

# Pyrylium-mediated Transformations of Natural Products. Part 1. Synthesis and Hydrolysis of 4-(4-Methoxy-3-sulphophenyl)-2,6-bis-(4-sulphophenyl)pyrylium Perchlorate: a New Water-soluble Pyrylium Cation

Alan R. Katritzky,\* Michael De Rosa,§ and Nicholas E. Grzeskowiak  
Department of Chemistry, University of Florida, Gainesville, Fl. 32611, U.S.A.

The title pyrylium cation (7) coexists in water with the enedione pseudobase (12) and the anion [*cf.* (13)]. The kinetic and equilibrium interrelationships of these species and the corresponding 2*H*-pyran and oxodienol over a wide pH range have been studied and elucidated.

*Introduction to Present Series of Papers.*—The conversion of primary amino groups into other functionalities has been accomplished previously in a two-step sequence. First the amino group reacts with a pyrylium cation to give the corresponding pyridinium cation; this can subsequently undergo nucleophilic or free radical substitution to give product and a pyridine (Scheme 1).<sup>1</sup>

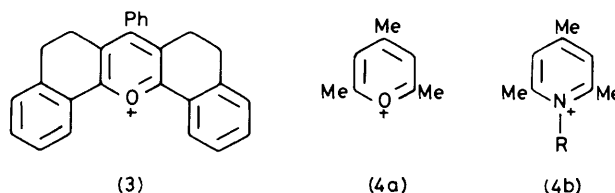
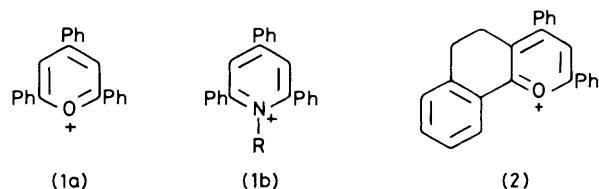
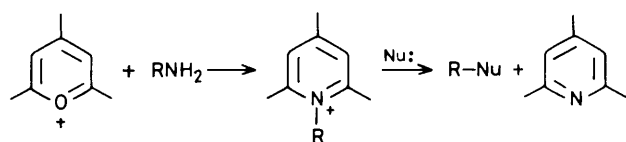
Whereas pyrylium ions react readily with primary amines at 25 °C to form the corresponding pyridinium ions, they are unreactive toward most other functional groups. Thus no irreversible reaction (reversible adducts can form in some cases) occurs between pyrylium ions and any of the following: aldehydes, ketones, alcohols, phenols, carboxylic acids, thiols, thiophenols, sulphides, secondary or tertiary amines, amides, and carbon-carbon multiple bonds.

Many transformations have been achieved with simple amines,<sup>1</sup> using suitably designed pyrylium ions in solution at 20–100 °C.<sup>2</sup> Moreover, primary-alkyl primary amines react with pyrylium ions more than a hundred times faster than secondary-alkyl primary amines.<sup>1</sup> Hence, highly selective reactions with complex products containing several amino groups are to be expected.

Therefore the prospect arises of being able to modify, at specific amino groups, large thermally sensitive substrates such as polypeptides, proteins, and β-lactam and aminoglycoside antibiotics which also contain a variety of other reactive substituents.

However, a major difficulty arises from the near insolubility of most such complex natural products in solvents other than water. Triphenylpyrylium salts (1a) and fused analogues (2) and (3) are rapidly hydrolysed by water to highly insoluble pseudobases<sup>1</sup> which immediately precipitate. Certain polar, non-aqueous solvents (*m*-cresol; mixtures of Et<sub>3</sub>N with acetic or trifluoroacetic acid) are suitable for conversion of amino acids and glycylglycine by triphenylpyrylium (1a) into the pyridinium (1b).<sup>3</sup> However, the more complex aminoglycoside antibiotics (kanamycins, neomycin) and proteins (chymotrypsin) fail to dissolve sufficiently in these solvents to permit pyridinium formation.<sup>4</sup>

