Keto–Enol Tautomerism and Ionisation of 1-Phenacylpyridinium Ions: a Model for Carbanion-stabilisation of Azomethine Ylides

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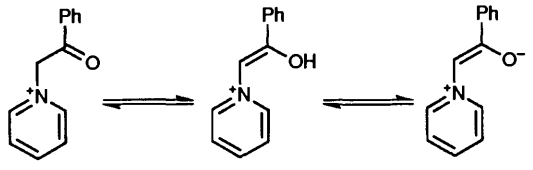
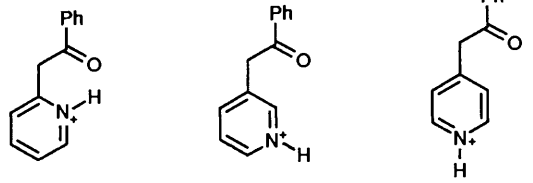
Measurement of equilibrium constants for keto–enol tautomerism (K_T) and ionisation (K_a) of 1-phenacylpyridinium and 1-phenacyl(4-dimethylamino) pyridinium ions gives pK_T ($-\log K_T$) = 6.10 and 5.55 and pK_a = 10.90 and 13.2 respectively. The enol content and acidity of the 1-phenacylpyridinium ion is lower than that of its 2-, 3- and 4-isomers, and the possibility that this reflects impaired −M resonance by a 1-pyridinium substituent is discussed. Notional (proton) activating factors reflecting the influence of the positive charge of the 1-pyridinium substituent upon equilibrium ionisation and rates of deprotonation by lutidine and hydroxide bases are estimated from free energy correlations as 10^3, 17 and 5×10^3 respectively. These compare with a (methyl) activating factor of 10^9 derived from equilibrium ionisations of 4-chlorobenzaldehyde oxime and nitrone and a (notional) value of 10^6 for pyridine-*N*-oxide. The implications of these values for the activating effect of *N*-protonation of an azomethine group in models for pyridoxal-catalysed azomethine rearrangements are discussed.

This paper describes the tautomerism and ionisation of the 1-phenacylpyridinium ion (**1**⇌**2**⇌**3**). The behaviour of this ion differs significantly from that of its 2-, 3- and 4-isomers (**4**, **5** and **6**) discussed in the preceding paper.[1] One difference is that it cannot undergo deprotonation at nitrogen and thus is subject only to keto–enol and not imine–enamine tautomerism. A further difference is the presence of a positive charge adjacent to the reaction site. The influence of this charge upon tautomerism and ionisation, and particularly upon the stability of the enol tautomer and enolate anion provide the principal topics of this paper.



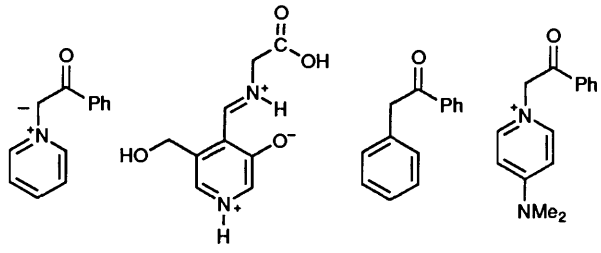
1 **2** **3**



4 **5** **6**

In basic solution, ionisation of the 1-phenacylpyridinium ion yields a 1,4-zwitterion **3** which, in its less favourable 1,2-zwitterionic form **7**, may be considered an azomethine ylide.[2] Azomethine ylides are of interest in connection with the catalytic action of the coenzyme pyridoxal (vitamin B_6) for which zwitterionic imine derivatives of amino acids such as **8** are probable intermediates in trans-amination, decarboxylation and racemisation reactions.[3] Although the aromatic ylide **7** is an imperfect model for the aliphatic azomethine function of the zwitterion **8**, it is more easily studied than many more closely related structures, and implications of the present results for the activating effect of *N*-protonation of an azomethine function will be considered.

The effect of a 1-pyridinium substituent upon the stability of



7 **8** **9** **10**

the enol tautomer **2** has been the subject of a preliminary report[4] and comment.[5] When tautomer **1** is compared with deoxybenzoin **9** it is found that replacement of an α-phenyl substituent by the 1-pyridinium ion decreases the enol content. This seemed surprising because the corresponding replacement by 2-, 3- or 4-pyridinium substituents increases the enol content.[4] For this reason, and because the low enol content and high reactivity of the 1-phenacylpyridinium ion make experimental measurements difficult, this study was extended to the more easily investigated 4-dimethylamino-substituted ion **10**.

