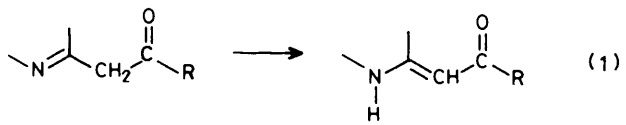
The Mechanism of Imine–Enamine Tautomerism of 2- and 4-Phenacylquinolines

A. R. Edwin Carey, Gouki Fukata, Rory A. More O'Ferrall,* and Michael G. Murphy
Department of Chemistry, University College, Belfield, Dublin 4, Ireland

Isomerisations of 2- and 4-phenacylquinolines to their enaminone tautomers *via* 1,3 or 1,5 carbon–nitrogen hydrogen shifts occur by stepwise acid- or base-catalysed pathways similar to those for the enolisation of ketones. The reactions are observed as relaxations of the unstable to stable tautomers by stopped-flow spectrophotometry or, where the aromatic imine is the stable form, by trapping the enaminone with iodine in the reverse reaction. Evidence of mechanism comes from observations of general acid and general base catalysis, agreement between kinetically determined pK_a values and independently measured values, and comparisons between rate and equilibrium constants for protonation of the enaminone tautomers and their *N*-methyl derivatives. The reactions show a primary isotope effect and yield normal Brönsted plots with α *ca.* 0.5. The kinetically determined pK_a values indicate *N*- rather than *O*-protonation of phenacylquinolines but for the enaminones *O*-protonation competes kinetically with the thermodynamically preferred *C*-protonation. Combination of pK_a values for *C*-, *N*-, and *O*-protonation leads to equilibrium constants K_T for enamine–imine and (protonated) keto–enol tautomerisation. The effect of 2- and 4-*N*-protonation (proton activating factors) upon rates and equilibria for ionisation of hydrogen from the methylene carbons is discussed and evidence of 'imbalance' in charge development on the carbon base in the transition state is noted. A concerted intramolecular 1,3-proton transfer is predicted but not observed.

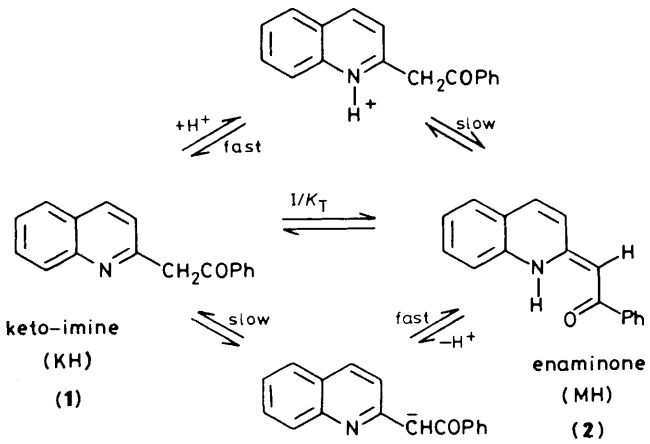
This and an earlier paper[1] report initial results of kinetic and equilibrium measurements for a family of proton transfers comprising ionisation and imine–enamine tautomerisation of 2- and 4-acylmethyl heterocycles [equation (1)]. The reactions are subject to wide variations in rate and equilibrium constants through changes in the heterocycle and the strength of the acid catalyst, and in this respect are suited to a general study of reactivity in proton-transfer reactions. Kinetic measurements complement existing data for simple ketones from the work of Bell[2,3] and others[4,5] and studies of *N*-alkylated 2- and 4-methyl heterocycles by Zoltewicz.[6] The substrates may be modified to include intramolecular bases, and the presence of adjacent co-ordinating sites in the 2-acylheterocycles allows comparisons of proton and metal ion catalysis.[7]



(1)

Here the imine–enamine tautomerisation of the representative substrates 2- and 4-phenacylquinoline is described. Structures of the tautomers have been assigned from comparisons of spectra with the corresponding *N*-methylenaminones, and measurements of tautomerisation constants and pK_a values for *N*-protonation and proton loss from carbon are available from the earlier paper.[1]

As shown in Scheme 1, acid–base ionisation reactions form a network of proton transfers providing pathways for tautomerisation analogous to those in the enolisation of ketones.[8,9] The reactions differ from enolisations in that interconversion of tautomers may be observed directly as well as by the halogen-trapping method used to detect enol formation.[2,8,10] The less stable tautomer is generated by quenching a solution of the conjugate acid or base of the substrate in a buffer of pH intermediate between its acidic and basic pK_a values.[11] Rapid proton transfer to or from nitrogen yields the imine from the base and enaminone from the acid, and tautomerisation follows at a convenient rate for measurement by stopped flow. Reactions may be observed in this way provided that ionisation



Scheme 1.

of the stable tautomer occurs in sufficiently dilute solutions of OH^- or H^+ (< 0.1 M) for convenient subsequent neutralisation.

Scheme 1 shows that measured rate constants consist either of a single rate constant for a 'slow' proton transfer to or from carbon or of the product of such a rate constant and an equilibrium constant for proton transfer between electronegative atoms. To compare rates with equilibria, rate and equilibrium contributions need to be separated and this paper shows how kinetic measurements may be used to evaluate the otherwise difficultly accessible ionisation constants of the thermodynamically unstable tautomeric species. Evidence supporting the mechanism of Scheme 1 is presented.

Results

Buffer Measurements.—Measured first-order rate constants for tautomerisation of 2- and 4-phenacylquinolines in buffer solutions show general acid, general base, and buffer-independent contributions reflected in the rate constants k_{GA}, k_{GB}, and k_o of equation (2). Normally either acid or base

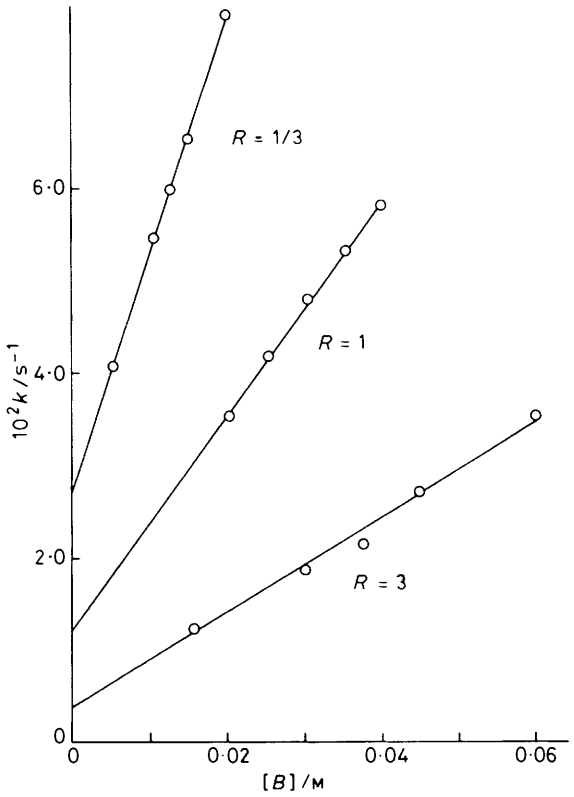
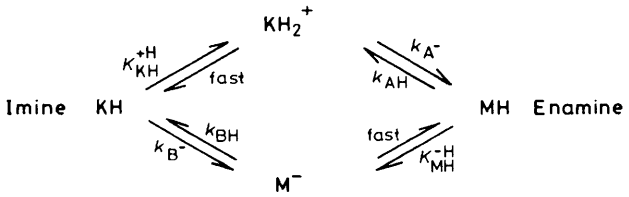


Figure 1. Plot of observed first-order rate constants against buffer base concentration for reaction of 2-phenacylquinoline with 2,6-lutidine buffers at various buffer ratios (R = [B]/[BH$^+$])



Scheme 2.

$$k_{obs} = k_o + k_{GA}[BH^+] + k_{GB}[B] \quad (2)$$

catalysis dominates, but for buffers with pK_a *ca.* 7 both terms are significant. Figure 1 shows plots of k_{obs} *versus* buffer acid concentration [BH$^+$] for reaction of 2-phenacylquinoline with 2,6-lutidine (pK_a 6.77) at different buffer ratios with $k_{GA} > k_{GB}$. The straight lines through the points are based on equation (2) with k_{GA} and k_{GB} chosen to fit the data best (k_o varies with the buffer ratio).

The constants k_{GA} and k_{GB} may be expressed as combinations of rate and equilibrium constants for the individual steps of Scheme 1. These constants are set out in Scheme 2 using a notation based on Toullec's description of keto–enol tautomerisation.[8] KH and MH denote (keto)-imine (sometimes referred to as 'aromatic' imine) and enaminone tautomers (EH would be enol) and K_{KH}^{+H} and K_{MH}^{+H} respectively their acid ionisation constants for proton addition and proton loss; k_{AH} and k_{BH} are rate constants for protonation of the enaminone and its conjugate base by an acid, and k_{A^-} and k_{B^-} the corresponding rate constants for the reverse reactions with base. The subscripts AH and A$^-$ refer to the upper acid-catalysed pathways of the Schemes and BH and B$^-$ to the lower base-catalysed paths. The rate constants refer to the slow steps involving proton transfer to or from carbon and the equilibrium constants to the fast proton transfers to or from nitrogen.