Trimethylpyrylium ion (4a) is water-soluble. Above pH 3 it reversibly forms the corresponding pseudobase,<sup>5</sup> which is also soluble in water, and which reacts with glycine,<sup>6</sup> alanine,<sup>7</sup> valine,<sup>7</sup> α-aminobutyric acid,<sup>7</sup> phenylalanine,<sup>7</sup> tryptophane,<sup>7</sup> β-alanine,<sup>8</sup> lysine, and ornithine<sup>9</sup> (ω-amino group) to give the corresponding pyridinium ions. The dipeptide glycylglycine gives<sup>7</sup> an analogous pyridinium ion. Trimethylpyridinium salts have been formed from lysine residues in the proteins chymotrypsin and acetoacetate decarboxylase.<sup>10</sup> Trimethyl-



Scheme 2.

pyridinium derivatives of 6-aminopenicillanic acid<sup>11</sup> and kanamycins A and B, and neomycin<sup>12</sup> have been reported.

Although readily formed, these trimethylpyridinium ions (4b) are not useful for nucleophilic displacement reactions owing to the low nucleofugacity of trimethylpyridine.<sup>13</sup> However, water-solubilising groups introduced into the pyrylium ions which correspond to better pyridine leaving groups,<sup>14</sup> should allow formation of pyridinium ions in aqueous solution and enable directed semisynthesis on unprotected complex natural products: a prospect of immense biological importance. The present series of papers is directed towards this objective.

In the present paper we present the synthesis of a prototype water-soluble pyrylium ion and a detailed study of the kinetics and equilibria of its reaction with water, prior to examining its reactions with primary amino groups of different types (see following paper).

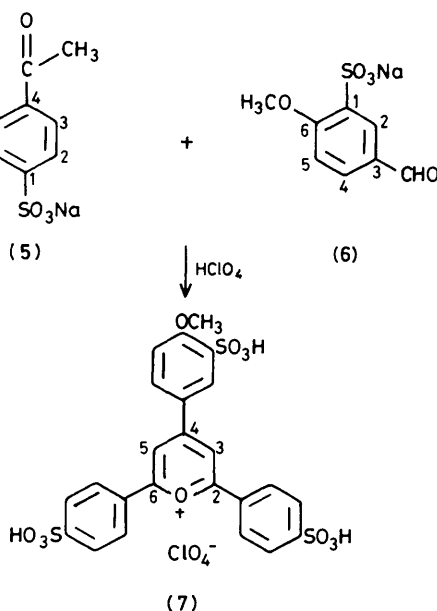
*Preparation of 4-(4-Methoxy-3-sulphophenyl)-2,6-bis-(4-sulphophenyl)pyrylium Perchlorate.*—The water-soluble tri-sulphonated pyrylium ion (7) was prepared analogously to (1a)<sup>15</sup> by the condensation of sodium 4-acetylbenzenesul-

§ On sabbatical leave from the Departamento de Química, Universidad Simon Bolivar, Caracas, Venezuela 1080A.

phonate (5) (2 mol equiv.) with sodium 3-formyl-6-methoxybenzenesulphonate (6) (1 mol equiv.) in  $\text{HClO}_4$ .

Spectral properties<sup>16,17</sup> (Tables 1–3) (see later discussion) and elemental analyses confirm the structure of (7).

<sup>1</sup>H and <sup>13</sup>C N.m.r. Spectra of the Pyrylium Ion (7) and Pseudobase (12).—The assignment of the structures discussed in this paper is supported by the n.m.r. spectra. In the <sup>1</sup>H spectra (Table 2), the pyrylium ion (7), the pseudobase (12), and the anion (13) all show the signals of the 4-aryl ring similar to those of the aldehyde (6); the 2- and 6-aryl ring protons in (7) appear



Scheme 3.

as one AB pattern, in (13) as a singlet, and in (12) as two singlets.

In the <sup>13</sup>C n.m.r. spectra (Table 3) the heterocyclic ring carbons of the pyrylium ion (7) gave signals close to those previously reported for 2,4,6-triphenylpyrylium ion.<sup>17</sup> The chain carbon signals of the 2-ene-1,5-dione (12) [the hydrolysis product of (7)] were similar to those of the pseudobase of 2,4,6-triphenylpyrylium ion.<sup>17</sup> Hydrogen atoms on C-3 and C-5 of (12) underwent H–D exchange and gave rise to small D-coupled signals. The pseudobase (12) gave clearly different values for C-4' and especially C-1' in the rings attached to the conjugated C-6 and the unconjugated C-2 carbonyls. The anion of (12) undergoes a cleavage reaction (discussed later) and it was not possible to obtain its <sup>13</sup>C n.m.r. spectrum.