Results

1-Phenacylpyridinium Bromide.—Spectrophotometric measurements of the ionisation of 1-phenacylpyridinium bromide in dilute aqueous sodium hydroxide and borate buffers are consistent with formation of the enolate (zwitter)ion **3** with a basic pK_a of 10.90. A previous report of 9.7 for this pK_a,[6] determined potentiometrically, refers to aqueous methanolic rather than aqueous solutions.[7]

A pK_a of 10.90 is corroborated by the pH dependence of stopped-flow kinetic measurements of the ionisation of the tautomer **1**. In aqueous sodium hydroxide rate constants are first order in substrate and first order in hydroxide ion and are presumed to correspond to k_1 of eqn. (1), in which KH and E^-

$$KH \underset{k_{-1}}{\overset{k_1[OH^-]}{\rightleftharpoons}} E^- \qquad (1)$$

refer to the 1-phenacyl pyridinium substrate and its enolate ion respectively. In borate buffers the rate constants for the back

Table 1 First order rate constants for H^+, OH^- and buffer independent reactions of phenacylpyridinium ions in aqueous solution at 25 °C

1-Phenacyl pyridinium ion				1-Phenacyl (4-dimethylamino) pyridinium ion			
Enolisation[a]		Ketonisation		Enolisation[a]		Ketonisation	
pH	k/s^{-1}	pH	k/s^{-1}	pH	k/s^{-1}	pH	k/s^{-1}
0.82	9.23×10^{-6}	0.62	12.1	1.40	2.47	0.69	0.925
1.17	9.14×10^{-6}	1.22	12.0	1.70	2.76	1.22	1.00
6.86	2.29×10^{-3}	6.86	99			1.70	0.917
9.23[b]	96	7.55	79				
9.85	122	8.64	102				
10.31	123	9.28	98				
		10.98	217				
		11.29	320				

[a] Measured by iodination or bromination except as indicated. [b] Kinetic measurements from observing formation of enolate anion

reaction k_{-1} could be measured as the intercept of a plot of rate constants extrapolated to zero buffer concentrations against $[OH^-]$. A value of k_{-1} could also be obtained by neutralising a solution of the enolate ion in dilute aqueous sodium hydroxide with excess acidic buffer at a pH below the pK_a of **1** and (again) extrapolating the measured rate constants to zero buffer concentration. Combining k_1 and k_{-1} then gives $k_{-1}/k_1 = K_b = 1.3 \times 10^3$ whence $pK_a = 10.9$ in agreement with the equilibrium measurement. The measured or extrapolated first order rate constants at different pHs from enolisation (ionisation) or ketonisation (protonation) measurements are listed in Table 1. At higher pH the range of protonation rate constants is limited by the pK_a of the substrate (10.90).

In principle, quenching the enolate anion **3** in more acidic buffers at pHs below the pK_a of the enol **2** should lead to rapid generation of this species (EH) and allow measurement of its rate of conversion to the keto tautomer. In practice, in acetic acid buffers this reaction is too fast to measure. However, it can be measured in solutions of percholic acid in the absence of buffer, and there the rate is found to be independent of acid concentration.

The reduction in rate between acetic acid buffers and strong acids, and the pH-independence of the rate constants, are consistent with a ketonisation reaction in which the quenching process yielding the enol is followed by ionisation to an enolate ion which is then protonated by H_3O^+ to form the ketone, as shown in eqn. (2). That the reaction occurs in this way was

$$EH \overset{K_a}{\rightleftharpoons} E^- \xrightarrow{H_3O^+} KH \qquad (2)$$

confirmed by measurements of the reverse enolisation process using bromine to trap the enol. In perchloric acid solutions the reaction again showed no acid catalysis, even at relatively high acid concentrations (pH ~ 1). The measured rate constants at different pHs are included in Table 1.

The rate of enolisation in acidic solutions was very slow in comparison with the rate of ketonisation, and this is consistent with a very small equilibrium ratio of enol to keto tautomer. Measurements were made using zero order kinetics at high concentrations of substrate and were corrected for loss of bromine through evaporation in control experiments in the absence of substrate. Combining the measured rate constants for ketonisation ($k_K^{H_2O} = 12.0 \pm 0.5\ s^{-1}$) and enolisation ($k_E^{H_2O} = 9.2 \times 10^{-6}\ s^{-1}$) gives a tautomeric constant $K_T = [EH]/[KH] = k_E^{H_2O}/k_K^{H_2O} = 7.7 \times 10^{-7}$ and pK_T ($= -\log k_T$) = 6.10. From the value of $pK_a = 10.90$ for the keto tautomer the pK_a of the enol can be evaluated as 10.90 − 6.10 = 4.80.