Relationships between k_{GA} and k_{GB} and the rate constants of Scheme 2 are shown in Scheme 3, with K_a the ionisation

Substrate	Observed reaction	k_{GA}	k_{GB}
2-PQ	KH ⟶ MH	$k_{A^-}K_a/K_{KH}^{+H}$	k_{B^-}
4-PQ	MH ⟶ KH	k_{AH}	$k_{BH}K_{MH}^{-H}/K_a$

Scheme 3.

constant of the catalysing acid. The relationship differs for the two substrates because for 2-phenacylquinoline (2-PQ) the enaminone tautomer is the more stable and reaction is observed from right to left in the Schemes, while for 4-phenacylquinoline (4-PQ) the reverse is true. The ratios of forward to reverse rate constants for both acid- and base-catalysed paths give the tautomeric constant K_T = [KH]/[MH]. K_T has been defined for the reverse of the reactions as written and is awkwardly inconsistent with the definition of K_T for keto–enol tautomerism (K_T = [EH]/[KH]).[12]

Strictly speaking k_{GA} and k_{GB} measure sums of forward and reverse rate constants. For 4-phenacylquinoline K_T = 200 is sufficiently large that the expressions of Scheme 3 represent satisfactory approximations, but for 2-phenacylquinoline K_T = 0.08 and an appreciable concentration of the reactant remains at equilibrium: in deriving k_{A^-} and k_{B^-} therefore contributions from the reverse rates need to be considered as shown in equation (3) and (4).

$$k_{B^-} = k_{GB}/(1 + K_T) \quad (3)$$

$$k_{A^-} = k_{GA}K_{KH}^{+H}/[(1 + K_T)K_a] \quad (4)$$

Ionisation of Substrate.—The above analysis assumes that ionised species are present in steady-state concentrations. For reactions involving pre-equilibrium ionisation this ceases to be true as the pH approaches the pK_a of the reactant. Retaining the sense of k_{GA} and k_{GB} as referring to un-ionised reactants, equation (2) is then modified to equation (5) for the acid reaction of keto-imine and to equation (6) for the base reaction of the enaminone. Since (5) and (6) apply only where either acid

$$k_{obs} = k_o + k_{GA}[BH^+]/(1 + [H^+]/K_{KH}^{+H}) \quad (5)$$

$$k_{obs} = k_o + k_{GB}[B]/(1 + K_{MH}^{-H}/[H^+]) \quad (6)$$

or base catalysis is dominant, contributions from alternative pathways may be neglected. Modification of equation (2) in this way leaves the relationships of Scheme 3 and equations (3) and (4) unaffected.

Equations (5) and (6) imply that appreciable ionisation of the reactant will lead to breakdown of the dependence of the observed rate constant on a single buffer species. If reaction of the un-ionised reactant is subject to general base catalysis, reaction of the ionised species will be general acid catalysed and *vice-versa*. Plots of k_{obs} *versus* buffer acid or buffer base concentration then depend on the pH and buffer ratio. Behaviour of this kind was seen for reaction of 2-phenacylquinoline with acetate, pyridine, and 3-hydroxypyridine buffers. The behaviour is distinguished from that arising from competing acid and base pathways without ionisation, seen in Figure 1, from the different pH ranges at which the two phenomena are observed.

From the pH dependence of the buffer catalysis the pK_a of the substrate may be determined. The observed rate constants at different pHs are fitted to equation (5) with k_{GA} and K_{KH}^{+H} chosen to best fit the experimental points. In this way the pK_a of the thermodynamically unstable tautomeric species is obtained. In practice pK_{KH}^{+H} for *N*-protonation of the aromatic imine form of 2-phenacylquinoline is not very precisely determined, but the value of *ca.* 4.5 obtained agrees satisfactorily with more precise independent measurements.

O-*Protonation of Enaminone.*—For 4-phenacylquinoline in acetic acid buffers the pH dependence of the buffer catalysis also points to the occurrence of substrate protonation. In this case, however, the reactant tautomer is the enaminone and proton transfer occurs in the first and rate-determining step of the reaction so there is no scope for pre-equilibrium protonation. The behaviour is interpreted in terms of *O*-protonation of the carbonyl group to yield protonated enol in competition with the slower reaction at carbon. The reaction is shown in equation (7)

$$EH_2^+ \underset{\text{fast}}{\overset{[H^+]/K_{MH}^{+H,O}}{\rightleftharpoons}} MH \underset{\text{slow}}{\overset{k_{GA}[H^+]}{\rightleftharpoons}} KH_2^+ \qquad (7)$$

with EH_2^+ denoting the *O*-protonated species and $K_{MH}^{+H,O}$ cumbersomely representing its acid dissociation constant to enaminone. Equation (7) implies a relationship between k_{obs} and the rate constant for general acid catalysis k_{GA} [equation (8)] similar to that for the pre-equilibrium protonation

$$k_{obs} = k_o + k_{GA}[BH^+]/(1 + [H^+]/K_{MH}^{+H,O}) \qquad (8)$$

[equation (5)] and allows separation of k_{GA} and the ionisation constant for *O*-protonation (pK_a 4.5) in the same way. For more acidic buffers, such as chloroacetic, *O*-protonation becomes complete, equation (8) reduces to equation (9) (in which K_a is

$$k_{obs} = k_o + k_{GA}[B]K_{MH}^{+H,O}/K_a \qquad (9)$$

the dissociation constant of the buffer acid), and the prevailing buffer catalysis changes to general base. Once pK_a values for pre-equilibrium and *O*-protonation have been determined values of k_{GA} and k_{GB} for each buffer may be obtained from equations (2), (5), (6), (8), or (9). These values are converted into rate constants k_{AH}, k_{A^-}, k_{BH}, and k_{B^-} of Scheme 2 for proton transfer to carbon using the relationships of Scheme 3 and equations (3) and (4).

Scheme 3 formally includes only rate constants for the thermodynamically favourable directions. Rate constants for the reverse reactions (*i.e.* k_{A^-} from k_{AH} and k_{B^-} from k_{BH} or *vice versa*) may be obtained from equation (10) provided that the

$$\frac{k_{AH}K_{KH}^{+H}}{k_{A^-}K_a} = \frac{k_{BH}K_{MH}^{-H}}{k_{B^-}K_a} = K_T \qquad (10)$$

equilibrium constant for tautomerisation K_T is known. Values of K_T may be determined either directly or, as outlined in the earlier paper,[6] from ratios of acid or base ionisation constants of stable and unstable tautomeric species. Ionisation constants of the stable species can be measured by conventional methods and, for 2-phenacylquinoline, the pK_a of the unstable keto-imine is reliably estimated as 4.8 from a free-energy correlation of the effects of 2-substitution in pyridines and quinolines.[1] This value is confirmed by the kinetically determined, if less accurate, values of 4.4—4.6 from the pH and buffer dependence of tautomerisation in pyridine, 3-hydroxypyridine, and acetate buffers and yields pK_T −1.09. For 4-phenacylquinoline the most satisfactory determination of K_T is from direct measurement of the back reaction by iodination (see below), which gives pK_T 2.30. Rate constants k_{AH}, k_{A^-}, k_{BH}, and k_{B^-} based on these values are listed for a variety of buffer acid and base species (mainly carboxylic acids and tertiary amines) in Table 3.

Reactions of H^+ *and* OH^- *Ions.*—The kinetics of catalysis by H^+ and OH^- are in principle similar to those for reaction of weaker acids or bases. First-order rate constants k_o may be obtained either from direct measurements in HCl or NaOH solutions, or as intercepts from buffer plots [equation (2)]. Values are listed in Tables 1 and 2.

Where no rapid ionisation precedes rate-determining proton transfer a simple first-order dependence on $[H^+]$ or $[OH^-]$ is expected and observed, *e.g.* for the reaction of 2-phenacylquinoline with hydroxide ion. When pre-equilibrium ionisation occurs it is reflected in a change in kinetic order with respect to $[H^+]$ or $[OH^-]$ in the same manner as for buffer catalysis. For the reaction of 2-phenacylquinoline with H^+ [*cf.* equation (11)] two changes in kinetic order can be expected: the first as

$$KH \overset{[H^+]/K_{KH}^{+H}}{\rightleftharpoons} KH_2^+ \underset{k_{-1}[H^+]}{\overset{k_1}{\rightleftharpoons}} MH \qquad (11)$$

the pH approaches the pK_a of the keto-imine reactant (KH), causing a change of reactant from neutral to protonated species (KH_2^+), and the second as the pH approaches the pK_a of the product and reaction of the protonated substrate becomes reversible. At pH values less than the pK_a of the product the only observable reaction is protonation of the thermodynamically stable enaminone. Under these conditions what was the product of reaction at higher pH values becomes the reactant.

