O}^{E}$) and

Table 1 Slopes and intercepts of buffer plots and rate constants for general acid- and general base-catalysis for relaxation (ketonisation) of the enols of 2-, 3- and 4-phenylacetylpyridines and the *N*-methyl-2-phenylacetylpyridinium ion in aqueous solution at 25 °C and ionic strength 0.1 M

Substrate/buffer	pH	R[a]	k_o/s^{-1}	k[b]/dm^3 mol^{-1} s^{-1}	k_{GB}/dm^3 mol^{-1} s^{-1}	k_{GA}/dm^3 mol^{-1} s^{-1}
2-Phenylacetylpyridine						
Acetate	3.58	12	0.038	9.4	5.0[c]	4.5[c]
	4.04	4.2	0.030	9.0		
	4.54	1.3	—	6.8		
	5.18	0.33	—	5.8		
Lutidine	6.66	1	0.12	19.1	18.8	
	7.27	0.25	—	18.6		
N-Methyl-2-phenylacetylpyridinium ion						
Acetate	4.60	1	—	7.32	7.8	
	5.08	0.33	0.05	7.13		
	5.51	0.125	—	5.74		
Lutidine	6.37	3	0.016	7.10	9.96	
	6.85	1	—	4.03		
	7.33	0.33	—	3.45		
N-Ethylmorpholine[c]	7.83	1	0.005	1.77	14.0[d]	
Borate[c]	9.07	1	0.022	4.32	34.3[d]	
3-Phenylacetylpyridine						
Acetate	3.92	4.6	—	18.8	13.0[c]	2.44[c]
	4.41	1.5	—	15.5		
	4.85	0.59	—	13.8		
	5.26	0.22	(0.07)	13.4		
Lutidine	6.50	1.5	—	184		
	6.85	0.66	1.0	176		
	7.18	0.25	6.0	186	182	
4-Phenylacetylpyridine						
Cyanoacetate	1.87	2.5	0.0090	0.068		4.34
	2.36	0.83	0.0074	0.068		
	2.70	0.40	0.0076	0.071		
Glycolate	2.97	4.9	0.0065	0.062	0.63[c]	1.56[c]
	3.43	1.7	—	0.060		
	3.82	0.77	—	0.60		
Acetate	3.93	4.6	—	4.0	3.65[c]	1.17[c]
	4.41	1.5	—	4.0		
	4.84	0.56	—	3.75		
	5.27	0.22	—	4.0		
Lutidine	6.50	1.50	—	55.1	49.0	
	6.85	0.67	—	49.8		
	7.17	0.25	—	50.8		

[a] Ratio of buffer acid to buffer base concentration. [b] Slope of plot of measured first order rate constants against concentration of buffer base. [c] Separation of k_{GA} and k_{GB} required correction for partial protonation of enol reactant using eqns. (12)–(14) and assumes that k_{GA}/k_{GB} is the same as in Table 2. [d] Rate constant for reaction of enol with base: the reverse of the measured reaction of ketone with base represented by k in preceding column.

ketonisation ($k_{H_2O}^K$) of the *N*-protonated keto and enol tautomers (KH_2^+ and EH_2^+ respectively). The ratio of these values $k_{H_2O}^E/k_{H_2O}^K$ thus corresponds to the keto–enol tautomeric constant $K_T^E = [EH_2^+]/[KH_2^+]$ for the *N*-protonated ketone. Rate measurements for solutions of HCl (<pH 2) yield $k_{H_2O}^E = 7.4 \times 10^{-4}$ s^{-1} and $k_{H_2O}^K = 3.2 \times 10^{-2}$ s^{-1}, from which $K_T^E = 0.023$ and $pK_T^E = 1.64$. For economy of notation the symbol K_T^E is used for both neutral and protonated ketones.

The lines through the experimental points for ketonisation in Fig. 1 are based on eqn. (5), in which the rate constants k_H^K and

$$k_o^K = \frac{k_H^K[H^+]}{(1 + [H^+]/K_a^{EH_2^+})} + \frac{k_{OH}^K[OH^-]}{(1 + K_a^{EH}/[H^+])} \qquad (5)$$

k_{OH}^K refer to the acid and base-catalysed reactions respectively (again the superscript K refers to the ketonisation reaction), and K_a^{EH} (= $[E^-][H^+]/[EH]$, where E^- denotes the enolate anion) and $K_a^{EH_2^+}$ (= $[EH][H^+]/[EH_2^+]$, where EH_2^+ is the *N*-protonated enol) are ionisation constants for the enol and its conjugate acid. The rate constants are chosen to give a best fit of calculated to experimental data, and the ionisation constants K_a^{EH} and $K_a^{EH_2^+}$ are based on combination of the corresponding ionisation constants for the keto tautomer ($K_a^{KH} = [E^-][H^+]/[KH]$ and $K_a^{KH_2^+} = [KH][H^+]/[KH_2^+]$) with values of the keto–enol tautomeric constant for the neutral ($K_T^E = K_a^{KH}/K_a^{EH}$) and protonated ($K_T^E = K_a^{KH}K_a^{KH_2^+}/K_a^{EH}K_a^{EH_2^+}$ ketones respectively. In principle K_a^{EH} and $K_a^{EH_2^+}$ could also have been obtained from a best fit of calculated to experimental data, but the precision of values of k_o extrapolated from the buffer plots [eqn. (2)] was not very high.

The buffer-independent rate constants for enolisation (k_o^E) may be fitted to eqn. (6) where k_H^E, k_{OH}^E and $K_a^{KH_2^+}$ are rate

$$k_o^E = \frac{k_H^E K_a^{KH_2^+}}{\{1 + K_a^{KH_2^+}/[H^+]\}} + k_{OH}^E[OH^-] \qquad (6)$$

constants and ionisation constants for the keto reactant analogous to those for the enol in eqn. (5), and the superscript E for the rate constants denotes enolisation. The line drawn through the points corresponds to a best fit of values of k_H^E and k_{OH}^E and the independently measured values of ionisation constants to the data. In the figure the vertical separation of the plot for enolisation from that for ketonisation in the pH range 4–9, where the reaction involves interconversion of neutral enol and ketone tautomers, corresponds to the effective tautomeric constant $pK_T = 3.35$. Below pH 3, where the enol and ketone are protonated, the separation reduces to $pK_T^E = 1.64$, the tautomeric constant for the protonated species.