Kinetic measurements in which enolate anion was quenched in lutidine and borate buffers at pHs greater than the pK_a of the enol (4.75) gave rate constants for protonation of the anion by buffer acids. Measurements at different buffer ratios confirmed that the buffer acid was indeed the reactive species. For 1 : 1 lutidine buffers, combining these rate constants with measurements of rates of iodination of the 1-phenacylpyridinium ion provided a further value for the pK_a of this ion. From the buffer rate constants ($k_K^{LutH^+} = 4.00 \times 10^3\ dm^3\ mol^{-1}\ s^{-1}$ for quenching the anion and $k_E^{Lut} = 0.288\ dm^3\ mol^{-1}\ s^{-1}$ for iodination) we obtain $pK_a = 10.91$ from eqn. (3), taking the pK_a

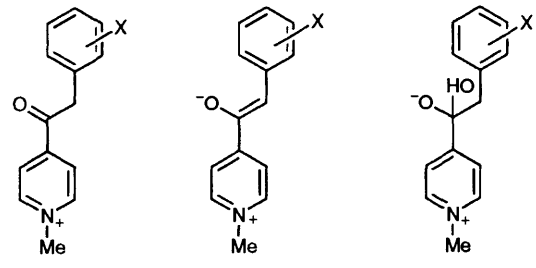
$$k_K^{LutH^+}/k_E^{Lut} = K_a^{LutH^+}/K_a \qquad (3)$$

of lutidinium ion as 6.77. This is in good agreement with the value (10.90) from the kinetic and equilibrium measurements described above.

$$\text{Enolate} \underset{k_B^-[B^-]}{\overset{k_{BH}[BH]}{\rightleftharpoons}} \text{Ketone} \qquad (4)$$

Second order rate constants k_{BH} for reaction of the enolate ion with H_3O^+, H_2O and buffer acids (BH) as in eqn. (4) are listed in Table 2 together with rate constants (k_{B^-}) for the reverse ionisation of the keto tautomer by base. These were derived from the buffer measurements in the same manner as in the previous paper.[1]

Decomposition in Basic Solutions.—In a recent study of the reaction of substituted benzyl *N*-methylpyridinium ketones **11** in sodium hydroxide Bunting and Stefanidis[8] observed that rates of ionisation to the enolate anion **12** became pH-independent above pH 12. They attributed this to rapid formation of the less stable hydrate anion **13** prior to ionisation.



11 **12** **13**

For the 1-phenacylpyridinium ion **1** the rate of ionisation was too fast to measure above pH 11.5 and, probably for this reason, no pH-independent reaction was observed. However, at high pH, a base-catalysed decomposition of the enolate ion **3** was observed. This seems best interpreted as reaction *via* the dianion of the hydrate **14** to yield *N*-methylpyridinium ion and benzoate anion as in eqn. (5) (although no attempt was made to isolate these products). Interestingly, for the substrates **11** containing strongly electron withdrawing substituents in the phenyl ring, at high pHs Bunting and Stefanidis observed a base-catalysed reaction of the hydrate anion **13** accompanied by a drop in absorbance of the enolate product **12**.[8] This was interpreted as implying a further (unknown) ionisation equilibrium, but unless the reversibility of the process was specifically established one may speculate that a reaction similar to that of eqn. (5) competes with the original ionisation.

1-*Phenacyl*(4-*dimethylamino*)*pyridinium Ion.*—As expected, the behaviour of this substrate was similar to that of the

Table 2 Molecular rate constants ($dm^3\ mol^{-1}\ s^{-1}$) for reaction of 1-phenaclpyridinium ions and their conjugate bases with oxygen and nitrogen acids (BH) or bases (B^-) in aqueous solution at 25 °C

	1-Phenacylpyridinium ion			1-Phenacyl(4-dimethylamino)-pyridinium ion	
BH	pK_a	k_{BH}	k_{B^-}	k_{BH}	k_{B^-}
H_3O^+	−1.74	7.2×10^5	$9.2 \times 10^{-6}/55.5$	4.27×10^7	
AcOH	4.76			$\sim 6 \times 10^5$	$2.62 \times 10^{-6}/55.5$
$LutH^+$	6.77	4.0×10^3	0.288		$\sim 2.7 \times 10^{-3}$
H_3BO_3	9.23	680	14.5		
H_2O	15.74	90/55.5	1.2×10^5		

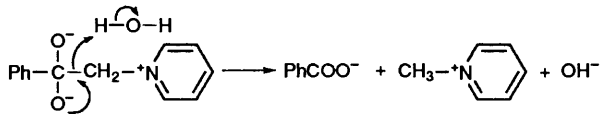
Table 3 Tautomeric and ionisation constants of the 1-phenacylpyridinium ion **1** and its 4-dimethylamino derivative **10**

