Pyrylium-mediated Transformations of Natural Products. Part 4.[1] Reactions of Water-soluble Pyrylium Salts with Water and with Amines

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Pyrylium cation equilibria and kinetics in aqueous solution have been measured and compared with existing data. Competing reactions of pyrylium cations with amines, water molecules, and hydroxide ions have been elucidated and rationalised. Conditions for maximising yields of pyridinium cations from pyrylium salts and amines in aqueous media have been deduced.

We have discussed the potential of pyrylium salts for the selective transformation of primary-alkyl primary amines into the corresponding pyridinium cations and hence into other functionality in aqueous solution.[2] The reactions of the water-soluble pyrylium salt (1d) with water [2] and with a series of amines have been investigated.[3] Previous work in non-aqueous media has shown the importance of tailoring the original pyrylium structure to optimise the reactivity of the pyridinium ions towards nucleophiles.[4] To this end, we prepared [1] several water-soluble pyrylium analogues of water-insoluble pyrylium salts of proven synthetic value.

This paper describes comparison studies of the reactions of five new pyrylium salts (1e—i) with water alone and with lysine in water. Thermodynamic and kinetic data have been obtained and compared with available data for pyrylium salts (1a—c). The preparations, spectral data, and some preparative reactions of (1e—i) with amines are discussed elsewhere.[1,5] U.v. spectral data for pyrylium salts and related species are reported in Table 1.

Pyrylium Equilibria in Aqueous Solution.—The behaviour of pyrylium salts (1e—i) in water † closely parallels that previously reported for (1a—c)[6] and (1d).[2] In water, (1e—i) equilibrate with the corresponding pseudobases (Scheme 1). [Stopped-flow studies suggest [7] that hydroxide ion also attacks the pyrylium salts at the γ-position in a fast equilibrium but reaction proceeds to (4) via (1) ⇌ (2) ⇌ (3) as shown.]

The rate-determining step in the (1) ⇌ (4) interconversion is thought [2,6,9] to be the enolisation–ketonisation (3) ⇌ (4). The overall pyrylium (1) to enedione pseudobase (4) equilibrium, characterised by the apparent dissociation constant pK_a', is found to be highly dependent on the substitution pattern of the pyrylium salt.
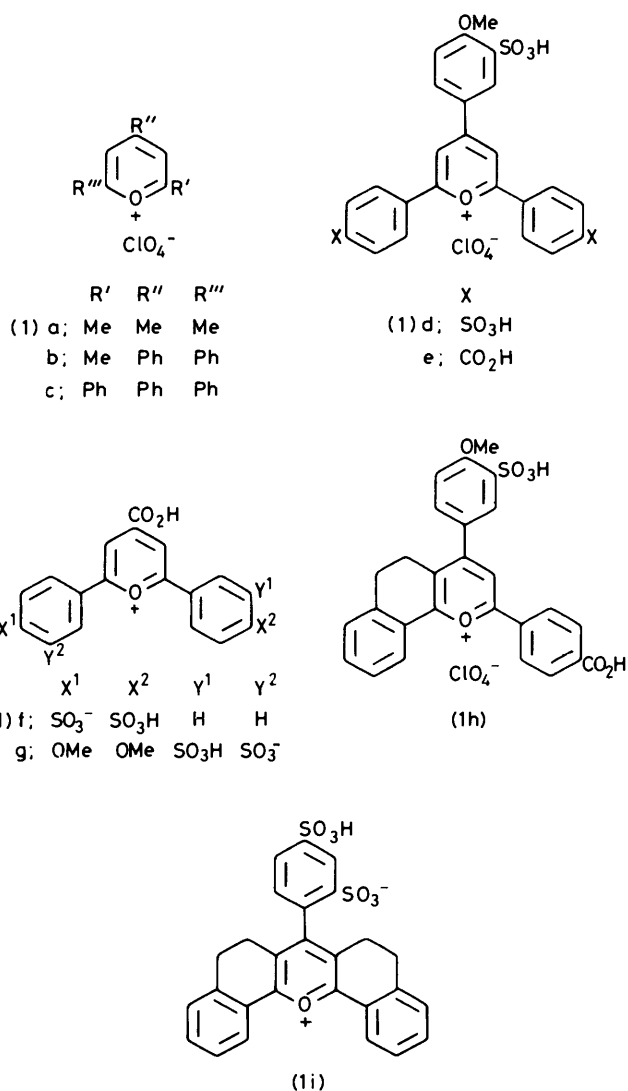
The treatment adopted here follows closely that of ref. 2. At each pH, the equilibrium constant $K = [PB]/[Py^+] = k_f/k_r$ is evaluated from the infinity point of the reaction. Individual forward (k_f) and backward (k_r) rate constants can be calculated at various pH values from $k_{obs.}$ and K using equations (i) and (ii); K_a' is defined as $[(4)][H^+]/[(1)]$.

$$k_{obs.} = k_f + k_r \qquad (i)$$

$$K = k_f/k_r \qquad (ii)$$

Values of $k_{obs.}$, K, k_f, and k_r are recorded in Tables 2—6. The pH–rate profiles for the forward reactions (Figure 1) show the expected increase in k_f with pH in acidic media followed by a plateau independent of pH, and, in two cases, further increase with pH at high pH values. This indicates [2,6] attack

	R'	R''	R'''
(1) a;	Me	Me	Me
b;	Me	Ph	Ph
c;	Ph	Ph	Ph

	X
(1) d;	SO₃H
e;	CO₂H

	X¹	X²	Y¹	Y²
(1) f;	SO₃⁻	SO₃H	H	H
g;	OMe	OMe	SO₃H	SO₃⁻

(1h)

(1i)

by both H_2O and OH^- as well as a pH-dependent pre-equilibrium.