Equation (12) describes the kinetic dependence upon $[H^+]$

$$k_o = \frac{k_1}{1 + K_{KH}^{+H}/[H^+]} + k_{-1}[H^+] \qquad (12)$$

over this pH range. At higher pHs where the reaction is reversible, the second term of (12) becomes unimportant, while at lower pH values the first simplifies to k_1. Values of k_1 and k_{-1} may be determined from a best fit of (12) to the measured rate constants, with pK_{KH}^{+H} assigned its measured value[6] of 4.82. The rate constants are listed in Table 3, making use of the notation for buffer rate constants in terms of which k_1 and k_{-1} correspond to k_{AH} for H^+ and k_{A^-} for H_2O, respectively. The behaviour may be represented on a log *k*–pH profile and

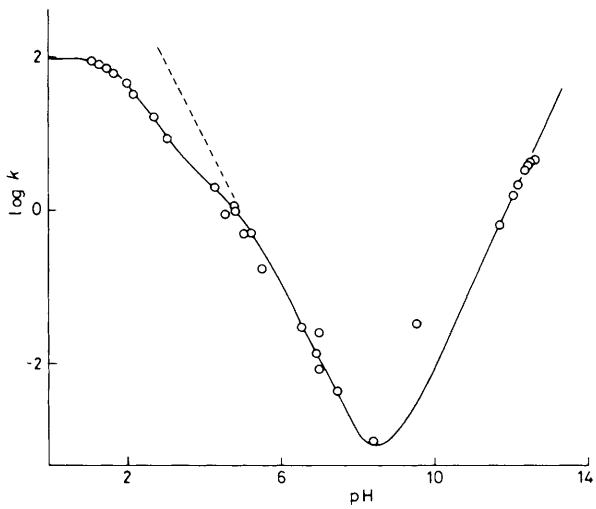


Figure 2. pH profiles for tautomerisation of 2-phenacylquinoline to its enaminone (○) and protonation of its *N*-methyl derivative (●). The lines are calculated

Table 1. Slopes (k) and intercepts (k_o) of plots of measured first-order rate constants against buffer acid concentration at 25 °C for constant buffer ratios and ionic strength 0.1

2-Phenacylquinoline			
Buffer	pH	k/l mol^{-1} s^{-1}	10^2 k_o/s^{-1}
Acetate	4.35	158	210
	4.82	221	110
	5.27	336	50
3-Hydroxypyridine	4.37		200
	4.84		100
	5.37		
Pyridine	4.60	49.4	90
	5.04	62.4	50
	5.48	81.5	17
2,6-Lutidine	6.42	0.83	2.9
	6.92	1.14	1.3
	7.42	1.51	0.43
2-(*NN*-Dimethylamino)-propiononitrile	6.72	12.5	
	7.21	15.7	
	7.71	20.5	
Imidazole	6.50	2.43	2.50
	6.95	2.83	0.8
	7.45	3.15	0.1
Borate	8.52	0.13	0.09
4-Aminopyridine	8.74	0.89	
NN-Dimethylbenzylamine	9.12	23.1	3.2
4-Aminopyridine	9.17	2.56	
	9.51	6.47	1.7
2-(*NN*-Dimethylamino)ethanol	9.47	18.5	
Phenoxide	9.80	223	
Trimethylamine	9.30	27.1	
	9.72	75.2	
	10.16	226	

4-Phenacylquinoline[a]			
Buffer	pH	k/l mol^{-1} s^{-1}	10^2 k_o/s^{-1}
Cyanoacetate	2.09	192	18.5
Chloroacetate	2.27	282	18.5
Glycolate	3.16	365	19.2
Acetate	4.03	700	14.1
	4.61	969	8.0
	5.22	1 360	1.9
	(4.03)[b]		
	(4.66)[b]		
Imidazole	6.51	34.4	0.22
	7.57	37.2	0.065
2,6-Lutidine	6.50	9.4	0.17
	6.92	19.6	0.17
Borate	8.8	2.95	0.08
	9.44	7.8	0.60
Phenoxide	9.71	9 400	
NN-Methyl-2-PQ-enaminone[c]			
Acetate	5.22	120	0.29
Lutidine	6.84	11.6	0.086
Imidazole	7.74	62	0.23
N-Methyl-4-PQ-enaminone[c]			
Acetate	4.03	1 040	6.9
	4.64	1 000	2.1
	5.21	260	1.6
Imidazole	7.69	104	

[a] Rate constants for reaction of the enaminone to imine except as indicated. [b] Rate constants for iodination of 4-phenacylquinoline imine. [c] PQ = phenacylquinoline.

Table 2. Rate constants for reaction of 2- and 4-phenacylquinoline and their *N*-methylenaminones with hydrogen and hydroxide ions

2-Phenacylquinoline									
N–Me				N–H					
10^2[H$^+$]/M	k_H[a]/s^{-1}	10^2[OH$^-$]/M	k_{OH}[b]/s^{-1}	10^2[H$^+$]/M	k_H[c]/s^{-1}	10^2[OH$^-$]/M	k_{OH}/s^{-1}	10^2[OD$^-$]/M	k_{OD}/s^{-1}
0.05	5.71	0.125	586	0.1	8.5	0.5	0.65	0.5	0.15
0.1	7.35	0.25	316	0.2	16.3	1.0	1.49	1.0	0.30
0.2	8.77			0.5	32	1.5	2.15	1.5	0.525
0.3	9.91			1.0	46	2.0	3.17	2.0	0.67
0.45	10.7			2.0	66	2.5	3.71	2.5	0.69
0.7	10.3			3.0	72.1	3.0	3.95	3.0	0.89
0.95	10.3			5.0	82.8	3.5	4.40	3.5	0.99
1.45	10.95			8.0	91.0				
2.45	11.25								

4-Phenacylquinoline							
N–Me				N–H			
0.1	9.76	0.049	13.1	0.25	13.5	0.5	5.38
0.2	9.54	0.073	19.6	0.5	14.4	1.0	5.63
0.3	9.27	0.098	25.8	1.0	14.0	1.5	5.98
1.0	9.46	0.147	40.4	1.5	14.5		
				2.0	15.8		
				3.0	15.8		

[a] λ 400 nm; rate constant slightly dependent on λ. [b] *N*-Methylquinolinium ion is reactant. [c] 400 nm; independent of λ.

Table 3. Rate constants[a] for reaction of 2- and 4-phenacylquinoline, their *N*-methylenaminones, and their conjugate acids and bases with oxygen and nitrogen acids and bases in aqueous solution at 25 °C

		2-Phenacylquinoline						4-Phenacylquinoline					
		N-Me		N-H				N-Me		N-H			
Acid (AH of BH)[b]	pK_a	k_{AH}[c]	k_{A^-}[d]	k_{AH}[c]	k_{BH}[e]	k_{A^-}[d]	k_{B^-}[f]	k_{AH}[c]	k_{A^-}[d]	k_{AH}[c]	k_{BH}[e]	k_{A^-}[d]	k_{B^-}[f]
H_3O^+	−1.74	3.6×10^4	$4.5 \times 10^{-2}/55.5$	1.0×10^4		2.0/55.5[g]		1.6×10^5	$1.6 \times 10^{-2}/55.5$	4.0×10^5		$1.1 \times 10^{-2}/55$	
$NCCH_2COOH$	2.43									2.23×10^4		0.173	
$ClCH_2COOH$	2.86									1.85×10^4		0.387	
$HOCH_2COOH$	3.83									3.0×10^3		0.585	
CH_3COOH	4.76	372	26.9	48.6		521		1.02×10^3	5.61	1.37×10^3		2.27[g]	
3-Hydroxypyridinium	4.86			88.2		1 190							
Pyridinium	5.17			11.1		305							
2,6-Lutidinium	6.77	1.38	10.2	0.061	8.07×10^4	66.4	0.300	11.62	6.53	5.95	2.72×10^4	1.01	0.0683
$NCCH_2CH_2NHMe_2^+$	7.0			0.88	4.9×10^5	1 640	3.09						
Imidazolium	7.2	3.05	60.9	0.184	2.23×10^4	544	0.223	14.7	22.2	26.3	2.25×10^4	12.02	0.152
$PhCH_2NHMe_2^+$	8.93				4.08×10^4		21.9						
4-Aminopyridinium	9.11			0.016	3.75×10^3	3 910	3.04						
Boric acid	9.24							4.67×10^{-2}	7.75		53		0.0391
$HOCH_2CH_2NMe_2H^+$	9.26				1.49×10^4		17.1						
Me_3NH^+	9.76				1.82×10^4		66.0						
PhOH	9.95				3.66×10^3		20.6				3.72×10^3		14.1
H_2O	15.74	$2.0 \times 10^3/55.5$	2.5×10^5	$5 \times 10^{-5}/55.5$[h]	3.3/55.5		140	$2.80 \times 10^{-3}/55.5$	2.68×10^4	$1.3 \times 10^{-4}/55.5$[h]	3.8/55.5[h]		185

[a] Units l mol^{-1} s^{-1} including rate constants for H_2O. [b] AH and BH are designations of acid used in subscripts to rate constants. A^- and B^- refer to conjugate base. [c] For reaction of acid with enaminone. [d] For reaction of base with protonated imine. [e] For reaction of acid with enaminone anion. [f] For reaction of base with imine. [g] In this case k_{A^-} was measured directly by iodination. Other values of k_{A^-} for 4-phenacylquinoline are derived from k_{AH} and $pK_T = 2.30$. [h] Estimated from values of k_{NH}/k_{NMe} for other acids and their dependence on pK_a.