Compound	pK_T	pK_a (keto)	pK_a (enol)
1	6.10	10.90	4.80
10	5.55	13.21	7.66

Table 4 Tautomeric constants of phenacyl-pyridines (PP) and -pyridinium ions (PP^+) and pK_as of their keto and enol tautomers in aqueous solution at 25 °C

Substrate	pK_T	pK_a^{KH} (keto)	pK_a^{EH} (enol)
$PhCOCH_2Ph$[a]	5.15	14.8	9.6
1-PP^+	6.10	10.90	4.80
2-PP^+	2.51	5.91	3.40
3-PP^+	3.89	10.74	6.85
4-PP^+	2.86	7.05	4.19
2-PP	2.0	13.27	11.27
3-PP	4.86	13.65	8.79
4-PP	(4.4)	12.74	(8.3)

[a] A. J. Kresge, personal communication and preceding paper



14 (5)

unsubstituted 1-phenacylpyridinium ion, except that the pK_a and enol content are higher. The pK_a was measured spectrophotometrically in aqueous sodium hydroxide as 13.21. The tautomeric constant was measured in aqueous HCl as a ratio of pH-independent rate constants $k_K^{H_2O} = 0.935\ s^{-1}$ for ketonisation (from quenching the enolate anion) and $k_E^{H_2O} = 2.62 \times 10^{-6}\ s^{-1}$ for enolisation (from bromination measurements) to give $K_T = 2.80 \times 10^{-6}$ and $pK_T = 5.55$. Combining pK_T with $pK_a = 13.21$ for the keto tautomer gives $pK_a = 7.66$ for the enol.

No kinetic measurements were made for the 1-phenacyl(4-dimethylamino)pyridinium ion in basic solutions but rate constants for acid solutions are included in Table 1. Rates of reaction in acetic acid buffers were just slow enough for measurements of approximate rate constants for ketonisation. Molecular rate constants for ionisation of the ketone by acetate ion and water acting as bases and for the reverse reactions of enolate anion with acetic acid and hydronium ion are given in Table 2.

Discussion

The kinetic and equilibrium measurements provide a straightforward picture of the keto-enol tautomerism of the 1-phenacylpyridinium ion **1** and its 4-dimethylamino derivative **10**. Fig. 1 shows pH-rate profiles for the ketonisation and enolisation reactions of the tautomer **1**. No acid catalysis is observed and the slower enolisation process shows reactions of the keto tautomer with water and hydroxide ions only. The same is true of ketonisation, but there are now also 'breaks' in the pH profile corresponding to the pK_as of the keto and enol tautomers (although the latter is inferred from combining the pK_a of the keto tautomer with the keto–enol tautomeric constant K_T rather than from the kinetic measurements). Also included in Fig. 1 are rate constants for the base-catalysed decomposition of the ionised 1-phenacylpyridinium ion described above.

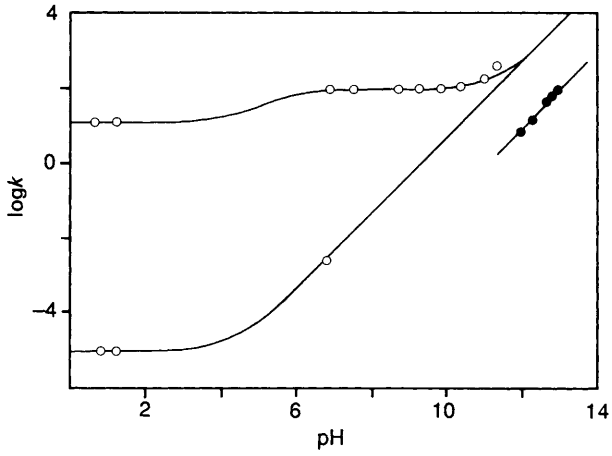
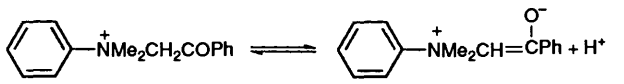


Fig. 1 pH Profiles for enolisation (○, lower curve), ketonisation (○, upper curve) and base-catalysed decomposition (●) of 1-phenacylpyridinium ion at 25 °C in aqueous solution

Tautomeric and ionisation constants of the 1-phenacylpyridinium ion and its 4-dimethylamino derivative are shown in Table 3. As expected, the dimethylamino substituent has a significant moderating effect on both rates and equilibria.