*Previous Studies of the Hydrolysis of Pyrylium Ions.*—These have been shown to give acyclic pseudobases (2-ene-1,5-diones)<sup>5,16,18–31</sup> in pH-dependent processes.<sup>5,19,27,30</sup> A previous study on the hydrolysis of 2,4,6-triphenyl-, 2,4,6-trimethyl-, and 4-methyl-2,6-diphenylpyrylium ions proposed that in each case the initial product was a 2H-pyran,<sup>5</sup> which gave the acyclic pseudobase (11) directly. Studies on the acid catalysed cyclisation of 1,3,5-triphenylpent-2-ene-1,5-dione to 2,4,6-triphenylpyrylium ion<sup>28,32,33</sup> indicated that the oxodienol (10) tautomer of (11) was formed prior to the 2H-pyran. Therefore, by the principle of microscopic reversibility

Table 1. U.v. absorption for the trisulphonated pyrylium ion (7) and related species in water

Species	$\lambda_{\text{max.}}/\text{nm}$ ( $\epsilon/l \text{ mol}^{-1} \text{ cm}^{-1}$ )		
Pyrylium ion (7) <sup>a</sup>	407 (65 000)	274 (27 500)	238 (28 500)
Pseudobase (12) <sup>b</sup>	339 (19 500)	252 (35 500)	
Anion (13) <sup>c</sup>	487 (40 000) <sup>d</sup>	260 (23 000) <sup>d</sup>	
High pH product <sup>e</sup>	330 (16 000)	250 (20 000)	230 (30 000) <sup>d</sup>

<sup>a</sup> 0.1M-HCl. <sup>b</sup> pH 8. <sup>c</sup> 0.1M-NaOH. <sup>d</sup> Approximate  $\epsilon$  value. <sup>e</sup> Product formed in the slow component of the biphasic disappearance of the anion (13); see text.

Table 2. <sup>1</sup>H N.m.r. spectra in D<sub>2</sub>O of the trisulphonated pyrylium ion (7) and related species<sup>a</sup>

Species	$\delta$ (p.p.m.)						
	Heterocycle 3-, 5-H	2-, 6-Aryl		4-Aryl			OMe
		2', 6'-H	3', 5'-H	2'-H	5'-H	6'-H	
Aldehyde (6)				8.25 <sup>d</sup>	7.20 <sup>e</sup>	7.90 <sup>g</sup>	4.05 <sup>b</sup>
Pyrylium ion (7)	8.60 <sup>b</sup>	8.30 <sup>c</sup>	8.00 <sup>c</sup>	8.35 <sup>d</sup>	7.25 <sup>e</sup>	<i>f</i>	3.95 <sup>b</sup>
Pseudobase (12)	<i>h</i>	8.10 <sup>b</sup>	8.10 <sup>b</sup>	8.20 <sup>d</sup>	7.05 <sup>e</sup>	7.70 <sup>g</sup>	3.95 <sup>b</sup>
Anion (13)	<i>h</i>	7.95 <sup>b</sup>	7.95 <sup>b</sup>	8.0	6.95 <sup>e</sup>	7.45 <sup>g</sup>	3.90 <sup>b</sup>
		7.85 <sup>b</sup>	7.85 <sup>b</sup>				

<sup>a</sup> Referenced to DSS [sodium 3-(trimethylsilyl)propane-1-sulphonate]. <sup>b</sup> Singlet. <sup>c</sup> Doublet, *J* 8 Hz. <sup>d</sup> Doublet, *J* 2 Hz. <sup>e</sup> Doublet, *J* 9 Hz. <sup>f</sup> Concealed. <sup>g</sup> Double doublet, *J* 9 and 2 Hz. <sup>h</sup> Deuteriated.