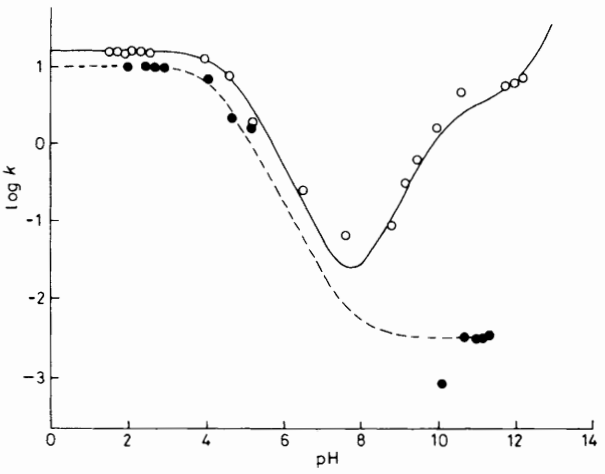


Figure 3. The pH profiles for tautomerisation of 4-phenacylquinoline enaminone (○) and protonation of its *N*-methyl derivative (●). The lines are calculated

corresponds to the double inflection in the left hand (low pH) branch of the profile for 2-phenacylquinoline in Figure 2.

At higher concentrations of H^+ there is a further change in kinetic order from first to zeroth, consistent with the onset of a second protonation equilibrium. In this pH region the enaminone is the reactant and, as for 4-phenacylquinoline in acetic acid buffers, the behaviour is ascribed to kinetically controlled *O*-protonation forming protonated enol. Modification of equation (12) to include this behaviour gives (13) with $K_{MH}^{+H,O}$ the ionisation constant of the *O*-protonated species. Only the second term of (13) is important at pHs where *O*-

$$k_o = \frac{k_1}{1 + K_{KH}^{+H}/[H^+]} + \frac{k_{-1}[H^+]}{1 + [H^+]/K_{MH}^{+H,O}} \qquad (13)$$

protonation occurs, and from a best fit of this term to the measured rate constants a value of 2.0 is derived for $K_{MH}^{+H,O}$. On the pH profile of Figure 2 the behaviour corresponds to the transition to a limiting pH-independent reaction at low pH. The calculated line in Figure 2 is based on equation (13) + $k_{OH}[OH^-]$.

For the tautomerisation of 4-phenacylquinoline, the enaminone is the reactant throughout the acid pH range. There is thus no pre-equilibrium *N*-protonation, but *O*-protonation causes a change in kinetic order analogous to that for 2-phenacylquinoline as indicated by equation (14) and shown in the pH

$$k_o = \frac{k_{-1}[H^+]}{(1 + [H^+]/K_{MH}^{+H,O})} \qquad (14)$$

profile of Figure 3. A best fit of measured rates to equation (14) gives k_{-1} (k_A for H^+) 1.6×10^5 and a pK_a for *O*-protonation of 4.5 (compared with 4.0 from acetic acid buffers).

Between pH values 6 and 8 H^+ catalysis for 4-phenacylquinoline changes to catalysis by OH^- with no indication of a pH-independent reaction. At higher pH (9—13) the kinetic dependence mirrors that of 2-phenacylquinoline at low pH values (except for *O*-protonation) and the order in hydroxide ion changes from first to zero and back to first again. As shown in equation (15) the first change may be ascribed to ionisation

$$MH \underset{}{\overset{K_a[OH^-]}{\rightleftharpoons}} M^- \underset{k_{-1}[OH^-]}{\overset{k_1}{\rightleftharpoons}} KH \qquad (15)$$

of the reactant, with a change in reactant from the neutral enaminone (MH) to its anion (M^-), and the second to increasing dominance of the back reaction of keto-imine (KH) to its anion. At pH values above the pK_a of the imine, reaction is observed from right to left with imine as reactant. The behaviour is described by equation (16), the basic counterpart (with

$$k_o = \frac{k_1}{1 + K_b/[OH^-]} + k_{-1}[OH^-] \qquad (16)$$

enaminone rather than imine as reactant) of equation (12). A best fit to equation (16) gives k_1 and k_{-1} and a value of $-\log(K_w k_1/k_{-1}) = pK_{KH}^{+H} = 12.5$, the p$K_a$ for ionisation of the imine in basic solution, which is in good agreement with the directly determined spectrophotometric value in the same OH^- concentration range, *i.e.* 12.37.[1] Values of k_1 and k_{-1} correspond to k_{BH} and k_{B^-} for H_2O and HO^- and are listed in Table 3. For the full range of basic pH values a best fit of equation (16) to the measured rate constants gave pK_b 3.6 [corresponding to a pK_a (pK_{MH}^{-H}) of 10.4] for ionisation of the unstable enaminone. This agrees well with the best value of 10.7 based on measurements of K_T described below. Again the behaviour appears as a double inflection on the pH profile as seen in Figure 3, but in contrast to Figure 2 the inflection occurs on the high rather than low-pH branch of the profile. The calculated line in the profile is based on equation (16) + $k_H[H^+]$.

For 2-phenacylquinoline measurements were also made for reaction of deuteriated substrate with DO^- in D_2O and these rates are included in Table 2. The derived isotope effect k_H/k_D = 4.6. This shows the expected presence of a primary contribution but because reversible tautomerisation leads to exchange of the methylene group in the keto-imine, reaction of the deuteriated substrate could not be measured in H_2O, and the primary effect is modified by an inverse solvent contribution ($k_{OH^-}/k_{OD^-} < 1$) as well as by a secondary effect [equation (17)].

$$QCD_2COPh + OD^- \longrightarrow QCD{=}\overset{O^-}{\overset{|}{C}}{-}Ph \qquad (17)$$

(Q = 2-quinolyl)

Brönsted Plots.—Figure 4 shows Brönsted plots for 2- and 4-phenacylquinoline. That for the 4-isomer refers to protonation of the enaminone by carboxylic acids (k_{AH} in Table 3) with slope α = 0.56: the point for H_3O^+ (not shown) falls below a linear extrapolation of the plot by a factor of 18 if its pK_a is taken as −1.74. For 2-phenacylquinoline the plot is for proton transfer from 2-phenacylquinoline to substituted dimethylamine bases (k_{B^-}) with slope β = 0.44. The Brönsted plots are confined to carboxylic acids and substituted dimethylamines to allow correlation lines to be based on reasonably homogeneous sets of acid and base structures. Other acids and bases deviate significantly from the plots. For example borate and lutidine show strong negative deviations; however, their buffers are convenient for investigating buffer-independent rate contributions at near-neutral pH values.

N-Methylphenacylquinolines.—Reaction of *N*-methylenaminones of 2- and 4-phenacylquinolines were observed as protonations to form their conjugate acids or as the reverse deprotonations (Scheme 4) from appearance or disappearance of the enaminone chromophore. For reactions at pH values less than the pK_a values (3.7 for the 2-isomer and 7.0 for the 4-isomer) the neutral species form the reactants and the kinetic behaviour is analogous to that for reaction of the 4-phenacylquinoline enaminone at acidic pH values. *O*-Protonation of both isomers is observed with the kinetics described by equations (7) and (8) for acetic acid buffers (4-isomer only) and

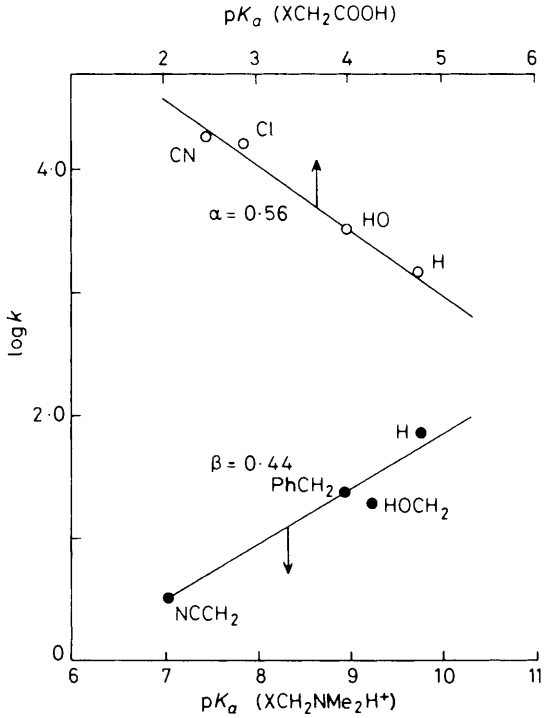
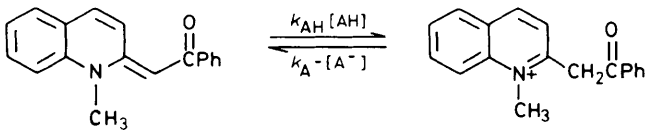