Steady-state considerations [2,6] lead to equation (iii) where

$$k_f = \frac{k_{H_2O} \cdot k_2}{k_2 + k_{-1}[H^+]} + \frac{k_{OH} k_3 [OH^-]}{k_{-3} + k_0} \qquad (iii)$$

the rate constants k_{H_2O}, k_2, k_{-2}, k_{-1}, k_0, and k_3 are as defined by equations (v) and (vi).

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† We also studied the u.v. spectra of pyrylium salts in strong acids: large medium effects were noted (for full details see ref. 8).

Table 1. U.v. spectral data for pyrylium salts and related species

Cpd. no.	Species	pH	λ/nm	$10^{-3} \varepsilon/1$ mol^{-1} cm^{-1}	f λ	$10^{-3} \varepsilon$	g λ	$10^{-3} \varepsilon$	h λ	$10^{-3} \varepsilon$	i λ	$10^{-3} \varepsilon$
(1)	Pyrylium	2.0	409	38.7	430[a]	23.2	510[a]	24.9	418	32.1	455	1.5
			275	22.5	215[a]	11.0	370[a]	8.0	284	20.7	413	2.6
(4)	Pseudobase	8.0	328	14.2	250[b]	27.3	280[b]	22.0	330	25.0	282	19.5
			250	27.9					285	6.2	290	17.7
(5)	Pseudobase anion	13.0	485	27.0	480	54.9	480	39.7	515	26.7	e	e
(6)	Divinylogous amide[c]	10.1	480	33.0	f	f	473	13.2	g	g	g	g
(7)	Pyridinium[d]	10.1	350	20.7	f	f	333	8.4	348	20.1	289	10.5
											385	1.2

[a] In 17.25M-H_2SO_4. [b] pH 4.8. [c] By extrapolation of rate data to zero time. [d] From authentic samples. [e] Does not form. [f] Reactions not studied. [g] Ring closure fast; no build-up of vinylogous amide.
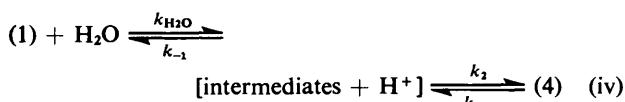
Table 2. Effect of pH on the rates of equilibration of pyrylium salt (1e) and pseudobase (4e)

(a) Ring opening of pyrylium salt [a] to pseudobase

pH	$10^3 k_{obs}/s^{-1}$	Error (%)[b]	$A_\infty^{m\,c}$	$A_\infty^{KS\,d}$	K^e	$10^3 k_f/s^{-1\,f}$	$10^3 k_r/s^{-1\,g}$
5.43	1.84	0.69	0.143	0.181	0.9	0.9	0.97
5.90	1.45	1.50	0.093	0.122	2.0	0.96	0.49
6.30	1.26	1.60	0.029	0.048	10.0	1.2	0.11
6.82	1.33	0.62	0.010	0.023	64.0	1.3	0.02
7.73	1.90	0.73	0.008	0.013	∞	1.9	0
8.27	3.57	0.54	0.007	0.013	∞	3.6	0
8.68	7.53	0.59	0.006	0.014	∞	7.5	0

(b) Ring closure of pseudobase [h] to pyrylium salt

−0.98[i]	4.93	0.60	0.466	0.481	∞[j]	0	4.9
−0.26[i]	4.51	0.40	0.428	0.434	∞	0	4.5
0.41	4.61	0.50	0.473	0.479	∞	0	4.6
1.63	3.42	1.10	0.448	0.445	∞	0	3.4
3.20	3.18	0.60	0.472	0.464	∞	0	3.2
4.02	2.94	0.90	0.470	0.473	∞	0	2.9
5.02	2.08	0.80	0.413	0.408	8.5	0.22	1.9
6.12	1.13	1.50	0.120	0.135	0.3	0.84	0.3

[a] 0.98×10^{-5}M; kinetic wavelength 410 nm. [b] 90% Confidence limit. [c] Measured absorbance at infinite time. [d] Calculated from Kezdy–Swinbourne plot. [e] $K = (0.265 - A_\infty^{KS})/(A_\infty^{KS} - 0.015)$. [f] $k_f = k_{obs}./(1 + 1/K)$. [g] $k_r = k_{obs}. - k_f$. [h] 1.69×10^{-5}M. [i] H_0. [j] $1/K = (A_\infty^{KS} - 0.015)/(0.457 - A_\infty^{KS})$.

$$(1) + H_2O \underset{k_{-1}}{\overset{k_{H2O}}{\rightleftharpoons}}$$

$$[\text{intermediates} + H^+] \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} (4) \quad (iv)$$

$$(1) + OH^- \underset{k_0}{\overset{k_{OH}}{\rightleftharpoons}} [\text{intermediates}] \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} (4) \quad (v)$$

$$k_f = \frac{k_{H_2O}}{K'[H^+] + 1} + k''[OH^-] \quad (vi)$$

Equation (vi) is equivalent to equation (iii) where $K' = k_{-1}/k_2$ and $k'' = k_{OH}k_3/[k_3 + k_0]$. As before,[2] at the pH when the rate profile slope changes from positive to zero, $K' = 1/[H^+]$.

$$k_r = \frac{k_{-1}k_{-2}[H^+]}{k_{-1}[H^+] + k_2} = \frac{k_{-2}[H^+]}{[H^+] + k_2/k_{-1}} \quad (vii)$$

Ring Closure of Pseudobases.—As before,[2] k_{obs}. for conversion of pseudobases (4e—i) to pyrylium salts (1), together with K, gave k_r, which is related to k_{-1} and k_{-2} by equation (vii). It follows,[2] that at low pH $k_r = k_{-2}$ and at pH > 6, $k_r = k_{-2}k_{-1}[H^+]/k_2$.