Table 3. <sup>13</sup>C N.m.r. chemical shifts<sup>a</sup> of the pyrylium ion (7) and related compounds in D<sub>2</sub>O

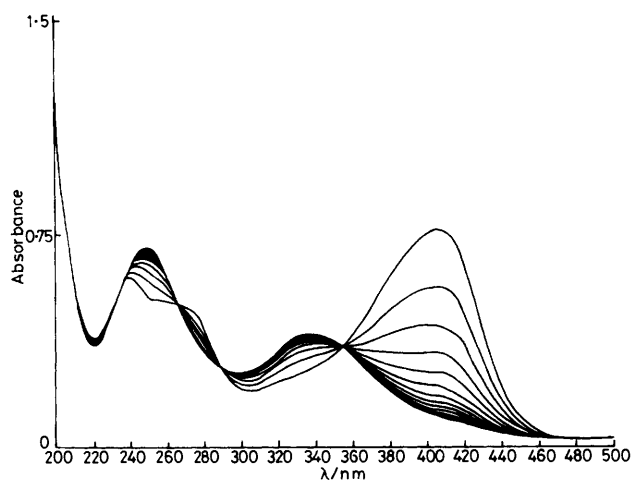
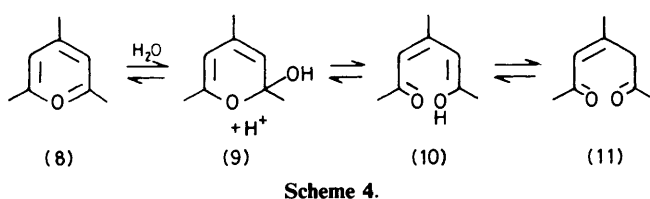
Compound	$\delta$ (p.p.m.)							
	C-1	C-2	C-3	C-4	C-5	C-6	CH <sub>3</sub>	C=O
Acetophenone (5) <sup>b</sup>	147.3	126.3	129.5	138.7	129.5	126.3	26.9	203.0
Benzaldehyde (6) <sup>c</sup>	167.3	141.6	136.5	135.8	118.6	133.6	62.1	199.6
Pyrylium ion (7) <sup>c,d</sup>		169.0	114.6	164.6	114.6	169.0	57.4	
Pseudobase (12) <sup>c</sup>		199.5	43.1	153.1	121.3 <sup>e</sup>	191.2	56.6	

<sup>a</sup> For numbering see Schemes 3 and 5. The substituent phenyl carbon signals were assigned as follows. (7): 2-, 6-phenyl *i* 135.9, *o* 129.3, *m* 127.5, *p* 149.0; 4-phenyl 1' 123.6, 2' 130.9, 3' 130.4, 4' 163.7, 5' 115.0, 6' 133.4. (12): 2-, 6-phenyl *i* 138.8, *o* 129.3, *m* 126.5, *p* 147.4; 4-phenyl 1' 132.1, 2' 129.3, 3' 127.2, 4' 158.3, 5' 113.4, 6' 132.0. <sup>b</sup> *p*-Dioxane internal standard. <sup>c</sup> DSS [sodium 3-(trimethylsilyl)propane-1-sulphonate] internal standard. <sup>d</sup> At 80 °C. <sup>e</sup> Small D-coupled signals.

**Table 4.** Effect of pH on the hydrolysis rates and equilibria of the pyrylium ion (7)

pH	$10^3 k_{\text{obs.}}/\text{s}^{-1}$	$10^3 k_t/\text{s}^{-1}$	$10^3 k_r/\text{s}^{-1}$	$K^a$	$A_\infty^b$
4.46	$3.29 \pm 0.06^c$	0.611	2.68	0.228	0.909
4.95	$2.76 \pm 0.01$	1.18	1.58	0.749	0.645
5.46	$2.90 \pm 0.01$	2.05	1.20	2.41	0.342
5.95	$2.84 \pm 0.03$	2.53	0.342	8.30	0.140
6.48	$2.92 \pm 0.04$	2.81	0.114	25.5	0.064
6.99	$3.06 \pm 0.07$	$3.06^d$			0.022
7.48	$3.53 \pm 0.06$	3.53			0.027
7.88	$4.84 \pm 0.06$	4.84			0.023
8.41	$10.6 \pm 0.1$	10.6			0.017
8.94	$26.7 \pm 0.3$	26.7			0.024
9.49	$72.2 \pm 1.4$	72.2			0.024