Figure 4. Brönsted plots for reaction of 4-phenacylquinoline enaminone with carboxylic acids (k_{AH}) (○) and 2-phenacylquinoline with tertiary amines (k_{B^-}) (●)

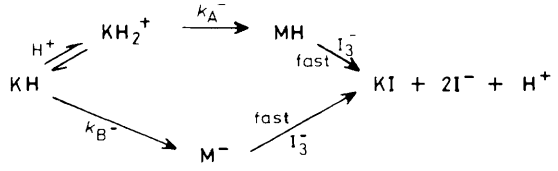


Scheme 4.

by equation (14) for reactions with H^+. Slopes and intercepts of buffer plots are included in Table 1. Equilibrium constants for *O*-protonation and rate constants for *C*-protonation ($k_{GA} = k_{AH}$) were derived from best fits of the appropriate equation to the first-order rate measurements as before. The pK_a values measured were identical with that for the N–H enaminone in the case of the 4-isomer (4.2), and somewhat larger than for the N–H enaminone for the 2-isomer (3.5 compared with 2.0).

For reactions at pH values less than the pK_a values, the protonated species form the reactants and a simple first-order kinetic dependence on buffer base or hydroxide ion concentrations was observed, yielding rate constants $k_{GB} = k_{A^-}$. For an acid or base for which either k_{AH} or k_{A^-} was measured directly the corresponding value of k_{A^-} or k_{AH} was obtained from the pK_a for *C*-protonation using the relationship $K_a = k_{A^-}/k_{AH}$ implied in Scheme 4. Values of k_{A^-} and k_{AH}, for H^+, OH^-, and H_2O as well as acetate, imidazole, lutidine, and borate buffers are included in Table 3. The pH profiles are shown in Figures 2 and 3 and refer to reaction from left to right in Scheme 4. Thus the observed reaction of *N*-methyl cation with hydroxide ion is shown as the reverse protonation of *N*-methylenaminone by water.

Iodination of 4-Phenacylquinoline.—When the aromatic imine is the more stable tautomer, as in the case of 4-phenacylquinoline, its rate of ionisation to anion, or acid-catalysed conversion into enaminone, may be measured by trapping the product with iodine. By analogy with iodination of simple

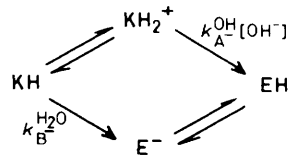


Scheme 5.

ketones,[2,8-10] attack of iodine occurs in a rapid step and, for reaction in buffers, measured rate constants for general acid or base catalysis correspond to the reverse of the reactions seen in the directly observed tautomerisation of 4-phenacylquinoline enaminone to imine.

The reaction steps are shown in Scheme 5 with KI denoting the iodinated ketone (*sic*). For 4-phenacylquinoline, kinetics were measured spectrophotometrically from the decrease in absorbance of I_3^-, and, with iodide ion and substrate in large excess, showed the normal zero-order kinetics. In acetic acid buffers the reaction was subject to general base catalysis corresponding to base attack on the dominant protonated form of the substrate present at the prevailing pH values. The reactions were fast and were measured by stopped flow. Measurements of slower rates were possible under first-order conditions with a small excess of I_3^- over substrate, and the rate constants obtained agreed with those from the zero-order conditions; slopes and intercepts for measurements in acetate buffers are included in Table 1. The second-order rate constant for reaction with acetate k_{GB} corresponds to the molecular rate constant k_{A^-} and is listed in Table 3.

Water Reactions.—The possibility of contributions from uncatalysed 'water' reactions in addition to hydroxide and hydrogen ion contributions was investigated. Kinetic measurements with the weakly catalytic lutidine and borate buffers in the pH range 6—9 were extrapolated to zero buffer concentration, and rate constants were measured directly in neutral, unbuffered, aqueous solutions. For neither 2- or 4-phenacylquinoline was evidence of a significant pH-independent rate found. This indeed is consistent with estimates that may be made of rate constants for the possible stepwise water reactions. As shown in Scheme 6, for the aromatic keto-imine a pH-



Scheme 6.

independent reaction could occur by rate-determining attack of hydroxide ion upon an equilibrium concentration of protonated reactant (KH_2^+) or by direct attack of water on the imine itself. Rate constants for the first pathway can be predicted from the measured rate constants for hydroxide attack on the corresponding *N*-methyl cations combined with ratios of N–H to *N*-methyl reactivities estimated from measurements for other bases (and their pK_a dependence) as 3×10^{-4} and 10^{-3} s^{-1} for 2- and 4-phenacylquinoline, respectively. These values are less than the corresponding minimum first-order rate constants for hydroxide and hydrogen ion catalysis of 10^{-3} and 3×10^{-2} s^{-1}, respectively.

The second reaction pathway is less firmly excluded but if it were assumed that the rates are ten times greater than the minimum combined H^+ and OH^- contributions this would

imply rate constants for water attack on 2- and 4-phenacylquinoline that are only 5 and 100 times respectively greater than for attack on the corresponding protonated substrates. The minimum reactivity difference between neutral and protonated species for stronger bases than water are respectively 15 and 200 times (for lutidine). These ratios should provide lower limits for the weakly basic water molecule so no more than a marginal influence from such reactions could be expected.

Discussion

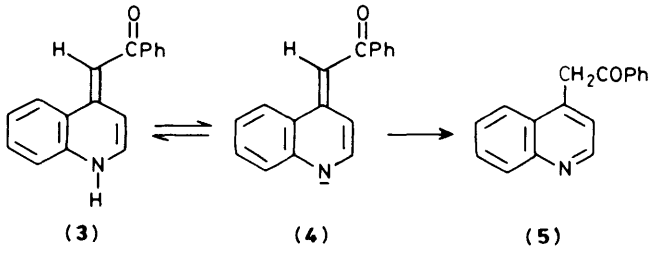
Mechanism of Tautomerism.—Kinetic measurements provide ample evidence for the mechanisms of imine–enamine tautomerisation of 2- and 4-phenacylquinolines shown in Scheme 1. Measurements with buffers indicate general acid- and general base-catalysed pathways consistent with fast and slow proton-transfer steps and formation of the conjugate acid or base of the substrate as intermediates. Buffer rate constants yield normal Brönsted plots with β *ca.* 0.44 for reaction of 2-phenacylquinoline with tertiary amine bases and α *ca.* 0.56 for protonation of 4-phenacylquinoline enaminone by carboxylic acids (Figure 4). Reaction of 2-phenacylquinoline with hydroxide ion shows the expected primary isotope effect.

For 2-phenacylquinoline the stable tautomer is the enaminone and reaction is observed from left to right in Scheme 1. For reaction by the acid-catalysed pathway the imine reactant is protonated in a rapid pre-equilibrium and, from the pH dependence of buffer catalysis in pyridine or acetic acid buffers, a pK_a of *ca.* 4.6 is indicated for the process. This pK_a agrees with a value of 4.82 for *N*-protonation of the reactant estimated from a free-energy correlation of substituted quinolines and pyridines.[1] The ease of reaction implies that the *N*-protonated (rather than *O*-protonated) species is an intermediate.

Protonation of the substrate is also seen from the pH profile. For 2-phenacylquinoline the pH profile in Figure 2 shows, in addition to the predominant H^+- and OH^--catalysed reactions, two inflexion points at mildly acidic pH values. This is characteristic of tautomerisation reactions proceeding *via* conjugate acid or base intermediates common to both tautomers. The first inflexion from slope -1 to 0 with decreasing pH reflects protonation of the reactant (pK_a 4.8) and the second from 0 back to -1 protonation of the product (pK_a 3.7). At pH values below the pK_a of the product, reaction is observed only in the 'reverse' direction as an H^+-dependent protonation of the enaminone tautomer.

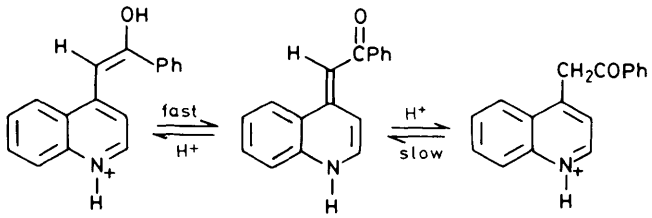
In contrast to the acid region no breaks are expected or occur in the base region of the pH profile because here the initial proton transfer to hydroxide ion is rate determining. For 4-phenacylquinoline however, for which the imine forms the stable tautomer and reaction is observed from right to left in Scheme 1, the situation is reversed. Now the conjugate base in the hydroxide reaction is formed in a pre-equilibrium and the pH profile shows inflexion points at high pH (Figure 3) corresponding to the changes in reactant species from enaminone (**3**) to its anion (**4**) to imine (**5**) in Scheme 7. It yields pK_a values for the enaminone and aromatic imine tautomers of 10.4 and 12.4, respectively. There are no comparable inflexions at acidic pH values.