Values of k_r are recorded in Tables 2—6 and Figure 2, and
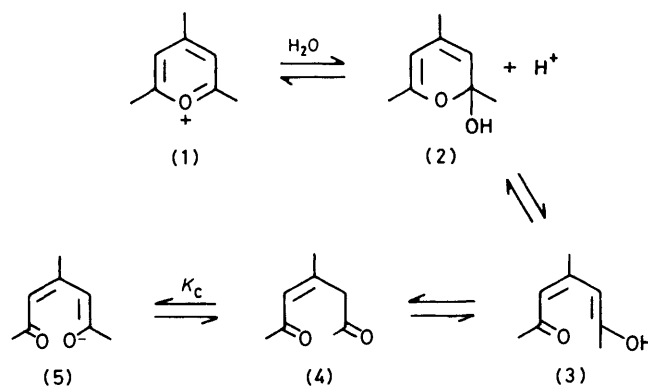
Scheme 1.

values of k_{-2} and $K' = k_{-1}/k_2$ in Table 11. K' Values can be obtained either from equation (viii), which holds at pH > 6, or from equation (ix), which holds at pH < 4.

$$K' = k_r/(k_{-2}[H^+]) \quad (viii)$$

$$k_f = k_{H_2O}/([H^+]K') \quad (ix)$$

Table 3. Effect of pH on the rates of equilibration of pyrylium salt (1f) and pseudobase (4f)

(a) Ring opening of pyrylium salt [a] to pseudobase

pH	Kinetic λ/nm	$10^3 k_{obs.}$/s^{-1}	Error (%) [b]	A_∞^{m} [c]	A_∞^{KS} [d]	K [e]	$10^3 k_f$/s^{-1} [f]	$10^3 k_r$/s^{-1} [g]
0.24	415	2.37	0.5	0.196	0.227	2.93	1.7	0.60
1.10	415	6.47	0.3	0.151	0.166	4.76	5.4	1.1
2.27	415	16.5	2.0	0.038	0.050	∞	17	0
2.77	415	17.3	1.2	0.033	0.048	∞	17	0
3.63	415	16.4	0.6	0.045	0.058	∞	16	0

(b) Ring closure of pseudobase [h] to pyrylium salt

pH	Kinetic λ/nm	$10^3 k_{obs.}$/s^{-1}	Error (%) [b]	A_∞^{m} [c]	A_∞^{KS} [d]	K [e]	$10^3 k_f$/s^{-1} [f]	$10^3 k_r$/s^{-1} [g]
−4.40 [i]	430	0.693	1.2	1.035	1.029	∞ [j]	0	0.69
−2.06 [i]	430	0.352	0.6	1.210	1.150	∞	0	0.35
−0.98 [i]	430	0.513	1.3	1.035	0.960	4.8	0.094	0.42
−0.26 [i]	430	1.16	0.7	0.440	0.448	0.50	1.3	0.38
0.34	445	2.46	0.3	0.261	0.253	0.2	2.0	0.46

[a] 2.719×10^{-5}M. [e] $K = (0.79 - A_\infty^{KS})/(A_\infty^{KS} - 0.035)$. [h] 4.32×10^{-5}M. [j] $1/K = (A_\infty^{KS} - 0.035)/(1.15 - A_\infty^{KS})$. Other footnotes as Table 2.

Table 4. Effect of pH on the rates of equilibration of pyrylium salt (1g) and pseudobase (4g)

(a) Ring opening of pyrylium salt [a] to pseudobase

pH	Kinetic λ/nm	$10^3 k_{obs.}$/s^{-1}	Error (%) [b]	A_∞^{m} [c]	A_∞^{KS} [d]	K [e]	$10^3 k_f$/s^{-1} [f]	$10^3 k_r$/s^{-1} [g]
−1.04	495	0.040	6.1	0.650	0.616	0.25	0.080	0.17
0.20	495	0.160	2.3	0.505	0.563	0.38	0.10	0.28
1.08	485	0.624	2.2	0.195	0.353	1.3	0.35	0.28
2.31	465	1.63	1.3	0.111	0.237	2.5	1.1	0.49
3.95	465	3.22	1.4	0.016	0.077	14	3.0	0.23
4.34	465	3.80	1.7	0.028	0.029	∞	3.8	0
4.41	465	3.67	2.5	0.018	0.026	∞	3.7	0

(b) Ring closure of pseudobase [h] to pyrylium salt

pH	Kinetic λ/nm	$10^3 k_{obs.}$/s^{-1}	Error (%) [b]	A_∞^{m} [c]	A_∞^{KS} [d]	K [e]	$10^3 k_f$/s^{-1} [f]	$10^3 k_r$/s^{-1} [g]
−2.06 [i]	495	0.210	0.7	0.465	0.465	∞ [j]	0	0.210
−0.98 [i]	495	0.090	1.8	0.433	0.394	5.3	0.010	0.080
−0.26 [i]	495	0.093	2.4	0.396	0.343	2.7	0.023	0.070
0.34	495	0.128	3.9	0.314	0.281	1.4	0.080	0.050

[a] 1.98×10^{-5}M. [e] $K = (0.765 - A_\infty^{KS})/(A_\infty^{KS} - 0.026)$. [h] 1.2×10^{-5}M. [j] $1/K = (A_\infty^{KS} - 0.20)/(0.465 - A_\infty^{KS})$. Other footnotes as Table 2.