<sup>a</sup>  $A_0$  = absorbance of pyrylium ion (7) (1.088) at 407 nm,  $A_\infty$  = absorbance of final equilibrium mixture at 407 nm,  $A_{\text{PB}}$  = absorbance of pseudobase (0.023) at 407 nm,  $[\text{Py}^+] = A_\infty - A_{\text{PB}}$ , and  $[\text{PB}] = A_0 - (A_\infty - A_{\text{PB}})$ . Using this symbolism  $K = [\text{PB}]/[\text{Py}^+] = (1.11 - A_\infty)/(A_\infty - 0.023)$ . <sup>b</sup>  $\epsilon = A_\infty/1.86 \times 10^{-5}$  at a given pH. <sup>c</sup> 90% Confidence limit of slope. <sup>d</sup>  $k_{\text{obs.}} = k_t$  when  $k > 25$ .



**Figure 1.** Hydrolysis of the pyrylium ion (7) at pH 6.5 (taken at 120 s intervals) 0–1.5 absorbance range): the initial peak at 407 nm decreases with time

it should be an intermediate in the conversion of pyrylium ion into pseudobase. The enol of 1,2,4,5-tetraphenylpent-2-ene-1,5-dione cyclised much faster than the acyclic pseudobase itself.<sup>33</sup>

Recent work on the hydrolysis of flavylum cations has provided additional support for this mechanism.<sup>30</sup>

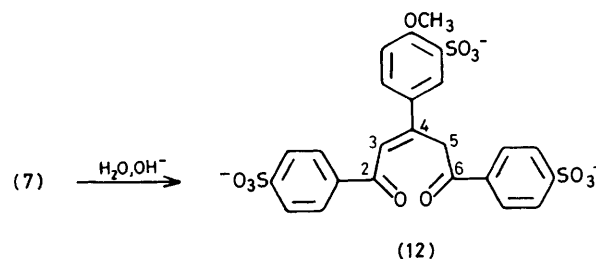
**Hydrolysis of the Pyrylium Ion (7).**—pH 4.5–9.5. Figure 1 summarises the results of a u.v. study of the hydrolysis of the pyrylium ion (7) at pH 6.5: (7) was rapidly and completely converted into a new product which absorbed at 339 nm. Similar behaviour was observed over the pH range 6.5–9.5. The <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra (Tables 2 and 3) \* of this species

\* Ref. 34 contains corresponding spectral data for the triphenyl analogues.

**Table 5.** General base catalysis terms <sup>a</sup> for the pyrylium ion (7)

Buffer	pH	[Buffer]/M <sup>b</sup>	$10^3 k/\text{s}^{-1}$	$10^3 k_B/\text{l mol}^{-1}$
Acetate	4.80	0.0100	2.94	8.96
		0.0500	3.34	
		0.1000	3.75	
		Intercept = $2.86 \times 10^{-3} \text{ s}^{-1}$		
Phosphate	7.10	0.0011	3.68	24.9
		0.0140	3.99	
		0.0510	4.92	
		Intercept = $3.65 \times 10^{-3} \text{ s}^{-1}$		
Borate	8.36	0.0050	4.26	24.4
		0.0300	5.04	
		0.0660	5.77	
		Intercept = $4.20 \times 10^{-3} \text{ s}^{-1}$		

<sup>a</sup>  $25.0 \pm 0.1^\circ\text{C}$ . <sup>b</sup> Ionic strength held at 0.5 (NaCl).



in aqueous 0.5M- $\text{Na}_2\text{HPO}_4$  were consistent with the 2-ene-1,5-dione structure (12) (see foregoing discussion).

These reactions showed pseudo-first-order kinetics and the  $k_{\text{obs}}$  values are recorded in Table 4. Working with the corresponding buffers indicated general base catalysis (Table 5) by the  $\text{CH}_3\text{CO}_2^-$ ,  $\text{HPO}_4^{2-}$ , and  $\text{B}_4\text{O}_7^{2-}$  anions. However, this affected the rate ( $k_{\text{obs}}$ ) by less than 5% at  $I$  0.01. Uncorrected values of  $k_{\text{obs}}$  were used to determine the other kinetic parameters.