Table 2 Slopes and intercepts of buffer plots and rate constants for general acid- and general base-catalysis of halogenation of 2-, 3- and 4-phenylacetylpyridines and *N*-methyl-2-phenylacetylpyridinium ion in aqueous solution at 25 °C and ionic strength 0.2 M

Substrate/buffer	pH	R^a	$k_o/10^{-4}$ s^{-1}	$k^b/10^{-2}$ dm^3 mol^{-1} s^{-1}	$k_{GB}/10^{-2}$ dm^3 mol^{-1} s^{-1}	$k_{GA}/10^{-2}$ dm^3 mol^{-1} s^{-1}
2-Phenylacetylpyridine						
Acetate (I_2)	3.68	9	(0.26)	1.85	0.202	0.18
	4.04	4.2	(0.12)	1.05		
	5.29	0.25	—	0.258		
	5.66	0.11	—	0.166		
Lutidine (I_2)	6.67	1.0	—	1.01	1.0	
	7.30	0.25	(0.53)	1.00		
	7.66	0.11	0.99	0.987		
N-Methyl-2-phenylacetylpyridinium ion						
Acetate (Br_2)	4.02	4	0.0035	90.0	100.0	
	4.64	1	0.0035	109.0		
(I_2)	5.28	0.25	—	60.5[c]		
3-Phenylacetylpyridine						
Acetate (I_2)	3.44	14	0.10	0.632	0.165	0.031
	3.86	5.1	0.10	0.256		
	4.54	1.2	—	0.227		
	5.17	0.28	—	0.156		
	5.57	0.13	0.06	0.183		
Lutidine (I_2)	6.46	1.5	0.12	0.603	0.577	
	6.94	0.53	0.18	0.586		
	7.35	0.19	0.74	0.581		
4-Phenylacetylpyridine						
Acetate (I_2)	3.43	14	0.54	2.20	0.428	0.133
	3.86	5.2	—	1.28		
	4.54	1.2	0.18	0.519		
	5.17	0.28	—	0.476		
	5.57	0.13	0.22	0.441		
Lutidine (I_2)	6.48	1.5	0.47	1.92	1.87	
	6.94	0.53	1.6	1.89		
	7.35	0.19	0.31	1.88		

[a] Ratio of buffer acid to buffer base concentration. [b] Slope of plot of measured first order rate constants against concentration of buffer base. [c] Not used in evaluating k_{GB} (see text).

Table 3 First order rate constants for ionisation[a] and bromination of 2-, 3- and 4-phenylacetylpyridines and the *N*-methyl-2-phenylacetylpyridinium ion (2-NMe$^+$) and relaxation of their enols in aqueous HCl, NaOH and borate buffers[b] at different pHs at 25 °C

	2-Isomer		2-NMe$^+$[c]		3-Isomer		4-Isomer	
	pH	k_o/s^{-1}	pH	k_o/s^{-1}	pH	k_o/s^{-1}	pH	k_o/s^{-1}
Relaxation	0.70	0.0326	0.62	2.41	0.04	0.0478	0.92	0.008 15
	0.30	0.0329	1.4	2.72	0.92	0.0491	1.69	0.007 99
	2.20	0.0314	1.82	2.93	1.69	0.0490	1.91	0.008 70
	8.50	2.94			1.98	0.0475		
	9.41	3.06						
	10.05	3.58						
Ionisation	12.0	3.14	11.2	8.46				
	12.1	4.51	11.4	15.2				
	12.5	15.4	11.7	30.1				
	12.65	21.7	12.0	58.1				
	12.8	25.2						
	13.0	35.3						
		$k/10^{-4}$ s^{-1}		$k/10^{-4}$ s^{-1}		$k/10^{-4}$ s^{-1}		$k/10^{-4}$ s^{-1}
Bromination	0.90	7.42	0.70	20.2	0.78	0.89	0.78	2.38
	1.20	8.02	1.47	20.4	1.17	1.06	1.78	2.44
	1.60	6.90	2.17	25.8	1.78	0.98	2.17	2.32
	1.88	7.42			2.47	0.86	2.69	2.06
	2.20	5.69			2.57	0.61	2.77	1.93
	2.60	4.28			2.88	0.41	2.87	1.64

[a] Reaction of ketone with OH^- to form enolate anion. [b] The ionic strength is 0.1 M in the borate buffers, and was not maintained constant in solutions of HCl or NaOH. [c] *N*-Methyl-2-phenylacetylpyridinium ion.

The rate constants for base catalysis of the tautomerisation, k_{OH} and k_{GB}, can be converted to microscopic (or 'molecular')[6] rate constants for the individual steps of *C*-protonation of the enolate anion k_{BH} and proton abstraction from the α-carbon of the ketone k_B based on the usual mechanism for base-catalysed interconversion of ketone and enol tautomers shown in Scheme

1, in which again KH, EH and E^- represent ketone, enol and

$$KH \underset{k_{BH}[AH]}{\overset{k_{B^-}[A^-]}{\rightleftharpoons}} E^- \overset{[H^+]/K_a^{EH}}{\rightleftharpoons} EH$$

Scheme 1

enolate anion respectively and K_a^{EH} the ionisation constant of the enol.

Values of k_{B^-} correspond to k_{GB}^{E} and k_{OH}^{E} for the enolisation reaction and k_{BH} to $k_{GB}^{K}(K_a/K_a^{EH})$ for ketonisation, where K_a is the ionisation constant of the buffer acid AH. If K_T is known these relationships may be combined with eqn. (4) to obtain values of both k_{BH} and k_{B^-} for each acid base pair. Using the same equation k_{BH} for H_2O ($k_{BH}^{H_2O}$) may be obtained from k_{OH}^{K} ($= k_{OH}^{E}/K_T$) as $k_{BH}^{H_2O} = k_{OH}^{K}K_w/K_a^{EH}$, where K_w is the autoprotolysis constant of water. Values of k_{B^-} and k_{BH} for lutidine, acetate and hydroxide bases are listed in Table 4.

The interpretation of the acid-catalysed tautomerisation reaction is less straightforward than that for the base reaction, as was previously found for phenacylpyrazine.[5] This is a consequence of the expectation that enolisation proceeds not by a two-step mechanism with protonation occurring on the oxygen atom of the ketone, as is the case for simple ketones, but by the three-step mechanism shown in Scheme 2, in which protonation

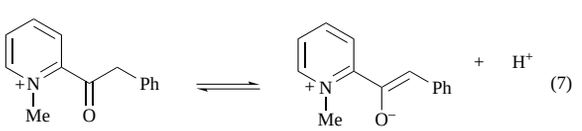
$$KH \overset{[H^+]/K_a^{KH^+}}{\rightleftharpoons} KH_2^+ \underset{k_{AH}[AH]}{\overset{k_{A^-}[A^-]}{\rightleftharpoons}} ZH \overset{1/K_T^{EZ}}{\rightleftharpoons} EH$$

Scheme 2

yields the *N*-protonated ketone, KH_2^+, and is followed by deprotonation from carbon to form initially the zwitterion tautomer (ZH) which then rapidly tautomerises to the enol (EH). Evidence that the reaction proceeds in this manner comes from measurements of rate constants that are considerably larger than expected for enolisation of a non-heterocyclic ketone of comparable reactivity: thus $k_H = \sim 0.15\ M^{-1}\ s^{-1}$ for 2-phenylacetylpyridine compared with an expected value of $\sim 10^{-5}\ M^{-1}\ s^{-1}$.[5]

The rate constant k_{A^-} for proton abstraction from the protonated ketone presents no difficulty. This is related to k_{GA}^{E} for enolisation as $k_{A^-} = k_{GA}^{E}K_a^{KH_2^+}/K_a$ where $K_a^{KH_2^+}$ and K_a are ionisation constants for the *N*-protonated ketone and buffer acid respectively. However, to obtain k_{AH} knowledge of the equilibrium constant for tautomerisation of enol (EH) to zwitterion (ZH, **6**), $K_T^{EZ} = [ZH]/[EH]$ is required. Thus from Scheme 2, $k_{AH} = k_{GA}^{K}/K_T^{EZ}$.