Table 5. Effect of pH on the rates of equilibration of pyrylium salt (1h) and pseudobase (4h)

(a) Ring opening of pyrylium salt [a] to pseudobase

pH	$10^3 k_{obs.}$/s^{-1}	Error (%) [b]	A_∞^{m} [c]	A_∞^{KS} [d]	K [e]	$10^3 k_f$/s^{-1} [f]	$10^3 k_r$/s^{-1} [g]
6.03	1.19	3.5	0.251	0.270	0.39	0.33	0.86
6.83	1.00	0.4	0.124	0.125	1.8	0.65	0.35
7.25	0.960	0.6	0.065	0.072	4.6	0.79	0.17
7.78	1.61	0.9	0.025	0.024	16	1.52	0.09
8.31	3.70	0.3	0.007	0.013	37	3.60	0.10
8.70	9.22	1.8	0.004	0.012	—	9.22	0

(b) Ring closure of pseudobase [h] to pyrylium salt

pH	$10^3 k_{obs.}$/s^{-1}	Error (%) [b]	A_∞^{m} [c]	A_∞^{KS} [d]	K [e]	$10^3 k_f$/s^{-1} [f]	$10^3 k_r$/s^{-1} [g]
−0.98 [i]	2.87	1.6	0.318	0.329	∞ [j]	0	2.9
−0.26 [i]	2.69	1.0	0.269	0.314	∞	0	2.7
0.41	3.18	3.2	0.324	0.302	∞	0	3.2
1.08	2.43	1.0	0.320	0.304	∞	0	2.4
3.12	2.53	0.9	0.323	0.307	∞	0	2.5
4.92	2.72	0.6	0.297	0.288	∞	0	2.7

[a] 1.098×10^{-5}M; kinetic wavelength 422 nm. [e] $K = (0.347 - A_\infty^{KS})/(A_\infty^{KS} - 0.004)$. [h] 1.98×10^{-5}M. [j] $1/K$. Other footnotes as Table 2.

Pseudobase–Anion Equilibria.—U.v. spectral measurements confirmed the expected [2] conversion of pseudobases (4) into anions (5). Tables 7—10 give values for K_c, the relevant equilibrium constants. The anion (5i) does not form to any appreciable extent in NaOH (7M) solutions. Anion formation requires coplanarity, which is precluded for steric reasons in this case. As previously noted,[2] cleavage occurs in basic solution.

Reaction of Pyrylium Salts with Lysine.—(a) *Pyrylium salts with free α-phenyl groups* [(1e),(1g)]. On treatment with lysine in water, the salt (1) gives pseudobase (4), pseudobase anion

Table 6. Effect of pH on the rates of equilibration of pyrylium salt (1i) and pseudobase (4i)

(a) Ring opening of pyrylium salt [a] to pseudobase

pH	$10^3 k_{obs.}/s^{-1}$	Error (%) [b]	A_∞^m [c]	A_∞^{KS} [d]	K [e]	$10^3 k_f/s^{-1}$ [f]	$10^3 k_r/s^{-1}$ [g]
7.65	0.097	16	0.15	0.15	0.61	0.037	0.060
8.22 [h]	0.083	1.5	0.080	0.085	3.0	0.062	0.018
8.96	3.0	1.8	0.032	0.025	∞	3.0	0
9.74	13.8	4	0.032	0.04	∞	14	0
10.44	61.1	1	0.028	0.031	∞	61	0
11.18	99	3	0.028	0.033	∞	99	0

(b) Ring closure of pseudobase [a] to pyrylium

pH	$10^3 k_{obs.}/s^{-1}$	Error (%) [b]	A_∞^m [c]	A_∞^{KS} [d]	K [e]	$10^3 k_f/s^{-1}$ [f]	$10^3 k_r/s^{-1}$ [g]
−1.61 [i]	0.12	1.3	0.170	0.170	∞ [j]	0	0.12
−0.4	0.054	0.5	0.168	0.168	∞	0	0.054
0.925	0.032	2	0.152	0.150	∞	0	0.032
3.43	0.021	5	0.150	0.150	∞	0	0.021