O-Protonation of Enaminone Tautomers.—A further feature of the pH profiles of both 2- and 4-phenacylquinoline is the appearance of limiting pH-independent reactions at low pH. This is interpreted as diffusion-controlled *O*-protonation of the enaminone reactant (**7**) to yield protonated enol (**6**), preceding slower formation of the more stable *C*-protonated species (**8**) which at the pH values in question forms the product of the reaction. For 4-phenacylquinoline this protonation is inferred from the pH dependence of catalysis by carboxylic acid buffers.



(3) (4) (5)

Scheme 7.



(6) (7) (8)

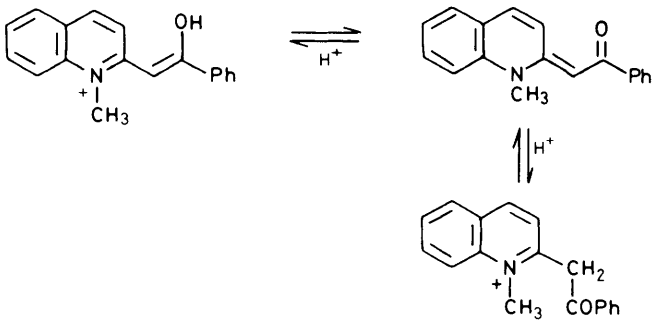
Scheme 8.

This interpretation is supported by the facts that oxygen provides the only likely site for rapid protonation and that for aliphatic enaminones it is the thermodynamically favoured reaction.[13]

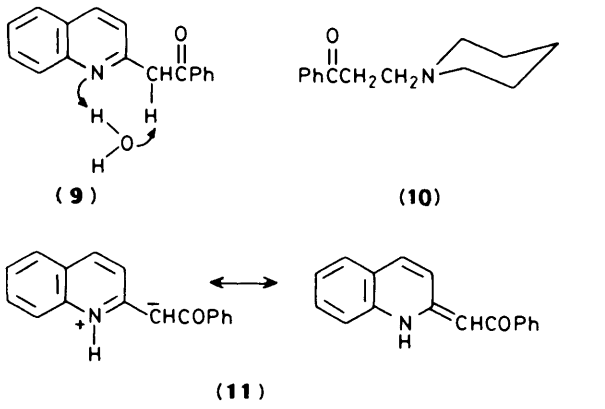
For 2-phenacylquinoline the pH profile yields pK_a 2.0 for *O*-protonation which, when combined with pK_a 3.7 for *C*-protonation, gives a keto–enol tautomerisation constant pK_T of 1.7 indicating the presence of *ca.* 2% enol in the predominantly ketonic protonated substrate. This is consistent with the appearance of a weak absorption at 390 nm in acidic solutions of 2-phenacylquinoline, the intensity of which is consistent with a normal extinction coefficient ε *ca.* 10^4 for this species. Comparable absorptions are seen in solutions of other acylquinoline and -pyridine derivatives, especially in trifluoroacetic acid solutions where n.m.r. measurements by Rosario and Mondelli support assignment of the enol structure.[14] For 4-phenacylquinoline the fraction of protonated enol is much smaller (pK_T 3.3) and no corresponding u.v. absorption is seen.

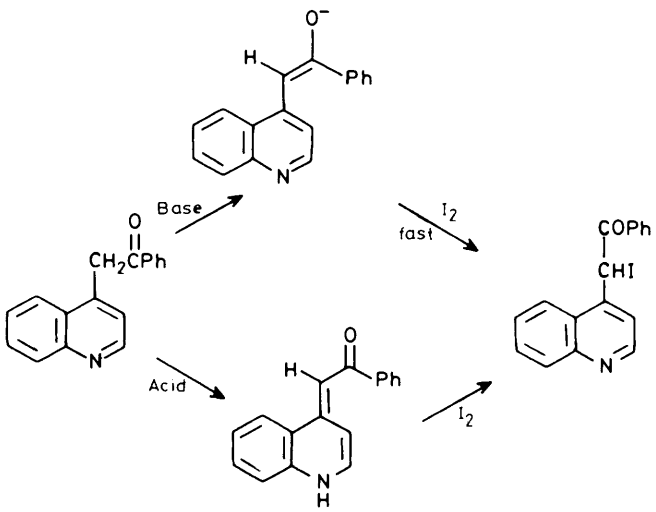
N-Methylenaminones.—The mechanisms of the acid-catalysed pathway of Schemes 1 and 8 are corroborated by comparison with the corresponding reaction of *N*-methyl-2- and -4-enaminones (Scheme 9). Rate constants are compared in Table 3, and Figure 3 illustrates the similar pH dependences at low pH values for the N–H and *N*-methyl-4-enaminones. The pH profiles imply identical pK_a values for *O*-protonation of the N–H and *N*-methyl-4-isomers and values of 2.0 and 3.5, respectively, for the N–H and *N*-methyl-2-isomers. At higher pH values the profiles diverge because *N*-methylation precludes reaction of enaminones with base. However, reaction with hydroxide ion is seen for the protonated *N*-methyl species (though not observable for the N–H) and the pH-independent rate appearing at intermediate pH values in Figure 3 (dashed line) corresponds to the reverse of this reaction, protonation of the enaminone by water.

Absence of 'Water' Reactions.—The small rate constant for the water reaction of the 4-*N*-methylenaminone in Figure 3 confirms that no such reaction could compete with the hydroxide-catalysed tautomerism of the N–H species and the same is true of the 2-isomer. The alternative possibility of water attack as a base on the aromatic imine tautomer is also made unlikely by the small rate constants of the corresponding reactions with the more reactive protonated species.



Scheme 9.





Scheme 10.

More interestingly the absence of a pH-independent reaction for 2-phenacylquinoline (apparent from the pH profile of Figure 2) also precludes a concerted 1,3-hydrogen transfer. Instances of such reactions, which presumably would occur *via* a water molecule, have been discussed recently by Bernasconi[15] who has also considered what factors would allow the process to compete with stepwise reactions of H^+, OH^-, and H_2O.

Clearly of importance in determining an intramolecular rate is the effective molarity of the base. Bernasconi argues that a reasonable lower limit for the ionisation of ketones is 3×10^{-3}M. For 2-phenacylquinoline, pyridine provides a reasonable model for the base and an expected intramolecular rate constant is then most obviously predicted to be 3×10^{-3} times the rate constant k_B^- for reaction of pyridine with 2-phenacylquinoline. However, as Bernasconi points out, electrostatic and resonance interactions between acid and base centres of the product (**11**) gives a thermodynamic advantage to the intramolecular reaction which compensates in some degree for its low effective molarity. Thus for (**9**) $\Delta pK = -1.1$ (the log of the tautomerisation constant) compared with $\Delta pK = +7$ for the intermolecular reaction with pyridine. More appropriate[15] then is 3×10^{-3} times the rate constant k_A^- for the reaction of pyridine with *N*-protonated phenacylquinolinium ion, which from Table 3 (k_A^- 305) gives an intramolecular rate constant of *ca.* 1.0 s^{-1}.

Inspection of Figure 2 shows that the calculated rate is 1 000 times greater than the minimum rate observed from the pH profile. The fact that nevertheless no intramolecular reaction is seen may mean that the strong resonance between acid and base centres in the enamine (**11**), which strongly stabilises the product and leads to a high calculated intramolecular rate constant, also creates an unfavourable geometry for proton transfer. By contrast Bernasconi's examples of 1,3-hydrogen transfer comprise anionic or neutral and zwitterionic species without charge delocalisation between tautomeric centres. On the other hand intramolecular proton transfer also appears to be absent for β-piperidinopropiophenone (**10**)[16] where it might have been expected. It appears that further work will be required to establish the scope of these reactions.

4-Phenacylquinoline: the Reverse Reaction.—Assuming that the mechanism is similar to that for simple ketones[2,8-10] (Scheme 10) rate constants for iodination correspond to the reverse of the reaction measured from relaxation of the unstable enaminone. The ratio of relaxation to iodination rate constants then yields the tautomeric constants K_T for enamine–imine conversion. From measurements in acetic acid buffers the value of log K_T so obtained is -2.3, which is in reasonable or good agreement with indirectly estimated values of -1.8 and -2.3 based on pK_a measurements and apparent extinction coefficients using the *N*-methyl derivative as model for the less stable enaminone tautomer.[1] Direct evaluation of K_T by iodination is useful. From measurements of acidic and basic pK_a values of the stable tautomer all the equilibrium constants of Scheme 1 may be derived using the relationship of equation (18) in which K_a^{KH} K_a^{MH} are either acidic or basic pK_a values of the keto-imine and enaminone tautomers respectively.

$$K_T = K_a^{MH}/K_a^{KH} \qquad (18)$$

From equation (18) the pK_a for ionisation of 4-phenacylquinoline enaminone in basic solution is 10.07. The agreement between this value and pK_a 10.4 from the pH profile of Figure 4 confirms both that the enaminone anion is an intermediate in the hydroxide-catalysed tautomerisation and that the iodination does indeed measure rates of enamine-into-imine conversion.