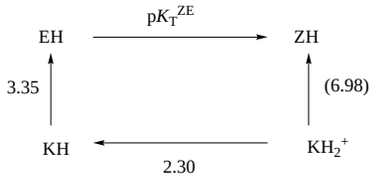
In the absence of a direct measurement of K_T^{EZ} a value may be inferred by taking the *N*-methyl zwitterion (**12**) formed from ionisation of the *N*-methyl-2-phenylacetylpyridinium cation (**11**) as a model for the N–H zwitterion. A pK_a for this ionisation (Scheme 3) was measured spectrophotometrically in



KMeH$^+$ (**11**) ZMe (**12**)

Scheme 3

borate, lutidine and acetate buffers as 6.98, and this value was substituted for $pK_a^{KH_2^{+(O)}}$, the pK_a for deprotonation of the *N*-protonated phenylacetylpyridine (KH_2^+) at its methylene carbon atom, in the cycle shown in Scheme 4, in which, again, ZH, EH and KH represent the zwitterion, enol and ketone tautomers and the equilibria are shown as single rather than double arrows to indicate the directions of reaction to which the p*K*s refer. Substituting $pK_T = 3.35$ for the keto–enol equilibrium



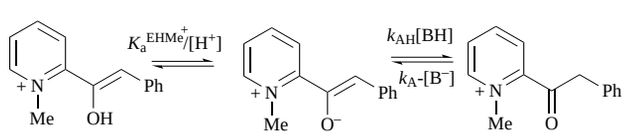
Scheme 4

constant and $pK_a^{KH_2^+} = 2.30$ for the pK_a of the *N*-protonated ketone allows pK_T^{ZE} to be evaluated as $6.98 - 3.35 - 2.30 = 1.33$, which implies that the zwitterion is more than 20-fold less stable than the enol.

A deficiency in this evaluation of pK_T^{ZE} is the lack of correction for the substituent effect of replacing H by methyl in the ionisation reaction of Scheme 3. However, an indication that this correction should be small comes from measurements of the keto–enol tautomeric constant for the *N*-methylphenylacetylpyridium ion **11** described below. It should also perhaps be noted that the value of $pK_T^{E} = 3.35$ used in Scheme 4 is a corrected value based on the relationship $K_T = K_T^{E} + K_T^{Z}$ where K_T is the experimentally measured constant ($pK_T = 3.33$). Since K_T^{E} cannot be evaluated without knowing K_T^{Z}, it is obtained in principle by iterative substitution in Scheme 4. In practice, the correction is very small and iteration is unnecessary.

1-Methyl-2-phenylacetylpyridinium toluene-*p*-sulfonate

A keto–enol tautomeric constant for this compound (**11**) was determined in the same way as for its unmethylated counterpart, 2-phenylacetylpyridine (**1**), by combining kinetic measurements of rate constants for ketonisation and enolisation. As before rates of ketonisation were measured by quenching the (zwitterionic) conjugate base of the ketone (**12**) into solutions of a strong acid or acidic buffers at pHs below the pK_a of the ketone (6.98) and observing relaxation of the initially formed *N*-methylated enol (**13**) to its keto tautomer. Rates of enolisation were measured from reaction of the ketone with bromine or iodine. The observed rate constants may be expressed as in eqns. (1)–(3) and derived rate constants k, k_o and k_{GB} from measurements in acetate and lutidine buffers as well as hydrochloric acid are listed in Tables 1–3. Values of k_{GB} were converted to microscopic rate constants k_{A^-} and k_{AH} based on Scheme 5, with $k_{A^-} = k_{GB}^{E}$ for enolisation and $k_{AH} =$



EHMe$^+$ (**13**) ZMe (**12**) KHMe$^+$ (**11**)

Scheme 5

$k_{GB}^{K}(K_a/K_a^{EHMe^+})/(1 + K_T^{E})$ for ketonisation, where $K_a^{EHMe^+}$ is the dissociation constant for the enolic hydrogen of **13** and $K_T^{E} = [EHMe^+]/[KHMe^+]$ is the tautomeric constant for enolisation of the methylated ketone (**11**). As expected only base catalysis of the tautomerisation was observed but the microscopic rate constants are denoted k_{A^-} and k_{AH} (rather than k_{B^-} and k_{BH}) because of the analogy between *N*-protonated and *N*-methylated substrates. The term $(1 + K_T^{E})$ appears in the expression for k_{AH} because the tautomeric equilibrium does not lie strongly in favour of the ketone. Rates of ketonisation, therefore, comprise a sum of rate constants $k_K + k_E = k_K(1 + K_T^{E})$.

In practice interpretation of the buffer measurements for the ketonisation reaction also depended upon the pH. In acetic acid buffers the measured rate constants for reaction of acetate ion correspond to $k_{GB}^{K} + k_{GB}^{E}$, with only a minor correction for deprotonation of the reactant ($EMeH^+ \rightleftharpoons ZMe + H^+$). For

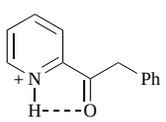
Table 4 Rate constants[a] for reaction of 2-, 3- and 4-phenylacetylpyridines, their enol and zwitterion tautomers and *N*-methyl-2-phenylacetylpyridinium ion with oxygen and nitrogen acids and bases in aqueous solution at 25 °C

	2-Phenylacetylpyridine					*N*-Methyl-2-phenylacetylpyridinium ion			3-Phenylacetylpyridine			4-Phenylacetylpyridine			
Acid (AH or BH)[b]	pK_a	k_{AH}[c]	k_{A^-}[d]	k_{BH}[e]	k_{B^-}[f]	k_{AH}[c]	k_{A^-}[d]	k_{AH}[c]	k_{A^-}[d]	k_{BH}[e]	k_{B^-}[f]	k_{AH}[a]	k_{A^-}[d]	k_{BH}[e]	k_{B^-}[f]
H_3O^+	−1.76	7.44×10^3	7.44×10^{-4}/55.5			2.24×10^3/55.5	2.24×10^{-3}/55.5	7.8×10^5	9.8×10^{-5}/55.5			1.19×10^5	2.38×10^4/55.5		
$CNCH_2COOH$	2.43											4.34×10^3	2.33×10^{-3}		
$HOCH_2COOH$	3.83											1.56×10^3	2.10×10^{-2}	1.34×10^5	4.98×10^{-7}
CH_3COOH	4.76	90.0	0.52	3.68×10^4	2.02×10^{-3}	170.0	0.98	6.3×10^3	4.8×10^{-2}	4.34×10^5	1.65×10^{-3}	1.17×10^3	0.134	9.17×10^4	2.91×10^3
2,6-Lutidinium ion	6.69			2.14×10^3	1.0×10^{-2}	2.5	2.4			1.87×10^4	5.77×10^{-3}			6.95×10^3	1.87×10^{-2}
N-Ethylmorpholinium ion	7.70					0.30	1.77								
Boric acid	9.24					2.49×10^{-2}	4.32								
H_2O	−15.76			3.63/55.5	347	5.80×10^{-4}/55.5	5.80×10^3			6.02/5.55[g]	38[g]			1.10/55.5[g]	60.3[g]

[a] Units $mol^{-1}\ s^{-1}$. [b] AH and BH (and their conjugate bases A^- or B^-) are the acids (or bases) indicated in subscripts of rate constants. [c] Rate constants for protonation of zwitterion tautomer of substrate by acid AH. [d] Rate constant for reaction of *N*-protonated (or *N*-methylated) ketone with base. [e] Rate constant for protonation of enolate anion. [f] Rate constant for reaction of ketone to enolate anion. [g] Rate constants calculated from data in ref. 12.

more basic buffers, however, the enol reactant becomes largely deprotonated and for lutidine the observed reaction is the reversible protonation of the zwitterion to form the ketone ($EMe + AH \rightleftharpoons KMeH^+ + A^-$), from which the microscopic rate constants k_{AH} and k_{A^-} are directly determinable (with now a minor correction for protonation of the zwitterion). In *N*-ethylmorphine and borate buffers (and aqueous sodium hydroxide) the only reaction observable is conversion of the ketone reactant to enolate zwitterion, with rate constant k_{A^-}. Values of k_{GB} for these buffers, therefore, are calculated from k_{A^-}. The appropriate rate constants are included in Tables 1–4. For the lutidine buffers the values of k_{AH} and k_{A^-} may be combined to evaluate the pK_a of the ketone (KMe^+) as 6.7, in fairly satisfactory agreement with the spectrophotometrically determined value of 7.0.