[a] 9.29×10^{-5}M; kinetic wavelength 412 nm. [e] $(0.223 - A_\infty^{KS})/(A_\infty^{KS} - 0.032)$. [h] Average of two runs. [j] $1/K$. Other footnotes as Table 2.
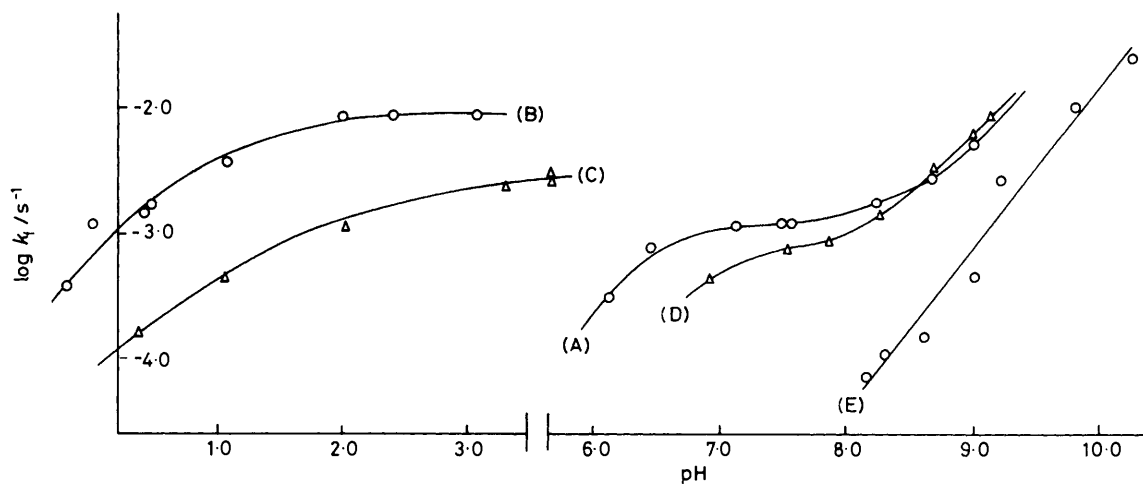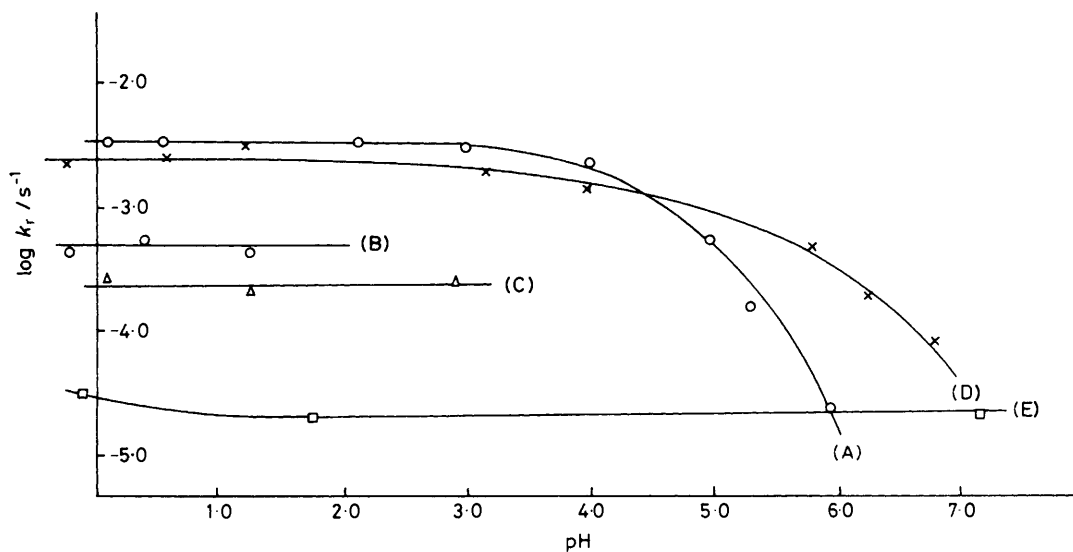

Figure 1. Plot of hydrolysis rate (log k_f) vs. pH for (A) (1e), (B) (1f), (C) (1g), (D) (1h), and (E) (1i)

Figure 2. Plot of ring-closure rate (log k_r) vs. pH for formation of pyrylium salts (A) (1e), (B) (1f), (C) (1g), (D) (1h), and (E) (1i)

Table 7. Determination of pK_c of deprotonation of pseudobase (4e)

pH	A_{485} [a]	$\log\left(\dfrac{0.219 - A_{485}}{A_{485} - 0.002}\right)$	pK_c
9.77	0.018	1.099	10.87
9.92	0.023	0.970	10.89
10.45	0.070	0.341	10.79
11.11	0.145	−0.286	10.82
(0.4M-NaOH)	0.219		

Mean $pK_c = 10.8$ (s.d. $= 0.06$ [b])

[a] Maximum extrapolated value of absorbance at 485 nm. [b] Standard deviation.

Table 8. Determination of pK_c of deprotonation of pseudobase (4f)

pH	A_{480} [a]	$\log\left(\dfrac{A_{480}}{1.50 - A_{480}}\right)$	pK_c
4.98	0.000		
8.97	0.300	−0.600	9.57
9.22	0.415	−0.420	9.64
9.40	0.470	−0.340	9.74
9.60	0.577	−0.200	9.80
9.82	0.713	−0.040	9.86
10.01	1.140	+0.500	9.51
(0.1M-NaOH)	1.500		

Mean $pK_c = 9.7$ (s.d. $= 0.12$ [b])

[a] Maximum extrapolated value of absorbance at 485 nm. [b] Standard deviation.