Activation by the 1-Pyridinium Substituent.—The absence of acid catalysis of tautomerisation of the 1-phenacylpyridinium ion reflects both the inhibiting effect of the pyridinium positive charge on this pathway and its activating effect on reaction *via* an enolate ion. In Table 4 this activating effect is compared with that of the isomeric 2-, 3- and 4-pyridinium ions (**4**–**6**) in terms of pK_as of enol and keto tautomers. As might be expected, the acidity of the 1-phenacylpyridinium enol **2** is greater (pK_a = 4.80 compared with 6.85) than that of its 3-isomer, but less than that of the 2-phenacylpyridinium ion (pK_a = 3.40) in which the $C{=}N^+$-entity is directly conjugated with the negative charge. For the 4-isomer, in which conjugation is weaker, the pK_as are comparable.

A similar comparison of the acidities of the keto tautomers reveals a slightly different pattern reflecting the different values of K_T for the isomeric ions. Most significantly the acidity of the



15 (6)

1-phenacylpyridinium ion (pK_a = 10.90) is now less than that of its 3-isomer (pK_a = 10.74). Since the inductive effect upon ionisation of a positive charge at the 1-position of the pyridine ring should be greater than that at the 3-position, this would seem to imply that resonance stabilisation by the 1-pyridinium ion is less effective than that of the 3-pyridinium ion, and thus that resonance stabilisation by the 1-pyridinium group is abnormally weak.[9]

This conclusion is not self-evident because calculations of π-electron distributions in the protonated pyridine ring show considerable charge dispersal through π-electron polarisation[10] and, in principle, this could lead to a charge distribution giving a larger −I inductive effect for the 3- than the 1-pyridinium ion.

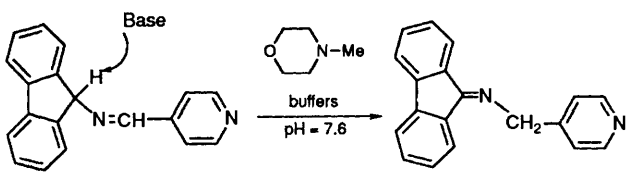
A further comparison may be made with the pK_a of the *N*-phenacyl-*N*,*N*-dimethylanilinium ion **15**. Dimethylaniline has a similar pK_a to pyridine (5.07 compared with 5.20) and this ion might be expected to show a similar inductive effect to the phenacylpyridinium ion but without the resonance. The relevant pK_a [eqn. (6)] was measured in aqueous sodium hydroxide as 12.5. Compared with pK_a = 10.9 for 1-phenacylpyridinium ion therefore we might say that the resonance effect of the pyridinium substituent increases the stability of the enolate anion by a factor of $10^{\Delta pK_a} = 10^{1.6}$.

The corresponding stabilising effect of a phenyl substituent may be estimated as $10^{4.4}$ based on the difference in pK_as of acetophenone (19.2) and deoxybenzoin (**9**, 14.8). This includes resonance and inductive effects, but if only half the stabilisation is due to resonance it is greater than for the pyridinium ion. These comparisons are rough and ready, and still do not allow for charge dispersion in the pyridinium ion but it seems safe to conclude that −M resonance for this ion is comparable to or less than that of a phenyl group.

Carbanion Stabilisation of Azomethine Ylides.—Measurements of the activating effect of the 1-pyridinium substituent are useful for assessing the influence of the positive charge of a protonated azomethine group **16** upon ionisation of a C–H bond to yield an azomethine ylide **17**.

16 17

As already noted, this process is of interest in relation to model studies of the catalytic action of pyridoxal in promoting carbanion formation from imine derivatives of amino acids **8**. A reaction with which we have been concerned is the azomethine rearrangement of 9-pyridyliminofluorene **18** shown in Scheme 1.[11] This system is sufficiently reactive that rearrangement occurs



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Scheme 1

Table 5 Kinetic and equilibrium proton activating factors (paf) for ionisation of phenacylpyridines (keto tautomers)

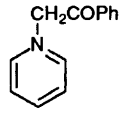
			k^b/mol^{-1} dm^3 s^{-1}		paf (kinetic)	
Substrate[a]	pK_a[b]	paf (equilib)	Lut	OH^-	Lut	OH^-
2-PP^+	5.91	2.3×10^7				
4-PP^+	7.05	4.9×10^5	54.6	7.6×10^4	250	472
3-PP^+	10.74	8.1×10^2	1200	5.3×10^3	20	166
1-PP^+	10.90	1.0×10^3	0.29	1.2×10^5	17	5000

[a] PP^+ denotes phenacylpyridinium ion. [b] For phenacylpyridinium ion

in *N*-methylmorpholine buffers at pH 7.6. The reaction is subject to catalysis by the basic but not the acidic component of the buffer,[12] indicating that there is no protonation of the azomethine nitrogen prior to ionisation of the 9-fluorenyl hydrogen. It follows that the proton activating factor (paf) for this process (*i.e.* the increase in rate or equilibrium constant accompanying protonation)[11] is relatively small. Indeed if the pK_a of the nitrogen is estimated as ~3.5 the upper limit for this activation, based on the difference of pH (7.6) and pK_a, is ~10^4.