Values of the tautomeric constant K_T^E for the methylated ketone were obtained by combining corresponding rate constants for enolisation and ketonisation measured in HCl solutions and acetic acid buffers. These gave a mean value of $K_T^E = 0.13$ and $pK_T^E = 0.9$.



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The value of pK_T^E for **11** may be compared with the corresponding value of 1.64 for the *N*-protonated ketone (**14**). The larger value for the protonated ketone is at first surprising in the light of previous measurements showing that pK_T^E for *N*-protonated 3-phenacylpyridine is smaller (3.89 compared with 4.23) than for its *N*-methylated counterpart.[3] The most likely explanation of this would seem to be that the ketone (**14**) is stabilised by hydrogen-bonding. It seems likely that the substituent effect of replacing H by methyl upon the dissociation of protonated and methylated ketones to their respective zwitterions (Scheme 3) will be small, because replacement of methyl by H in the zwitterion **12** should lead to a similar stabilising influence from hydrogen-bonding to that in the ketone. No correction is applied therefore to the value of K_T^{ZE} based on use of the ionisation constant of Scheme 3 in Scheme 4. An ionisation constant for the enol of the *N*-methyl-2-phenylacetylpyridinium ions ($pK_a^{EHMe^+} = 6.1$) was obtained by combining the measured value of the pK_a for the ketone and the tautomeric constant $pK_T^E = 0.9$. The pH dependence of buffer catalysis of ketonisation measurements in acetic acid buffers provided a qualitative conformation of this value.

Values of k_o from the buffer plots and direct measurements in solutions of HCl and NaOH were used to construct the pH-profiles of log k_o plotted against pH shown in Fig. 2 for both enolisation (filled circles) and ketonisation (open circles). The ionisation measurements above pH 7–8 are included with the enolisation rate constants as filled circles. As already noted, the 'ketonisation' rate constants are really relaxation rate constants corresponding to sums of rate constants for ketonisation and enolisation. At high pHs, when enolisation (strictly ionisation to the enolate anion) becomes faster than ketonisation the two plots merge. A similar pH-profile has been reported by Bunting and Kanter for the tautomerisation of ketoesters,[7] which also have relatively large enol contents. The pH-dependence of the 'true' ketonisation rate constants are shown by the dashed line.

The lack of acid catalysis of the tautomerisation reactions is evident in Fig. 2 from the pH-independence of the reactions in acidic solutions. The reactions correspond in acid to rate-determining deprotonation of the ketone by a water molecule in the enolisation direction and to protonation of the enolate anion by H_3O^+ in the reverse ketonisation. Above pH 7–8 the hydroxide ion replaces water as the base leading to base-catalysed enolisation (ionisation). The pH-profile for ketonisation shows an inflection at pH 6 corresponding to the pK_a of the enol. At pHs below the pK_a of the ketone (6.9) ketonisation is no longer separately observable from enolisation, but the dashed line traces the pH-dependence of the reaction of the enolate anion with H_3O^+ and its pH-dependent (and thermodynamically unfavourable) protonation by water.

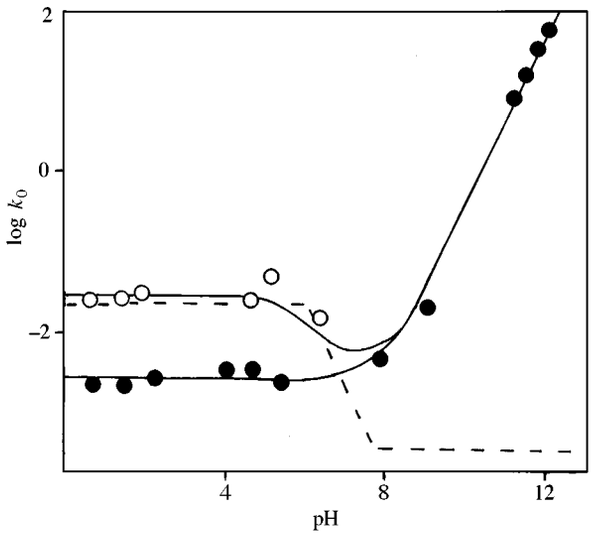


Fig. 2 Log *k*–pH profiles for enolisation (or ionisation) of *N*-methyl-2-phenylacetylpyridine **11** (●) and relaxation of its enol tautomer **13** (○). The dashed line represents ketonisation of the enol and its conjugate base **12**.

The line drawn through the points of the pH-profile for enolization (or enolate anion formation) is based on eqn. (7) in

$$k_o^E = k_{H_2O}^E + k_{OH}^E[OH^-] \quad (7)$$

which $k_{H_2O}^E$ and k_{OH}^E represent rate constants for the pH-independent and hydroxide ion-catalysed reactions respectively. The dashed line for ketonisation is based on eqn. (8) in which

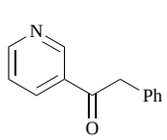
$$k_o^K = \frac{k_{H_2O}^K + k_{OH}^K[OH^-]}{1 + K_a^{EMeH^+}/[H^+]} \quad (8)$$

$k_{H_2O}^K$ and k_{OH}^K are the corresponding rate constants for ketonisation (with unionised enol as reactant) and K_a^{EH} is the acid dissociation constant of the enol. The full line drawn through the experimental points for 'ketonisation' represents the sum of these two expressions. The rate constants were chosen to give a best fit to the experimental points and the ionisation constant of the enol is taken as $pK_a^{EMeH^+} = 6.1$, as determined above.

The hydroxide and water rate constants for enolisation correspond to the microscopic rate constants $k_{A^-}^{H_2O}$ and $k_{A^-}^{HO}$. Those for ketonisation yield rate constants $k_{AH}^{H_3O} = k_{H_2O}^K/K_a^{EHMe^+}$ and $k_{AH}^{H_2O} = k_{OH}^K/k_wK_a^{EHMe^+}$. Values for these are listed in Table 4.

3- and 4-Phenylacetylpyridines

Studies of the 3- and 4-phenylacetylpyridines (**15** and **16**) closely



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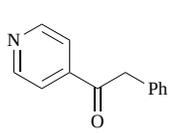

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followed the pattern for the 2-isomer (**1**) save that the *N*-methyl compounds, which had been previously studied by Bunting and Stefanidis,[12] were not prepared. Measurements of pK_as for *N*-protonation gave 2.59 and 2.66 for the 3- and 4-isomers respectively, and the pK_as of 13.1 and 12.26 for ionisation to their

enolate anions were measured or estimated by Bunting and Stefanidis.[12] Rate constants for ketonisation and enolisation were measured in the same way as for the 2-compound, and slopes of buffer plots for lutidine and acetate buffers are given in Table 1, together with corresponding values of k_o from intercepts of buffer plots; rate measurements in aqueous HCl are shown in Table 3.