Table 9. Determination of pK_c of deprotonation of pseudobase (4g)

pH	A_{476} [a]	$\log\left(\dfrac{A_{476}}{0.787 - A_{476}}\right)$	pK_c
4.80	0.009		
11.95	0.671	0.756	11.19
12.14	0.702	0.911	11.23
12.53	0.753	1.340	11.19
(4M-NaOH)	0.787		

Mean $pK_c = 11.2$ (s.d. $= 0.02$ [b])

[a] Maximum extrapolated value of absorbance at 485 nm. [b] Standard deviation.

(5), divinylogous amide (6), and the pyridinium ion (7), by the previously described [3] route (Scheme 2). The kinetic treatment follows closely that of ref. 3. In lysine buffer (pH 10.1) immediate reaction of (1d) gives a mixture of (5d) [in fast equilibrium with (4d)] and (6d). The λ_{max} values of (5d) and (6d) are coincident at 487 nm. This absorbance disappears in a biphasic manner resolving into two first-order rates by a subtraction method. The fast rate ($k_{obs.}$) is the rate of disappearance of (6d) [equation (x)]. The slow rate (k') is the rate of disappearance of (4d) [equation (xi)], where [lysine] is the free lysine

$$k_{obs.} = k_3 (1 + k_v/[\text{lysine}])\qquad\text{(x)}$$

$$k' = k_s + k_2 [\text{lysine}]\qquad\text{(xi)}$$

concentration corrected for ionic strength of the lysine buffer by an iteration method.[8]

The ratio $R = k_{VA}/(k_{H_2O}[H_2O] + k_{OH}[OH^-])$ is calculated from the initial concentrations of (6), $[VA]_0$, and (4), $[PB]_0$, using equation (xii). Values of $k_{obs.}$, k', and R are recorded in Tables A and B.*
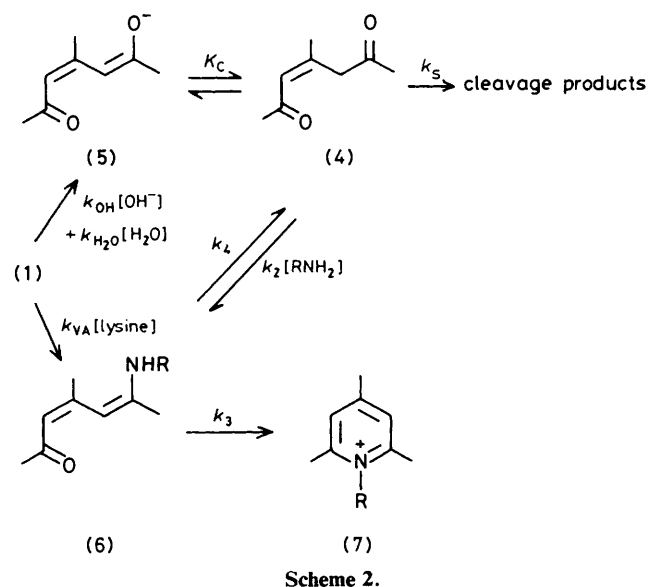
$$\frac{[\text{VA}]_0}{[\text{PB}]_0} = \frac{k_{VA}[\text{lysine}]}{k_{H_2O}[H_2O] + k_{OH}[OH^-]}\qquad\text{(xii)}$$

Table 10. Determination of pK_c of deprotonation of pseudobase (4h)

pH	A_{515} [a]	$\log\left(\dfrac{0.235 - A_{515}}{A_{515} - 0.001}\right)$	pK_c
8.20	0.001		
11.69	0.085	0.250	11.94
11.85	0.095	0.170	12.02
11.99	0.103	0.110	12.10
12.17	0.115	0.020	12.19
12.27	0.128	—0.070	12.20
(0.1M-NaOH)	0.235		

Mean $pK_c = 12.1$ (s.d. $= 0.11$ [b])

[a] Maximum extrapolated value of absorbance at 485 nm. [b] Standard deviation.

Scheme 2.

Solutions of pseudobases (4e and g) added to lysine buffers show only slow decomposition without formation of pyridinium salt. Evidently $k_s \gg k_2$ in these cases.

(b) *Pyrylium salts with fixed α-phenyl groups* [(1h),(1i)]. For pyrylium salts with one α-phenyl (1h) or both α-phenyl (1i) groups fixed to the ring by an ethano bridge, reaction also occurs by Scheme 2. Here k_3 is large and formation of the divinylogous amide (6) is not observed. Initial scans show formation of an amount of pyridinium salt (7) dependent on the lysine concentrations; later, further pyridinium salt forms slowly ($k'_{obs.}$) by the reaction of the pseudobase with lysine. For this reaction, $k'_{obs.}$ is [lysine]-dependent and greater than the maximum value of k_{-2} for ring closure to pyridinium salt (2×10^{-5} s^{-1} at pH 8.22) when [lysine] > 0.0007M, suggesting formation of (6) via Scheme 3 rather than via the pyrylium salt, (4) $\rightleftharpoons$ (1) $\rightleftharpoons$ (5). The possibility of a small amount of conversion into (7) via the pyrylium salt (1) cannot be entirely ruled out.

Only at high relative [lysine] is (1) completely converted into (7) (Tables 11 and C–E).* Formation of (4) inevitably leads to some degradation to cleavage products (k_s).

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* Tables A—E are available as Supplementary Publication No. SUP 23851 (5 pp.). For details of Supplementary Publications see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1984, Issue 1.