In the preceding paper, measurements of proton activating factors were reported for 2-, 3- and 4-phenacylpyridinium ions (**4**–**6**).[1] No such measurement is possible for the 1-phenacylpyridinium ion, but it is useful to estimate a notional activating factor by assigning a pK_a to a hypothetical '1-phenacylpyridine' lacking a charge on the nitrogen atom (**19**).

The required pK_a may be obtained by comparing pK_as of neutral phenacylpyridines and their positive ions. A linear relationship is defined by points for the 3- and 4-phenacylpyridines. Although the anomalously high pK_a of 2-phenacylpyridine **1** deviates from this line, the variation in pK_as is small (12.7–13.7) so the uncertainty in assigning ~14 to the 'neutral' 1-phenacylpyridine (**19**) is also small.



19

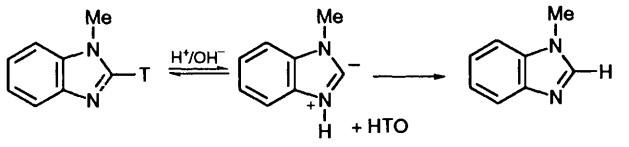
Combining pK_a = 14 with pK_a = 10.9 for the 1-phenacylpyridinium ion then yields a notional activating factor of ~10^3 for a positive charge at the 1-position of the pyridine ring with respect to proton loss from the α-carbon atom. In Table 5 this value is compared with proton activating factors for the corresponding 2- 3- and 4-pyridyl positions. It can be seen that, despite the proximity of the charge, the activating factor for **19** is practically the smallest among values ranging up to 2.3×10^7 for the 2-phenacylpyridinium ion **4**. Even that for the 3-isomers **5** (800) is hardly less than for the 1-position.

In practice, the effect of the 1-pyridinium substituent is further moderated because this activation refers to an equilibrium ionisation whereas the factor required is for a rate of ionisation which should be smaller. A kinetic activating factor can be estimated in the same way as for the equilibrium value from rate constants for reactions of phenacylpyridines and pyridinium ions with a common base. Suitable rate constants have been measured for lutidine and the real and notional activating factors they lead to are also listed in Table 5. The values are significantly less than for the equilibria and the (notional) value for the 1-pyridinium ion (17) is again smaller than that for its 3-isomer (20) and considerably smaller than for the 4-isomer (250).

If the value for the 1-pyridinium ion of 17 offers a reasonable guide to the effect of *N*-protonation on the reactivity of the azo-

Table 6 Equilibrium constants (log K) for transfer of X between phenyl and methyl groups [eqn. (7)]

X	^-O	HO	NMe_2	NH_2	CH_3	Cl	NMe_2H^+	NH_3^+
$-\log K$	12.6	7.7	7.2	6.5	4.3	0.6	2.5	0.4



20 21

Scheme 2

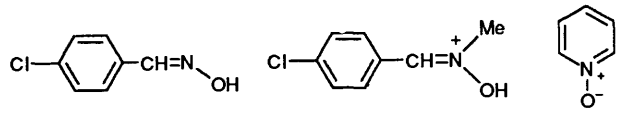
methine group of **18** in Scheme 1 it is understandable why no acid catalysis of this reaction is observed. However, for a number of reasons it may not be appropriate to pyridoxal itself. These include (a) the use of a neutral amine rather than an anion as base, (b) the presence of additional electron delocalising substituents on the azomethine carbon atoms of **18**, and (c) the aromatic character of the azomethine function of the 1-phenacylpyridinium ion. These may be examined briefly in turn.

It is evident that the presence of a positive charge on the azomethine function should be more favourable to reaction with anionic than neutral bases. This is confirmed by an estimate of paf for attack by hydroxide ion on compound **1** based on combining the measured hydroxide rate constant (1.2×10^5) from Table 1 with an estimated value of ~25 for the notional reaction with 'neutral' 1-phenacylpyridine (**19**) derived from a correlation of hydroxide rate constants with pK_as for phenacylpyridines and pyridinium ions established by Stefanidis and Bunting.[13] Keefe and Kresge have also found that the 1-phenacylpyridinium ion shows a large positive deviation from a correlation of log k with pK_a for reaction of a series of (uncharged) ketones with hydroxide ions.[14]

The effect of the additional electron delocalising substituents and especially of PhCO in **1** and fluorenyl in **18** in moderating the influence of protonation may be judged by comparing reactions of these substrates with hydroxide-catalysed hydrogen isotope exchange of an sp^2 C–H bond of benzimidazole **20** studied by Jones and co-workers.[15] This exchange is catalysed by protonation of the benzimidazole nitrogen atom, and the *N*-protonated intermediate **21** (Scheme 2) is structurally similar to an azomethine ylide possessing a high degree of charge-localisation. The kinetic proton activating factors measured for benzimidazole and a number of its derivatives from comparisons with exchange in the unprotonated substrates fall in the range 10^7–10^9. These values are much larger than paf $\leqslant 5 \times 10^3$ for reaction of **1** with hydroxide ion.