Rate constants for the reactions in aqueous sodium hydroxide had been measured by Bunting and Stefanidis and were not duplicated.[12] For 4-phenylacetylpyridine, the buffer measurements were extended to cyanoacetic and glycolic acids. Contributions from both acid- and base-catalysed pathways were observed for acetate and glycolate buffers but only an acid contribution for the stronger cyanoacetic acid.

Values of k_{GA} and k_{GB} were converted to microscopic rate constants and these are included in Table 4. Again it was presumed that acid-catalysed tautomerisation occurs *via* a zwitterion tautomer and corrected values of pK_T^{ZE}, which were required to obtain values of k_{AH} for ketonisation, were derived from Bunting's and Stefanidis's measurements[12] of $pK_a^{KHMe^+}$ for the *N*-methyl-3- and *N*-methyl-4-phenylacetylpyridinium ions. For the 3-compound $pK_a^{KHMe^+} = 10.30$ and this is corrected to 10.00 for $pK_a^{KH_2^+(C)}$ on the basis of a previously estimated difference between $KHMe^+$ and KH_2^+ ionising to zwitterions for *N*-protonated and *N*-methylated 3-phenacylpyridine.[3] A similar correction was applied to $pK_a^{KMeH^+} = 9.02$ for the 4-isomer[12] to give $pK_a = 8.7$ for deprotonation from carbon of KH_2^+. These corrections contrast with the lack of correction to $pK_a^{KHMe^+}$ for the 2-isomer, where it is supposed that hydrogen bonding in KH_2^+ stabilises the ketone (above). It is also noteworthy that for the *N*-methyl-4-phenacylquinolinium ion, where deprotonation yields an enaminone rather than zwitterion, $pK_a^{KHMe^+} = 7.02$ is less than for the corresponding protonated ketone (7.54).[11]

Combining rate constants for ketonisation and enolisation gives values of $pK_T = 4.2$ and 3.1 for keto–enol tautomerism of the 3- and 4-phenylacetylpyridine isomers respectively. Rate constants from Table 2 may also be combined with Bunting's and Stefanidis's measurements in NaOH to construct pH profiles for ketonisation and enolisation. These are similar to those for the 2-isomer in Fig. 1 and are not shown, but rate constants k_H for ketonisation and enolisation reactions could be derived based on eqns. (5) and (6), and these were converted to the appropriate microscopic rate constants, as well as tautomeric constants $pK_T^E = 2.80$ and 1.54 for the *N*-protonated 3- and 4-isomers respectively, in the same manner as for the 2-isomer; values of k_{OH} were taken from the measurements of Bunting and Stefanidis.[12] These values are also included in Table 4.

Discussion

Tautomeric and ionisation constants

For all three phenylacetylpyridine isomers the order of tautomer stability in aqueous solution at 25 °C is confirmed to be keto > enol > zwitterion. Enol contents are greater than for many simple ketones[15] but in no case exceed one part in a thousand. Quantitative measurements of the tautomeric and ionisation constants are summarised in Scheme 6 as networks of p*K*s for equilibria linking keto (KH), enol (EH) and zwitterionic forms ($ZH^{\pm}$) with their common *N*-protonated conjugate acids (KH_2^+ and EH_2^+) and single conjugate base, the enolate anion (E^-).[3] As before, the normal double arrows depicting equilibria are replaced by single arrows indicating directions of reactions.[3] If opposite signs are assigned to p*K*s for clockwise and anticlockwise arrows the p*K*s in each reaction cycle sum to zero. The p*K*s of N–H compounds estimated from measurements for their *N*-methyl analogues are shown in brackets.

In Fig. 3 keto–enol tautomeric constants and ionisation constants of the keto tautomers of all the phenacyl- and phenylacetyl-pyridines are compared. Values for deoxybenzoin[3,16] are also shown and it can be seen that replacement of either of the two phenyl rings by pyridyl groups increases the enol content. Interestingly, for 3- and 4-pyridyl groups the enol content is increased to a greater extent when substitution occurs adjacent to the carbonyl group as in the phenylacetylpyridines ($PhCH_2COPy$) than at the α-carbon atom in the phenacylpyridines

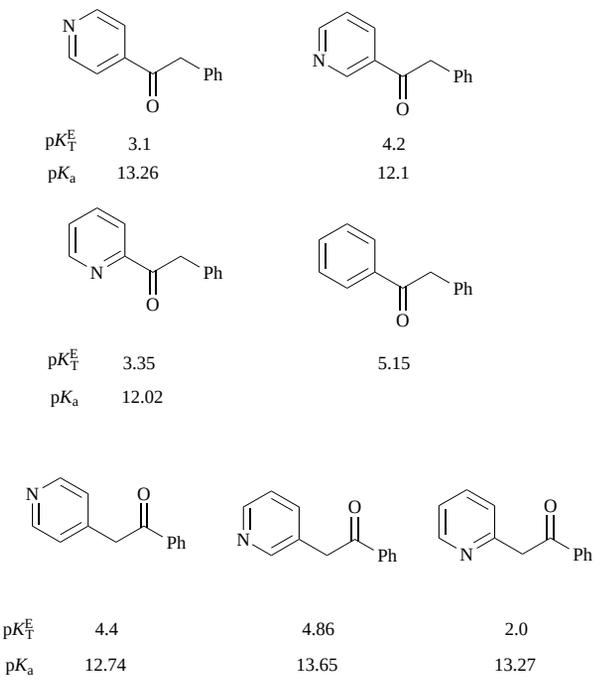
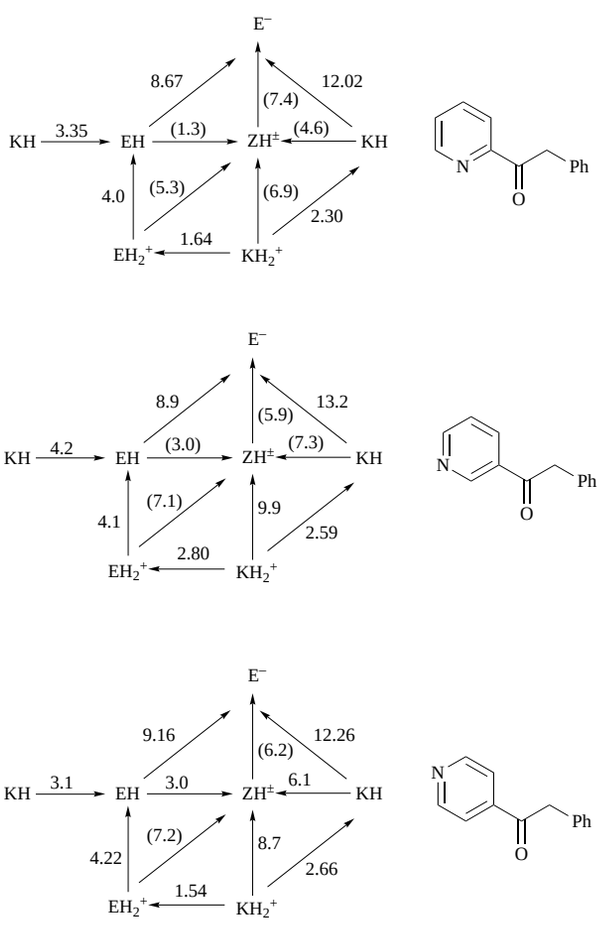


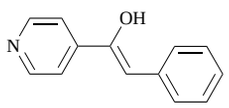
Fig. 3 Comparison of keto–enol tautomeric constants and ionisation constants of the keto tautomers of phenyl- and phenylacetyl-pyridines and deoxybenzoin



Scheme 6

(PyCH$_2$COPh). As discussed by Stefanidis and Bunting,[13] it is likely that in addition to stabilisation of the enols by conjugation between the pyridine and phenyl rings (**17** and **18**) replacement of phenyl by the electron-withdrawing pyridyl group decreases the stability of the ketone. The effect is greater for the phenylacetyl- than phenacyl-pyridines because of the greater proximity of the pyridyl and carbonyl groups. Apparently, this outweighs any stabilising conjugation between the pyridyl ring and hydroxy group in the enols of the latter (*e.g.* **18**).