Equilibrium Constants.—Best values of ionisation and tautomeric constants are listed in Table 4. Comparisons between N–H and *N*-methylenaminones are of interest because *N*-methylenamines are commonly used as models for the N–H species.[12] As discussed previously the rather large difference between N–H and *N*-methyl-2-phenacylquinoline enaminones (pK_a 5.90 and 3.73 respectively) probably reflects a difference of *E* and *Z* configurations, with the *Z* configuration for the N–H derivative stabilised by intramolecular hydrogen bonding.[2] For the 4-enaminones the difference in pK_a values is smaller (7.02 and 7.54) with the *N*-methyl compounds which are more rather than less basic than N–H. This is consistent with the more negative σ^+ for NMe_2 than NH_2 (-1.17 and -1.3)[17] and may be compared with the 30—100-fold greater kinetic basicities of

Table 4. pK_a and tautomerisation constants (K_T) for 2- and 4-phenacylquinoline (PQ) and their N–H and *N*-methylenaminones[a]

		pK_a			pK_T[b]	
		+H(C)[c]	+H(O)[d]	−H	KH/MH[e]	EH_2^+/KH_2^+ [f]
2-PQ	keto-imine	4.82		12.20	−1.09	
	N–H enaminone	3.73	2.0	13.29		1.7
	N–Me enaminone	5.90	3.5			2.4
4-PQ	keto-imine	5.24		12.37	2.30	
	N–H enaminone	7.54	4.2[g]	10.07		3.3
	N–Me enaminone	7.02	4.2			2.8

[a] From present work or ref. 1. [b] $-\log K_T$. [c] *C*-Protonation. [d] *O*-Protonation. [e] Keto-imine–enaminone. [f] Protonated enol–protonated keto-imine. [g] Average of values from pH profile and buffer measurements.

Table 5. The influence of *N*-methylation and anion formation upon kinetic and equilibrium basicities of 2- and 4-phenacylquinoline enaminones (PQ) at 25 °C

		k_{NME}/k_{NH}		k_{N^-}/k_{NH}[a]	
Acid	pK_a	2-PQ	4-PQ	2-PQ	4-PQ
H_3O^+	−1.74	2.5	0.45		
MeCOOH	4.76	7.7	0.74		
2,6-Lutidinium	6.77	22.6	1.95	1.3×10^6	4.6×10^3
$NCCH_2CH_2NMe_2H^+$	7.0			5.6×10^5	
Imidazolium	7.2	16.6	0.56	1.2×10^5	8.6×10^2
(Equilibrium)		147	0.30	3.0×10^8	6.8×10^4

[a] k_{BH}/k_{AH}. Note that for the reverse reaction k_{A^-}/k_{B^-} is the proton activating factor (p.a.f.) for quinoline ring protonation upon proton abstraction of a 2- or 4-methylene hydrogen by base: p.a.f.s[20] for 2-PQ are 220 (lutidine), 530 ($NCCH_2CH_2NMe_2$), 2 440 (imidazole); and for 4-PQ are 15 (lutidine) and 79 (imidazole).

enols than their *O*-methyl ethers,[9] which is again consistent with the relative σ^+ values (−0.92 for OH and −0.78 for OMe) despite the opposite effects of methylation in the two cases.

N-Methylation also influences keto–enol tautomerisation of the protonated species, especially in the case of 2-phenacylquinoline. The relatively high enol content of the protonated ketone (*ca.* 2%; pK_T 1.7) may reflect intramolecular hydrogen bonding and a greater stabilising effect upon enol, relative to ketone, of the more electron-withdrawing annular $C{=}NH^+$ than the $C{=}NCH_3^+$ group. For arylacetaldehydes the enol content in DMSO is increased by electron-withdrawing substituents with $\rho -0.76$.[18] For the other enaminones in Table 4 tautomeric constants (pK_T) fall in the range 2.4—3.3, somewhat closer to the estimate of pK_T *ca.* 4 for phenylacetone.[19]

Reactivity and Selectivity.—Table 5 shows the influence of *N*-methylation and ionisation upon kinetic and equilibrium protonation of 2- and 4-enaminones in terms of ratios of *N*-methyl to N–H (k_{NMe}/k_{NH}) and anionic to neutral (k_{N^-}/k_{NH}) rate and equilibrium constants, listed as a function of pK_a of the reacting buffer acid. For the 2-phenacylquinoline enaminone, N–H to *N*-methyl rate-constant ratios for the acids studied show a roughly inverse dependence on the reactivity of the acid, consistent with limiting selectivities of unity at high reactivity and the equilibrium value at low. This trend is hardly evident for the 4-isomer which by contrast shows only small variations in selectivity.

Table 5 also shows that ionisation of the annular N–H hydrogen is more strongly activating towards *C*-protonation from the 2- than from the 4-position. For the equilibria the factors are 3×10^8 and 7×10^4, respectively, and for rate constants somewhat less than this. Combination of k_{N^-}/k_{NH} values for rates and equilibria reveals that the influence of N–H ionisation upon rates of *C*-protonation of enaminones is significantly greater than upon the reverse reaction of the keto-imine and its conjugate acid with bases (which correspond to proton-activating factors[20] for the keto-imine), *e.g.* 10^6 compared with 10^3 for reaction of the 2-isomer with 2,6-lutidine. This contrasts with the selectivity characteristic of buffer acids and bases, for which Brönsted exponents of close to 0.5 imply similar effects of substituents on the reaction in either direction.

The above behaviour implies an imbalance between substituent effects in the oxygen and nitrogen bases and carbon bases. It is a common feature of proton-transfer reactions,[3,4] the ionisation of nitroalkanes providing the best known example.[21] The phenomenon has been characteristed by Hine as 'imperfect synchronisation' of bonding and structural changes between reactants and transition state relative to reactants and products,[22] and has been suggested as a major factor responsible for variations in 'intrinsic' activation barriers[23] (in the sense used by Marcus[24]) between related reactions. Usually the imbalance implies that charge delocalisation at the reacting carbon lags behind proton transfer, but in this instance the opposite is true. Apparently the keto group competes more effectively with the iminium ion for charge delocalisation at one transition state that in the products. Possibly the reason for this is steric in origin.

Experimental

Syntheses of 2- and 4-phenacylquinolines and their *N*-methyl derivatives have been described.[1] For kinetic measurements they were purified by crystallisation, p.l.c., or 'flash' column chromatography. Buffers were of AnalaR quality or recrystallised at least twice: amine buffers were normally purified as their hydrochloride salts.[25] Water was doubly distilled and protected from atmospheric CO_2: D_2O was distilled from glassware that had been washed in D_2O and baked at 120 °C. AnalaR sodium hydroxide pellets used to prepare solutions of NaOH were washed with water before dissolving.

Spectra and some kinetic measurements were recorded on Perkin-Elmer 124 or Pye–Unicam SP8-400 spectrophotometers. Most kinetic measurements made use of one of two stopped flow-spectrometers, a Durrum 110 or, as in previous work, [26] an instrument designed by Tregloan.[27] The latter comprised drive syringes encased in a thermostatted brass block and employed a stop on the solenoid-triggered pneumatic drive piston in place of the conventional stopping syringe. The optical path length was 2 mm and the instrument was equipped with a Xenon light source which was used for measurement of u.v. absorptions.

Kinetic Measurements.—Kinetic measurements were normally made by following the appearance or disappearance of enaminone or *N*-methylenaminone absorption maxima in the range 430—460 nm. Solutions of 2-phenacylquinoline enam-

inone and the *N*-methyl derivatives of the 2- and 4-enaminones were prepared in aqueous HCl, usually 0.04 or 0.1M. A solution was placed in one reactant syringe of the stopped-flow apparatus and in the other syringe excess of sodium hydroxide or buffer solutions of concentration such that 1:1 mixing would produce the desired buffer concentration and ionic strength (normally 0.1M). Neutralisation of the acid solution of 2-phenacylquinolinium ion gave the neutral imine tautomer, relaxation of which to the stable enaminone was observed kinetically. For the *N*-methyl enaminones the observed reaction was of *C*-protonated substrate with base. The reverse protonation of the N–H and *N*-methylenaminones by acids of lower pK_a was studied by mixing a neutral solution of substrate with a solution of HCl or an acidic buffer. When the solubility of substrates was low a microbalance or dilution from a methanol stock was used for a preparation of substrate solutions. The concentration of methanol in reactant solutions did not exceed 1%.