A similar factor, 5×10^9, relates pK_as for the equilibrium ionisation of the hydroxyl hydrogens of the 4-chlorobenzaldoxime **22** and the *N*-methyl nitrone **23**,[16] in which the activating positive charge is provided by methylation rather than protonation of the oxime nitrogen atom. Here the negative charge is localised but upon an oxygen atom rather than a carbon atom. Again, this paf is much larger than the corresponding value of 10^3 for the equilibrium ionisation of compound **1**.

Finally, the influence of aromaticity on paf may be roughly gauged by comparing the nitrone **23** with pyridine-*N*-oxide **24**. Once more we may derive a notional activating factor for the positive charge on the nitrogen atom of the *N*-oxide by assigning $pK_a = 7.0$ to a 'neutral' pyridine-*N*-oxide using a crude correlation of pK_as of neutral and protonated pyridinols.[17] The paf derived for pyridine-*N*-oxide is then 10^6.



22 $pK_a = 10.1$ **23** $pK_a = 0.4$ **24**

This is significantly less than that for the non-aromatic nitrone **22**, and may suggest that the aromatic phenacylpyridinium ion **1** underestimates the paf for protonation of an aliphatic azomethine group, *e.g.* in compound **18**.

These results should be extrapolated cautiously to the coenzyme pyridoxal where the azomethine protonation equilibria are more complex than in the model system **18**.[18] As already noted, the zwitterion **8** and other pyridoxal ylide structures are subject to extensive electron delocalisation, which will tend to reduce the activating effect of protonation. On the other hand, the small values for reactions of 1- and 3-phenacylpyridinium ions with lutidine in Table 5 probably represent lower limits when compared with pyridoxal insofar as they refer to a neutral rather than anionic base and to an aromatic rather than aliphatic azomethine group.

Enol Content of the 1-Phenacylpyridinium Ion.—We now return to the influence of a 1-pyridinium substituent upon the stability of an enol. Enol contents of isomeric phenacylpyridines and pyridinium ions are compared in Table 4. Replacement of the α-phenyl group of deoxybenzoin **9** by a 2-, 3-, or 4-pyridyl or pyridinium group (**4**–**6**) leads to an increase in enol content. This may be understood in terms of stabilisation of the enol by a weak −M effect and destabilisation of the ketone by an inductive effect.

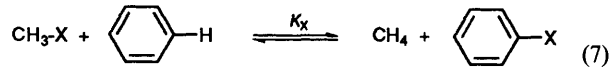
Surprisingly, however, the enol contents of the 1-phenacylpyridinium ions **1** and **10** are lower than that of deoxybenzoin, by a factor of 9 for the unsubstituted ion **1** and by a factor of 2.5 for its 4-dimethylamino derivative **10**. In a preliminary communication of these results, we suggested that this might be explained if binding of a positive charge to the sp_2 bond of the enol were more destabilising than its unfavourable inductive effect on the keto tautomer.[2]

This explanation was questioned by Toullec,[5] who argued that the adverse polar effect of the positive charge should be exerted most strongly on the keto tautomer, as it is with less electronegative substituents, and that the low enol content is caused by poor −M resonance stabilisation of the enol by the 1-pyridinium substituent. His interpretation is supported by the evidence discussed above that resonance stabilisation of an enolate anion by a 1-pyridinium substituent is also weak.

The effect of an adjacent positive charge upon an sp^2 bond may be assessed from equilibrium constants for the isodesmic reactions shown in eqn. (7), in which a group X is transferred between methyl and phenyl carbon atoms. Equilibrium constants for these reactions may be calculated from measured free energies of formation in aqueous solution (ΔG°_f) for 'reactants' and 'products'.[19] The phenyl group is chosen as a model for the vinyl group of the enol tautomer and CH_4 for the methylene group of the ketone because data are available for these molecules.

Values for the free energies of transfer for different X groups, including NH_3^+, are shown in Table 6 in the form of pKs ($-\log K = \Delta G/2.303RT$ for $T = 298$ K). As expected, transfer of O^-, OH or NH_2 from methyl to phenyl is associated with a considerable stabilising effect resulting from the favourable interaction of p and π orbitals. No such stabilisation is available for NH_3^+, but the transfer is not unfavourable and this suggests that indeed the dominant inductive effect in keto–enol tautomerism, even for a positively charged group, is upon the

keto group, the effect of which indeed is not included in eqn. (7).