The difference in enol contents between the phenylacetyl- and phenacyl-pyridines is even more marked for the *N*-protonated ketones, and indeed now extends to the 2-isomer (Scheme 6). For all three (neutral) isomers also ionisation to an enolate anion occurs more readily for the phenylacetyl pyridyl ketones.



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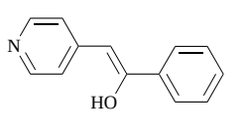

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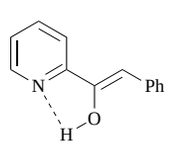
Only for the 2-isomers is there a greater enol content for a phenacyl- than phenylacetyl-pyridine. For 2-phenacylpyridine there is a large increase in enol content ($pK_T^E = 2.0$) relative to its 4-isomer ($p_T^E = 4.20$), which can be attributed to stabilisation of the enol by hydrogen-bonding (**3**).[1] For the phenylacetylpyridines, in contrast, the enol content is less for the 2-isomer ($pK_T^E = 3.35$) than for the 4-isomer ($pK_T^E = 3.1$).

Inspection of the pK_Ts and pK_as in Scheme 6 offers no evidence of hydrogen-bonding in 2-phenylacetylpyridine (**19**). Thus the pK_a for ionisation of the enol (8.67) is normal while that for phenacylpyridine enol is high (11.27), consistent with an additional stabilisation of the latter. On the other hand, Bunting and Kanter have proposed a small (ten-fold) stabilisation of the enol of pyridacyl esters and amides (*e.g.* **20**) on the basis of a correlation of pK_as of enols and ketones for a series of keto esters and keto amides.[7] Moreover, the difference in pK_as of *N*-methyl and N–H phenacylpyridinium ions is consistent with a similar degree of stabilisation for the structurally related ketone **16**. It seems likely therefore that there is some hydrogen-bonding in **19** but that its effect is substantially less than in the phenacylpyridine enol **3**. The difference presumably reflects more favourable hydrogen-bonding in the six- than five-membered ring.



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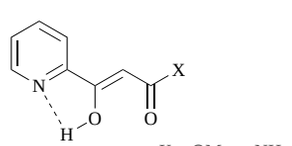

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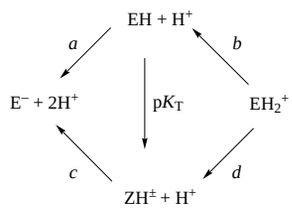
The proportion of zwitterion tautomer in the phenylacetylpyridines is consistently less than that of the enol. This contrasts with the phenylacylpyridines where for the 2- and 4-isomers the enaminone is more stable than the enol (*e.g.* $pK_T^M = 0.88$ {where K_T^M = [enaminone]/[ketone]} compared with $pK_T^E = 2.0$ for 2-phenacylpyridine). The largest proportion of zwitterion relative to enol is observed for the 2-phenylacetylpyridine (**1**) for which $pK_T^{ZE} = 1.3$ compared with 3.1 and 3.0 for the 3- and 4-isomers respectively (K_T^{ZE} = [zwitterion]/[enol]). This presumably reflects the juxtaposition of positive and negative charges in the 2-isomer. The stability of the 2-phenylacetyl zwitterion (**6**) is also apparent from the enhanced acidity of its *N*-methyl derivative, with $pK_a = 7.0$ compared with $pK_a = 10.30$ and 9.02 for the corresponding *N*-methylated 3- and 4-phenylacetylpyridines.

Proton activating factors

The measurement of rate and equilibrium constants for the phenylacetylpyridines allows evaluation of 'proton activating factors'[10] for these compounds. Proton activating factors measure the effect of protonation at one reaction site upon susceptibility to attack by a base or nucleophile at another. Originally they were conceived by Stewart and Srinivasan for reaction rates,[10] but there seems no reason not to apply them also to equilibria.[3,5]

The connection between proton activating factors and tautomeric equilibria may be seen by dissecting these equilibria into acid and base ionisation reactions for proton addition and proton loss to and from the two tautomers. This is illustrated for the interconversion of enol and zwitterion tautomers of a phenylacetylpyridine in Scheme 7, which shows that the proton



Scheme 7

transfer and tautomeric equilibria may be written as a network of thermodynamic cycles. In Scheme 7, the usual symbols for the tautomers and their ionised forms are used.

Reaction schemes similar to Scheme 7 have been widely used to represent tautomerisation and ionisation of amino acids.[17–19] They show that the position of a tautomeric equilibrium can be expressed in terms of acid dissociation constants relating the tautomers to a common conjugate acid or conjugate base. Thus in Scheme 7 if the pK_as of the reactant tautomer acting as acid and base respectively are denoted a and b and those of the product tautomer c and d, the tautomeric constant pK_T is given by $a - c$ or $d - b$.

For such equilibria normally one tautomer is considerably more stable than the other. The information readily available then is limited to the pK_as for the stable tautomer (say a and b). If the acid and base sites of the tautomers are well separated, as in a long chain amino acid [*e.g.* $^+H_3N(CH_2)_nCOO^-$ where n is large], extents of ionisation at the two sites are nearly independent of each other and, to a good approximation, pK_T corresponds to the difference in pK_as of acidic and basic sites $a - b$, which may be denoted ΔpK_{ab}. More commonly, however, ionisations at the two sites are not independent and ΔpK_{ab} has to be corrected for their interaction. The appropriate correction factor is provided by the (log of the) proton activation factor, PAF, which describes the effect of protonation at one tautomeric site upon proton loss at the other. Thus in Scheme 7 log PAF is given by $a - d$ or $c - b$ and its relationship to pK_T and ΔpK_{ab} is expressed by eqns. (9) and (10).

$$\Delta pK_{ab} = a - b \quad (9)$$

$$\log \mathrm{PAF} = c - b \quad (10)$$

$$pK_T = \Delta pK_{ab} - \log \mathrm{PAF} = a - c \quad (11)$$

Eqn. (11) summarises the relationship between pK_T, ΔpK_{ab} and log PAF. Normally it is not used for evaluating pK_T because this is better done by estimating one of the unknown pK_as in Scheme 7 from a free energy relationship. For amino acids, for example, use of a corrected pK_a for a methyl or ethyl ester, taken as a model for the neutral acid, provides the most effective method for evaluating pK_T.