Table 11. Collected kinetic and thermodynamic data for reactions of pyrylium salts (1a—i) with lysine in water

Cpd. no.	pK_a' [a]	pK_c	$10^3 k_{H_2O}/s^{-1}$ [b]	K [b]	$10^{-3} k''/s^{-1}$ [c]	$10^3 k_{-2}/s^{-1}$ [d]	$10^4 k_s/s^{-1}$ [e]	$10^4 k_3/s^{-1}$ [e]	$10^{-3} R/l\ mol^{-1}$ [f]
(1a)	3.0	g	21	500	13	g	g	g	g
(1b)	3.3	g	32	200	25	3	g	g	g
(1c)	4.4	g	1.3	10	6.5	5	g	g	g
(1d)	5.1	10.7	4.3	6	2.1	3	0.5	6.4	0.90
(1e)	5.7	10.8	1.3	20	1.3	5	0.2	14	1.5
(1f)	−0.5	9.7	16	0.001	h	0.4	g	g	g
(1g)	1.0	11.2	3.8	0.02	h	0.3	0.4	5.4	0.080
(1h)	6.3	12.1	0.69	6	1.8	3	g	>1 000	1.7
(1i)	7.8	>14	0.16	i	0.20	0.02	g	>1 000	1.3

[a] From plots of A_∞^{KS} against pH (Tables 2—6). [b] From $1/k_f = (K'/k_{H_2O})[H^+] + 1/k_{H_2O}$. [c] $k_f = k''[OH^-] + k_{H_2O}$. [d] $k_r = k_{-2}[H^+]/([H^+] + k_2/k_{-1})$. [e] See Tables B—E. [f] $R = k_{VA}/(k_{OH}[OH^-] + k_{H_2O}[H_2O]) = [VA]_0/[PB]_0L_F$. [g] No measurement attempted. [h] Too fast for accurate measurement. [i] k_f too small for measurement at pH <7.

Scheme 3.

Scheme 4.

Scheme 5.
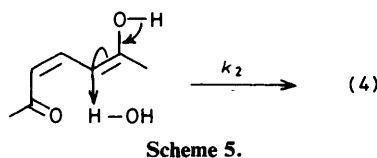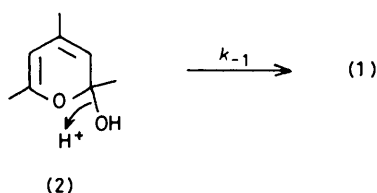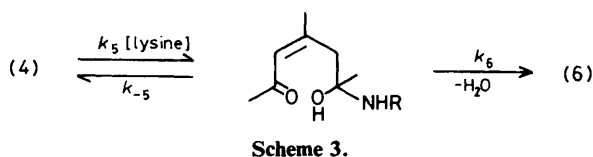
Solutions of pseudobases (4h and i), on reaction with lysine are also converted into (7). Values of $k'_{obs.}$ for these reactions are equivalent to those values obtained from reaction of (1) with lysine (Tables C—E).

Rates could not be measured accurately for the reaction of a solution of (4i) with lysine, owing to small spectral differences and their faster degradation in alkaline solution.

Plots of $k_{obs.}$ versus [lysine] for the reactions of (4h) and (4i) show an initial increase followed by a plateau. Presumably, at low [lysine], addition of lysine is the slow step and increasing [lysine] leads to increased $k_{obs.}$ (Scheme 3).

Eventually, loss of H_2O becomes rate-determining and $k_{obs.}$ becomes independent of [lysine].

Comparison of Rate and Equilibrium Data.—Data for pyrylium ⇌ pseudobase equilibration are collected in Table A.

(a) *Stability of pyrylium ions.* The pyrylium ion's apparent pK_a' value is a measure of its resistance to hydrolysis and ring opening. The pyrylium ions most susceptible to nucleophilic attack are the 4-CO_2H substituted examples (f and g), which are activated by the electron-withdrawing effect of the car-

Table 12. Optimal conditions for 98% conversion of pyrylium ions [a] into vinylogous amide at pH 10.1

Pyrylium ion	[lysine],[98] [b] (M)	[VA]$_0^1$ [c] (%)
(1d)	0.40	95
(1e)	0.24	97
(1g)	4.50	63
(1h)	0.21	97
(1i)	0.28	97

[a] 0.15M. [b] Stoicheiometric concentration of lysine required for 98% conversion into vinylogous amide. [c] % Vinylogous amide formed using [lysine]$_s$ = [(1)] = 0.15M.

boxy group attached directly to the ring. Pyrylium ions with at least one α-alkyl group (1a and b) are of intermediate stability. Triarylpyrylium ions (1c—e) are the most resistant; the mesomeric effect of a phenyl substituent stabilises the pyrylium ion relative to an alkyl group. Fusing the α-phenyl groups into plane with the pyrylium ring once, as in (1h), and twice, as in (1e), further increases the mesomeric overlap and stabilises the pyrylium ion.

(b) *Rates of hydrolysis of pyrylium ions.* The rate of attack by water at the pyrylium α-position (k_{H_2O}) is the fastest for pyrylium ions with at least one α-alkyl group (1a and b), which reflects less steric hindrance to attack relative to the triaryl examples. The reaction is almost as fast for the 4-CO_2H substituted examples (1f and g), in line with their electropositivity at the α-position. Fusing both α-phenyl groups into plane as in (1i) reduces the rate of attack further, probably owing to increased resonance overlap and decreased electropositivity.