For 4-phenacylquinoline kinetic measurements were made using a freshly prepared stock solution of its anion in aqueous NaOH, usually 0.04M. This was quenched by stopped flow with a buffer or HCl solution to yield a resultant solution of the desired concentrations at a pH below the pK_a of the substrate (12.37). Neutralisation of the anion leads initially to formation of the enaminone, followed by slower reaction to the stable aromatic imine. For reaction in strong acids where *O*-protonation of the enaminone reactant was extensive, measurements were made at shorter wavelengths than usual to accommodate the shift in absorption maximum accompanying protonation. Under these conditions there were minor indications of departure from first-order kinetics and a wavelength dependence of the rate constants at the highest acid concentrations. The behaviour might reflect kinetically significant interconversion of *E* and *Z* enaminone configurations. However, this was the only hint of possible kinetic complications from configurational differences between phenacylquinoline enaminones and discussion of the influence of enaminone configuration on reactivity is postponed to a later paper.

Kinetic measurements in borate buffers or in neutral solution in the absence of buffers gave reactions slow enough for study in a 10 mm cell by conventional spectrophotometry. For 4-phenacylquinoline the enaminone reactant was generated by use of a microlitre syringe to inject into water a small quantity of the substrate in methanol or dioxane solution in which a higher concentration of unstable tautomer exists than in aqueous medium. For 2-phenacylquinoline, for which the aromatic imine is the unstable species, an alternative method used was to scavenge the dominant enaminone tautomer in aqueous solution by injecting a small deficiency of I_3^- solution. The bulk of the enaminone reacted instantly, and the relaxation of the remaining ketimine to enaminone which followed was monitored at the $\lambda_{max.}$ (444 nm) for this species. Low concentrations of substrate were used to prevent precipitation of the highly insoluble iodinated phenacylquinoline. This rate was also measured by injecting a small excess of I_3^- and measuring the first-order reaction of I_3^- with imine at the $\lambda_{max.}$ for I_3^- (353 nm).

Iodination.—Rates of reaction of 4-phenacylquinoline with I_3^- were measured, following the usual procedure for iodination of ketones.[7,17] Solutions of I_2 in excess of potassium iodide were prepared and the concentration of I_3^- and I_2 established from the extinction coefficient,[28] of 2.6×10^4 for I_3^- and the equilibrium constant[28,29] $K = 723$ for dissociation of I_3^- to I_2 and I^- (both values were verified). Measurements were made by stopped flow under zero-order conditions with substrate in one syringe and I_3^- with excess of iodide ion and buffer in the other. They were confined to acetic acid buffers for which the stoicheiometric amount of iodine consumed was one: at lower pH values appreciable concentrations of I_3^- remained at equilibrium, indicating non-stoicheiometric iodination as observed in acidic solutions for other substrates.[9,30]

For zero-order kinetics a ten-fold excess or greater of substrate was used. Kinetics were also measured under first-order conditions with a small excess of I_3^- over substrate. The first-order rates were slow enough to be measured with a conventional spectrophotometer and rate constants agreed with values measured under zero-order conditions.

Data Analysis.—Stopped-flow kinetic measurements were recorded on a Datalab DL901 transient recorder interfaced with a VAX 11/780 computer. First-order rate constants were calculated with iteration of the limiting optical density at infinite time from optical density recordings over 3—4 half-lives of reaction. Zero-order measurements were read to a stripchart recorder.

For buffer measurements rate constants were calculated either from slopes and intercepts at single buffer ratios by least squares or by iteratively fitting measurements at several buffer ratios to equations (2), (5), (6), or (8). Normally one rate or equilibrium constant in the appropriate equation was iterated and the others evaluated by linear least-squares. Values of k_o the rate constants for reaction at zero buffer concentration in Table 3 were based on least-square extrapolations at a single buffer ratio. When the extrapolated value was within experimental error of zero no value was recorded.

Rate constants and ionisation constants from hydrogen and hydroxide ion-catalysed tautomerisation of 2- and 4-phenacylquinoline were calculated from a best fit of the appropriate rate and equilibrium constants to full or partial pH rate profiles using a generalised Harwell least-squares fitting program (VAO5A of the Harwell subroutine library). Rate (and where appropriate equilibrium) constants for reactions with hydroxide at higher pH values, both for these substrates and for reactions of the corresponding *N*-methylenaminones, were evaluated by simple (linear) least-squares. Reactions of the protonated *N*-methylenaminones with hydroxide were fast, and these rate constants and the values for the reverse reaction of the neutral *N*-methyl species with water are subject to somewhat greater uncertainty than other rate constants. Slopes of zero-order kinetic plots were measured graphically directly from the recorder output.

Acknowledgements

Financial support from the National Science Council of Ireland is gratefully acknowledged.

References

1 G. Fukata, C. O'Brien, and R. A. More O'Ferrall, *J. Chem. Soc., Perkin Trans. 2*, 1979, 792.
2 R. P. Bell, E. Gelles, and E. Möller, *Proc. R. Soc., London*, 1949, **A198**, 308; R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, London, 1973, 2nd. edn.
3 R. P. Bell and S. Grainger, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1367.
4 W. J. Albery, J. S. Curran, and A. N. Campbell-Crawford, *J. Chem. Soc., Perkin Trans. 2*, 1972, 2266.
5 D. S. Kemp and M. L. Casey, *J. Am. Chem. Soc.*, 1973, **95**, 6670.
6 J. A. Zoltewicz and H. L. Jacobson, *J. Org. Chem.*, 1978, **43**, 19; J. A. Zoltewicz and J. K. O'Halloran, *ibid.*, p. 1713.
7 B. G. Cox, *J. Am. Chem. Soc.*, 1974, **96**, 6023.
8 J. E. Toullec, *Adv. Phys. Org. Chem.*, 1982, **18**, 1.
9 J.-E. Dubois, M. El-Alaoui, and J. Toullec, *J. Am. Chem. Soc.*, 1981, **103**, 5393.
10 G. E. Lienhard and Tung-Chia Wang, *J. Am. Chem. Soc.*, 1969, **91**, 1146.

11 M. L. Ahrens, M. Eigen, W. Kruse, and G. Maass, *Ber. Bunsenges. Phys. Chem.*, 1970, **74**, 380.
12 'The Tautomerism of Heterocycles,' 'Advances in Heterocyclic Chemistry, Supplement 1,' eds. J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, Academic Press, New York, 1976, ch. 1.
13 J. V. Greenhill, *J. Chem. Soc. B*, 1969, 299.
14 R. Mondelli and L. Merlini, *Tetrahedron*, 1966, **22**, 3253.
15 C. F. Bernasconi, S. A. Hibdon, and S. E. McMurry, *J. Am. Chem. Soc.*, 1982, **104**, 3459; C. F. Bernasconi and C. J. Murray, *ibid.*, 1984, **106**, 3257.
16 B. G. Cox, P. De Maria, A. Fini, and A. F. Hassan, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1351; B. G. Cox, P. De Maria, and A. Fini, *ibid.*, 1984, 1647.
17 O. Exner in 'Correlation Analysis in Chemistry: Recent Advances,' eds. N. B. Chapman and J. Shorter, Plenum Press, New York, 1978.
18 H. Albrecht, W. Funk, and M. Th. Reiner, *Tetrahedron*, 1976, **32**, 479.
19 J. P. Guthrie, *Can. J. Chem.*, 1979, **57**, 1177.
20 R. Stewart and R. Srinivasan, *Acc. Chem. Res.*, 1978, **11**, 271.
21 F. G. Bordwell and W. J. Boyle, Jr., *J. Am. Chem. Soc.*, 1975, **97**, 3447.
22 J. Hine, *J. Am. Chem. Soc.*, 1971, **93**, 3701.
23 C. F. Bernasconi, *Pure Appl. Chem.*, 1982, **54**, 2335; J. R. Murdoch, *J. Am. Chem. Soc.*, 1983, **105**, 2660; M. M. Kreevoy and In-Sook Han Lee, *ibid.*, 1984, **106**, 2550; E. Grunwald, *ibid.*, 1985, **107**, 4310.
24 R. A. Marcus, *J. Phys. Chem.*, 1968, **72**, 891.
25 D. D. Perrin, W. L. Aramarego, and D. R. Perrin, 'Purification of Laboratory Chemicals,' Pergamon Press, Oxford, 1966.
26 F. Larkin and R. A. More O'Ferrall, *Aust. J. Chem.*, 1983, **36**, 1831.
27 P. A. Tregloan and G. S. Lawrence, *J. Sci. Instrum.*, 1965, **42**, 869; J. O'Shea, Ph.D. Thesis, National University of Ireland, 1975.
28 J. Awtrey and D. Connick, *J. Am. Chem. Soc.*, 1951, **73**, 1842; E. T. Harper and M. L. Bender, *ibid.*, 1965, **87**, 5625.
29 R. W. Ramette and R. W. Sandford, *J. Am. Chem. Soc.*, 1965, **87**, 5001.
30 R. P. Bell and E. Gelles, *Proc. R. Soc., London*, 1952, **A210**, 310.

Received 19*th November* 1984; *Paper* 4/1967