Occasionally, an unknown pK_T or pK_a may be estimated from eqn. (11). For the phenylacetylpyridines, for example, it is not

Table 5 Contributions of intrinsic acidity and basicity (ΔpK_{ab})[a] and proton activation (log PAF) to enol–zwitterion (or enaminone[b]) and keto–zwitterion tautomeric constants (pK_T) for phenacyl- and phenylacetyl-pyridines

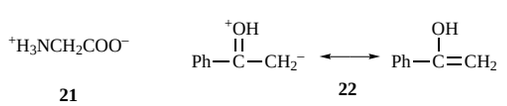
	EH ⟶ ZH±			KH ⟶ ZH±		
	ΔpK_{ab}	log PAF[c]	pK_T^{EZ}[d]	ΔpK_{ab}	log PAF[e]	pK_T^{KZ}[f]
Phenylacetyl						
2-	4.8	3.55	1.15	9.7	5.1	4.6
3-	4.8	1.7	3.1	10.4	3.1	7.3
4-	4.95	2.0	2.95	9.6	3.6	6.0
Phenacyl						
2-	6.75	7.70	−0.95	8.25	7.2	1.05
3-	2.95	1.95	1.0	8.80	2.9	5.9
4-	2.10	4.1	−2.0	8.1	5.7	2.4

[a] Difference in pK_as of basic and acidic ionisation sites of reactant tautomers. [b] For 2- and 4-phenacylpyridines the zwitterion structure is replaced by an enamine. [c] PAF measures the effect of *N*-protonation upon deprotonation from the oxygen of the enol (or *O*-protonation upon deprotonation from the nitrogen of the zwitterion or enaminone). [d] K_T^{EZ} = [enol]/[zwitterion]. [e] PAF measures the effect *N*-protonation upon *C*-deprotonation of the ketone (or of *C*-protonation upon *N*-protonation of the zwitterion). [f] K_T^{KZ} = [zwitterion]/[ketone].

possible to write a cycle corresponding to Scheme 7 for keto–enol tautomerism because, although pK_T^E is known, ionisation constants for *O*-protonation of the ketone (or *C*-protonation of the enol) are not known. However, we note that the difference in pK_as of *O*-protonated ketone and (unprotonated) enol corresponds to a proton activating factor. If for 4-phenylacetylpyridine (*e.g.*) we suppose that log PAF is the same as that for acetophenone, which has been evaluated as 14.34,[3] then from eqn. (11) or Scheme 7, the pK_a of the *O*-protonated ketone is given by $pK_a^{EH} - 14.34$. Since pK_a^{EH} for the enol is 9.16, the desired pK_a is estimated as −5.2.

This estimate may be compared with $pK_a = -4.0$ for acetophenone.[20] Considering the electron-withdrawing effect of the nitrogen atom the value appears to be reasonable and suggests the possibility of deriving pK_as for other phenylacetyl or phenacyl pyridines. Only the 2-derivatives, where the enol is stabilised by intramolecular hydrogen-bonding, might be expected to give unrealistic values.

However, probably the main usefulness of eqn. (11) lies in its factorisation of tautomeric constants into contributions from an 'intrinsic' term representing ionisation constants at the two protonation sites and an 'interaction' term expressing inductive, resonance or hydrogen-bonding interactions between them. For glycine for example $pK_T = 5.34$ for conversion of the zwitterionic to neutral form can be broken down into an intrinsic contribution $\Delta pK_{ab} = 3.38$ and interaction term log PAF = 1.94. The much smaller interaction term for glycine than acetophenone reflects a purely electrostatic interaction between charge centres compared with the strong resonance interaction for acetophenone (**21** and **22**).



21 **22**

log PAF = 1.94 log PAF = 14.34

With respect to the phenylacetylpyridines, Table 5 shows tautomeric constants for converting the enol to zwitterion tautomer (pK_T^{EZ}) and ketone to zwitterion (pK_T^{KZ}) factored into contributions from ΔpK_{ab} and log PAF. The same analysis is shown for 2- and 4-phenacylpyridines, for which the zwitterion tautomers are replaced by enaminones. As already explained the analysis cannot be applied to keto–enol tautomerism because of lack of ionisation constants for the *O*-protonated ketone.

It is evident from the table that when tautomeric constants are dissected in this way the interaction term makes a substantial contribution to pK_T. Indeed pK_T becomes quite a small difference between larger values of ΔpK_{ab} and log PAF.

Closer inspection of Table 5 shows that ΔpK_{ab} for enol–zwitterion and keto–zwitterion tautomerism varies little between 2-, 3- and 4-pyridyl substituents, except where there is strong stabilisation from hydrogen bonding, as in the case of the enol of 2-phenacylpyridine. On the other hand log PAF varies considerably. Relative magnitudes are consistently in the order 2- > 3- > 4-, although the difference between 3- and 4- is much greater (1.95 compared with 4.1) for the phenacylpyridines, where the 4-pyridinium substituent can interact strongly with a negative charge centre by resonance, than for the phenylacetylpyridines, where it cannot. The unusually large values for 2-phenyacylpyridine (log PAF = 7.7 and 7.2) again reflect the influence of hydrogen-bonding.

In conclusion, this analysis of the tautomeric measurements illustrates the use of proton activating factors to express the contributions of inductive, resonance and hydrogen-bonding interactions between ionising sites to magnitudes of tautomeric equilibrium constants.

Experimental

Preparations

The 2-, 3- and 4-phenylacetylpyridines were prepared by Grignard reactions following the procedure of Chu and Teague, and LaForge.[21] Details are given only for 2-phenylacetylpyridine. The 3- and 4-isomers have also been prepared recently by Stefanidis and Bunting.[12]

2-Phenylacetylpyridine. Benzyl chloride (11.4 g) was added slowly to magnesium turnings (2.2 g). The solution was stirred and 2-cyanopyridine was added at a rate to maintain gentle reflux. After standing overnight 20% aqueous ammonium chloride (100 ml) and concentrated hydrochloric acid (25 ml) were added. The mixture was filtered and the precipitate stirred into a solution of excess sodium hydrogen carbonate. Extraction with chloroform followed by drying (Na_2SO_4) and evaporation of solvent gave a brown solid. This was purified by silica flash chromatography using diethyl ether–light petroleum (40–60 °C) as eluent. On refrigeration, the product was obtained as a pale yellow low-melting solid (3.5 g). (Found: C, 79.3; H, 5.6; N, 7.1. $C_{16}H_{11}NO$ requires C, 79.1; H, 5.6; N, 7.0%); $\delta_H(CDCl_3)$ 4.55 (2H, s, CH_2), 7.2–7.35 (5H, m, Ar), 7.45–8.1 (3H, m, H-3, H-4 and H-5), 8.7–8.75 (1H, d, H-6). Satisfactory analytical data and expected NMR spectra were also obtained for the 3- and 4-isomers.

1-Methyl-2-phenylacetylpyridinium toluene-*p*-sulfonate. Methylation of 2-phenylacetylpyridine was achieved by reaction of 1.8 g with the same quantity of methyl toluene-*p*-sulfonate at 150 °C for 4 h. After cooling overnight the product was obtained as a brown oil that was crystallised from methanol–diethyl ether (yield 0.71 g) (Found: C, 65.3; H, 5.5; N,

Table 6 Spectra and conditions of measurement of pK_as of phenylacetylpyridines (PhAcPy) in aqueous solution at 25 °C

Substrate	Acid–base–buffer	λ/nm[a]	ε/10^{-4} dm^3 mol^{-1} cm^{-1}[b]	Species	I[c]/M	pK_a
2-PhAcPy	NaOH	345	1.43	anion	—	12.02
	HCl–acetate	340	0.030	cation	0.2	2.30
N-Me-2-PhAcPy$^+$	lutidine–borate–acetate	410	0.14	zwitterion	0.2	7/0[d]
3-PhAcPy	HCl	265	0.55	cation	—	2.59
4-PhAcPy	HCl–acetate	260	0.050	cation	—	2.66

[a] λ_{max} unless otherwise indicated. [b] From limiting absorbance at high or low pH. [c] More intense peaks at 232 and 270 nm gave small changes in absorbance with pH and less reproducible values of pK_a. [c] The ionic strength was not kept constant for measurements in HCl and NaOH solutions. [d] Corrected for presence of 10% enol so that K_a refers to the ketone tautomer.