(7)

The analogy between eqn. (7) and substituent effects upon keto–enol tautomerism is not perfect and more direct measurements would be desirable. Nevertheless, the results support Toullec's interpretation of the low enol content of the 1-phenacylpyridinum ion and suggests that poor −M resonance may be responsible not only for the low enol content but also the weak acidity of this ion.

Experimental

1-Phenacylpyridinium iodide was prepared by heating acetophenone and iodine in an excess of pyridine for 2 days. The product crystallised on cooling and was recrystallised from methanol.[6,20] 1-Phenacyl-4-(dimethylamino)pyridinium bromide was prepared by heating phenacyl bromide and 4-dimethylaminopyridine in ether under reflux overnight.[6] The crude product crystallised on cooling and was recrystallised from methanol and diethyl ether.

N-Phenacyl-*N*,*N*-dimethylanilinium ion was prepared from α-bromoacetophenone and *N*,*N*-dimethylaniline as described by Wedekind.[21] *N*-(4-bromophenacyl)-*N*,*N*-dimethylanilinium ion was prepared similarly from 4-bromophenacyl bromide.

Ionisation constants of phenacylpyridinium ions were measured spectrophotometrically in aqueous NaOH. Extinction coefficients for the enolate zwitterions were $\varepsilon = 4900$ mol^{-1} dm^3 cm^{-1} at $\lambda_{max} = 401$ nm for the unsubstituted ion and $\varepsilon =$ 28,300 mol^{-1} dm^3 cm^{-1} at $\lambda_{max} = 346$ nm for the 4-dimethylamino derivative. Ionisation of the latter was not complete in 0.5 mol dm^{-3} NaOH and ε was chosen to minimise the standard deviation in the pK_a determined from six absorbance measurements at hydroxide concentrations up to 0.1 mol dm^{-3}. A value of p$K_a = 13.05 \pm 0.02$ at ionic strength 0.5 was corrected to 13.21 at zero ionic strength. The pK_a for the unsubstituted ion was obtained as 10.90 in dilute solutions of sodium hydroxide and is not corrected for ionic strength.

Measurement of the ionisation in NaOH solutions of *N*-phenacyl and *N*-(4-bromophenacyl)-*N*,*N*-dimethyl anilinium ions gave values of pK_a = 12.5 and 11.0 respectively. A value of pK_a = 9.3 was reported previously for the latter compound[6] in an aqueous methanolic solvent.[7]

Kinetic measurements were carried out as previously[1] by (a) observing direct ionisation of the 1-phenacylpyridinium ion to its enolate ion, (b) quenching a solution of the anion in aqueous NaOH into acid or an acidic buffer at pHs below its pK_a, and (c) halogenation of the pyridinium ions. The ionisation and quenching measurements employed a Durrum D110 stopped flow spectrometer. For the more acidic 1-phenacylpyridinium ion, solutions of the anion were prepared in *e.g.* 2×10^{-3} mol dm^{-3} NaOH. For the less acidic dimethylamino derivative solutions of NaOH were typically 0.02 mol dm^{-3}. The substrate was only 10% ionised under these conditions but the absorbance change accompanying the reaction was sufficiently large for kinetic measurements to be made conveniently.

A number of the rates measured were fast. Quenching of 1-phenacylpyridinium enolate ion in perchloric acid solutions led to ketonisation with rate constants 12 s^{-1} and a half life of 60 ms. However, in lutidine buffers and aqueous sodium hydroxide rate constants as large as 300 s^{-1} and half lives of 2 ms were measured. On the other hand, because of the large values of the tautomeric constant, rates of halogenation were slow. In acid solutions it was necessary to use bromination rather than iodination because the equilibrium for the latter was unfavourable and corrections for evaporation determined from control measurements had to be applied. Use of zero order conditions with fairly high concentrations of soluble ionic substrate eased the measurements, but the usable concentrations were limited to 1.5×10^{-3} mol dm^{-3} by interference from the long wavelength absorbance by the substrate.

Kinetic measurements were also made of the decomposition of 1-phenacylpyridinium enolate ion in aqueous sodium hydroxide. From the drop in enolate absorbance with time the following first order rate constants were measured (units s^{-1}, hydroxide concentrations in parentheses): 7.1 (0.01), 15.6 (0.02), 43.1 (0.048), 70.4 (0.08), 111 (0.1). These results are plotted on the pH-profile Fig. 1.

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