The rate of formation of pseudobase via hydroxide ion attack $[k'' = k_{OH}k_3/(k_3 + k_0)]$ follows the same order and is approximately $10^6 k_{H_2O}$ in all cases.

(c) *Reactivity of intermediates* (2) *and* (3). The rate ratio $k' = k_{-1}/k_2$ measures the difference in the tendency of the intermediates (2) to return to pyrylium ion as compared with the tendency to proceed to pseudobase. Values of K' are lowest for the 4-CO_2H substituted examples (1f and g) and triarylpyrylium ions (1c—e and h) are intermediate.

The rate-determining stage for k_{-1} is probably (2) ⟶ (1), (Scheme 4) and that for k_2 is probably (3) ⟶ (4) (Scheme 5). On introducing CO_2H in the 4-position, the decrease in k_{-1} should be greater than that in k_2. The replacement of α-aryl by α-methyl should alter the (2) ⇌ (3) equilibration in favour of (2). These effects could lead to the observed order.

(d) *Pseudobase reactivity.* The rate of pseudobase enolisation (k_{-2}) is low for 4-CO_2H substituted pseudobases (4f and g) and

intermediate for (4a—e and h). The rate constant (k_{-2}) is very low for examples with fused α-phenyl groups. Here formation of the enol requires planarity which is sterically hindered in these cases.

The deprotonation equilibrium of the pseudobase (4) to its anion (5) is given by $pK_c = [(5)][H^+]/[(4)]$ and is less sensitive to substitution than pK_a'. Values of pK_c increase on fusion of one α-aryl ring as in (5h); on fusion of both as in (5i), the anion is not formed even in 7M-NaOH. The anions (5a—g) can adopt planar *trans–trans* configurations that allow through conjugation and are sterically more favourable than the *cis–cis* form. In (5i), considerable steric hindrance remains even in the *trans–trans* configuration.

The rate of cleavage (k_s) of the pseudobase in alkaline solutions although available for only three examples (4d, e, and g) appears relatively insensitive to substitution.

(e) *Ring closure of divinylogous amide.* The rates of ring closure (k_2) of the divinylogous amide derived from pyrylium ions with fused α-phenyl groups are much faster than those of the analogues with free α-phenyl.

Ring closure occurs on the divinylogous amide in the *cis–cis* configuration. This configuration is favoured for steric reasons in the fused α-phenyl group examples leading to faster ring closure in these cases.

(f) *Selectivity of the pyrylium ion for nucleophiles.* The ratio $R = k_{VA}/(k_{OH}[OH^-] + k_{H_2O}[H_2O])$ is a measure of the selectivity of the pyrylium ion between amine and HO^- or H_2O. R is 0.9—1.7 × 10³ 1 mol⁻¹ for triarylpyrylium ions, indicating rather constant selectivity over a range of reactivity. R is low (801 mol⁻¹) for the 4-CO₂H substituted pyrylium ion (1g). The reason for this is not clear although it may reflect the much higher value of k_{H_2O} for this pyrylium ion.

Optimum Conditions for Pyridinium Ion Preparation.— Pyridinium ions can be prepared [1] at the pH of the kinetic measurements (10.1) at which sufficient amine remains unprotonated, while attack by OH^- at the pyrylium cation is minimised. Given R for the pyrylium ion the optimum stoicheiometric amount of amine required to effect maximum conversion into vinylogous amide and hence pyridinium ion from pyrylium ion can be calculated from equation (xii) and the pK_a of the amine. Table 12 reports [lysine] necessary for 98% conversion of pyrylium ions (1d, e, and g—i) (0.15M) into vinylogous amide, calculated for pH 10.1. Also reported is the percentage conversion to divinylogous amide using [lysine] = [(1)] (0.15M).

Experimental

U.v. spectra were recorded with a Pye Unicam SP6 or SP8-200, or a Perkin-Elmer 330 spectrophotometer. The pH of solutions was measured in the cuvette with a Corning 130 pH meter fitted with a micro-combination electrode and calibrated with standard buffer solutions before use. All rates were measured at 25 ± 0.1 °C.

Samples of compounds (1e), (1h), (7e), and (7h) were provided by Mr. Yu-Kun Yang,[1] and of (1f), (1g), and (7g) by Dr. B. M. Gabrielsen.[1] Compounds (1e) and (7e) were prepared according to ref. 5.

Reactions of Pyrylium Salts and Pseudobases in Water.— These were performed as in ref. 2, except stock solutions of (1f and g) were prepared in 18M-H₂SO₄ and buffers were prepared with addition of 1M-NaOH (12 ml per 100 ml buffer). Stock solutions of (1e and h) were prepared in Me₂SO (distilled over CaH₂; stored on 4 Å molecular sieves) containing AcOH (*ca.* 1 ml per 200 ml Me₂SO). Stock solutions of (4e and g—i) were prepared in buffer solutions (for pH see Table 1) and used immediately.

Reactions were initiated by injection of 10 μl [(1e), (4e), (1f), (4f)], 20 μl [(1h), (4h)] or 40 μl [(1i), 4i)] of stock solution into 2.5 ml of buffer.

Reactions of Pyrylium Salts with Lysine.—These were carried out as in ref. 3, except stock solutions of (1e and g—i) were prepared in dry Me₂SO. Stock solutions of (4e and g—i) were prepared in appropriate buffer solutions (Table 1). Reactions were initiated by injecting 40 μl of stock solution into 2.5 ml of lysine buffer solution.

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