3.55. $C_{21}H_{21}NO_4S$ requires C, 65.8; H, 5.5; N, 3.7%); δ_H(CF_3-COOH) 2.50 (3H, s, CH_3), 4.48 (2H, s, CH_2), 4.66 (3H, s, NCH_3), 7.3–7.8 (13H, m, Ar).

NMR spectra were recorded on a Jeol JNM-GX 270FT spectrometer operating at 270.05 MHz.

Ionisation constants

Ionisation constants for *N*-protonation of 2-, 3- and 4-phenylacetylpyridines, for formation of an enolate anion from 2-phenylacetylpyridine and for formation of an *N*-methylenolate zwitterion from the *N*-methyl-2-phenylacetylpyridinium ion, were measured spectrophotometrically in aqueous solution at 25 °C. The pH-dependence of absorption maxima for cationic, anionic or zwitterionic species were monitored using a Pye-unicam SP8-400 or Perkin-Elmer Hitachi 124 spectrophotometer, as described earlier.[3,6] Measured pK_as, ionic strengths, wavelengths and extinction coefficients of absorption maxima used in the measurements are given in Table 6; further details of the measurements are provided elsewhere.[22] Spectral changes associated with the most intense absorption maxima ($\varepsilon \geqslant 10^4$) were too small for satisfactory determination of pK_as for *N*-protonation, but consistent results were obtained from measurements with weaker, longer wavelength absorptions. The pK_as obtained from these equilibrium measurements provided a satisfactory fit of calculated-to-observed measurements for the kinetic dependence of rate constants for enolisation upon pH in the appropriate pH-regions and, in the case of *N*-methyl-2-phenylacetylpyridinium ion, were corroborated by kinetic measurements in lutidine buffers. The pK_as in Table 6 are directly measured values at the ionic strength indicated. Normally no correction for ionic strength was required because under the conditions of the measurements positive and negative ions were conserved between reactants and products of the equilibrium. In the case of *N*-methyl-2-phenylacetylpyridinium ion the pK_a is corrected for the presence of a small amount of enol so that it refers specifically to the keto form.

Kinetic measurements

Kinetic measurements of ketonisation and enolisation were carried out in the same manner as described for the tautomerisation of the phenacylpyridines.[5] Normally rates of ketonisation were fast enough to require stopped flow measurements and a Durrum 110 spectrometer was used for these. A freshly prepared solution of enolate anion in dilute sodium hydroxide in one syringe of the instrument was quenched with excess HCl or buffer acid in the other, and reaction of the enol so generated monitored at a wavelength close to its λ_{max}, which was usually at a slightly shorter wavelength than that of the enolate anion. Reactions at pHs above the pK_a for enolate anion formation were measured by quenching ketone reactant into aqueous sodium hydroxide or buffer base, and were monitored from the increase in absorption arising from formation of enolate anion.

Rate constants for enolisation in acetic acid or lutidine buffers were measured spectrophotometrically from uptake of I_3^- ion accompanying conversion of the ketone reactant to its enol tautomer. At low pHs, however, iodine was replaced by bromine as scavanger of the enol because of reversibility of the iodination reaction.

In acetic acid buffers enolisation and ketonisation were subject to catalysis by both buffer acid and buffer base. In order to separate second order rate constants k_{GA} and k_{GB}, however, the measured first order rate constants k_{obs} had to be corrected for *N*-protonation of the reactant. For enolisation this presented little difficulty as the extent of protonation was small in the pH-range studied and the pK_a for protonation was independently known.

For ketonisation, on the other hand, the enol reactant was significantly protonated in acetic acid buffers. The dependence of observed rate constants upon buffer acid and buffer base concentration is then given by eqn. (12), in which R is the ratio

$$k_{obs} = \frac{k_o + k_{GB}[AcO^-] + k_{GA}[AcOH]}{1 + RK_a^{AcOH}/K_a^{EH_2^+}} \qquad (12)$$

of buffer acid to buffer base concentrations and RK_a^{AcOH} in the denominator of the equation has been substituted for [H^+].

Values of k_{GB} and k_{GA} may be extracted from this expression if the ionisation constant of the enol $K_a^{EH_2^+}$ is known. In principle this may be obtained by combining the pK_a of the ketone with keto–enol tautomeric constants for the neutral and *N*-protonated ketones evaluated from measurements of rates of enolisation in lutidine buffers and HCl respectively. In practice, an alternative procedure was followed, in which the ratio k_{GA}/k_{GB} was assigned the value independently determined from the enolisation reaction. This has the advantage that p$K_a^{EH_2^+}$ can also be evaluated. Values of k_{GA}, k_{GB} and $K_a^{EH_2^+}$ were then derived from the slopes of plots of k_{obs} against [AcO^-] which are given by eqn. (13), in which x (= 0.9 for 2-phenylacetyl

$$\frac{k_{obs} - k_o}{[AcO^-]} = \frac{k_{GB}(1 + xR)}{(1 + yR)} \qquad (13)$$

pyridine) is the ratio of k_{GB}/k_{GA} for enolisation and $y = K_a^{AcOH}/K_a^{EH_2^+}$.

Cross multiplying by (1 + xR) and taking reciprocals gives eqn. (14), from which it can be seen that a plot of the left hand

$$\frac{(1 + xR)[AcO^-]}{k_{obs} - k_o} = \frac{1}{k_{GB}} + \frac{yR}{k_{GB}} \qquad (14)$$

side against R yields $1/k_{GB}$ as intercept and y/k_{GB} as slope. This analysis gave k_{GA} = 5.0 M^{-1} s^{-1} and k_{GB} = 4.5 M^{-1} s^{-1} and p$K_a^{EH_2^+}$ = 4.5 (corrected for ionic strength)[19] for 2-phenylacetylpyridine. Although the value of p$K_a^{EH_2^+}$ agrees only moderately well with the more reliable value of 4.0 from combining the keto–enol tautomeric constants and pK_a of the ketone as described above, the agreement is probably within the limits of uncertainty of the analysis. Similar treatments of ketonisation in acetic acid buffers for 3- and 4-phenylacetylpyridines gave enol pK_as of 3.6 and 4.2 respectively, which gave similar and better agreement with the independently determined values of 4.1 and 4.22.

Some minor discrepancies were encountered in the measurements. For the *N*-methyl-2-phenylaceylpyridinium ion measurements of rates of enolisation in acetic acid buffers using

iodine rather than bromine as a trapping agent gave a reduction of 50% in k_{GB}. The iodine value was disregarded on the grounds that some interference from the reversibility of iodination might be expected; however, this rate constant gave better agreement with K_E determined in HCl solutions than the bromination constant. When the same substrate was reacted in lutidine buffers a similar discrepancy was observed in k_{GB} values when the reaction was carried out in forward and reverse directions. It is possible that this was due to the presence of a non-equilibrium mixture of *E* and *Z* enol structures formed from neutralisation of the enolate anion. The possible influence of *E* and *Z* structures of enols or enaminones upon rates and equilibria of tautomerisation will be the subject of a later paper.

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