The effect of pH on the pseudo-first-order rate constant ( $k_{\text{obs}}$ ) for the equilibration of the pyrylium ion (7) with its pseudobase (12) can be seen in Figure 2. This constant is the sum of the pseudo-first-order rate constants for the formation of pseudobase ( $k_t$ ) and its reversion to pyrylium ( $k_r$ ).<sup>19</sup> Individual rate constants can be calculated at each pH if both  $k_{\text{obs}}$  and  $K$  are known. We define  $K$  as the equilibrium constant  $[\text{PB}]/[\text{Py}^+]$  at a particular pH;  $K'_a$  is defined as  $[\text{PB}][\text{H}^+]/[\text{Py}^+]$  and was determined spectrophotometrically<sup>35</sup> to be

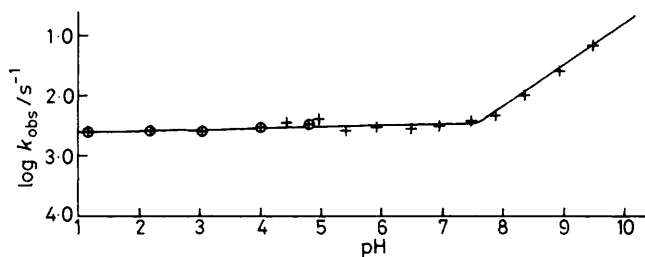


Figure 2.  $\log k_{\text{obs}}$  versus pH for equilibration of the pyrylium ion (7) with the pseudobase (12); kinetic data from Tables 4 and 7 (circled points)

$10^{-5.07}$ . Values for  $k_f$  and  $k_r$  are summarised in Table 4. The rate constants for the forward reaction ( $k_f$ ) obey the empirical equation (iv).

$$k_{\text{obs}} = k_f + k_r \quad (\text{i})$$

$$K = k_f/k_r \quad (\text{ii})$$

$$k_{\text{obs}} = k_f(1 + 1/K) \quad (\text{iii})$$

$$k_f = \frac{k_{\text{H}_2\text{O}}}{K'[\text{H}^+] + 1} + k''[\text{OH}^-] \quad (\text{iv})$$

Figure 3 displays the pH-rate profile for the forward reaction. Non-unit slopes of +0.74 and -0.52 were found for those sections of the pH-rate profile which were inversely proportional to  $[\text{H}^+]$  and directly proportional to  $[\text{OH}^-]$ , respectively. Such values usually imply a complex mechanism<sup>36</sup> in which there is a fractional order dependence on  $[\text{H}^+]$  and/or  $[\text{OH}^-]$ . However, good straight lines were obtained when  $1/k_f$  was plotted against  $[\text{H}^+]$  ( $r = 0.997$ ) and  $k_f$  against  $[\text{OH}^-]$  ( $r = 0.998$ ) for the appropriate regions. This confirmed the simple equilibrium ( $\text{A} \rightleftharpoons \text{B} + \text{H}^+$ ) indicated by the isosbestic points observed in the series of spectra in Figure 1.<sup>37</sup> The non-unit slopes are evidently caused by curvature in the pH-rate profile which is not readily apparent in Figure 3.

The similarity between the pH-rate profile observed in this study and those obtained by Williams<sup>5</sup> indicated that the sulphonic acid groups did not affect the mechanism of hydrolysis of (7). The pH-rate profile for the conversion of cation ( $k_f$ ) into pseudobase is expected to consist of a plateau region ( $k_{\text{H}_2\text{O}}$ , attack by water) and a region directly proportional to  $\text{pOH}^{19}$  ( $k_{\text{OH}}$ ). The rate expressions  $k^{\text{H}_2\text{O}}$  and  $k^{\text{OH}}$  can

$$k_f = k^{\text{H}_2\text{O}} + k^{\text{OH}} \quad (\text{v})^*$$

be obtained by applying the steady state approximation to the following reactions. The nature of the intermediate(s) will be discussed later. The complete kinetic expression is mathematically equivalent to equation (iv), where  $K' (= k_{-1}/k_2)$  was determined from a plot of  $1/k_f$  versus  $[\text{H}^+]$  and  $k'' = [k_{\text{OH}}k_3/(k_3 + k_0)]$  was obtained from a plot of  $k_f$  versus  $[\text{OH}^-]$ . Kinetic and thermodynamic data for the pyrylium ion (7) are collected in Table 6.

The apparent titration (inflection) in the pH-rate profile occurs because in the region pH 4–7 there is a change in the rate-determining step: when  $k_{-1}[\text{H}^+] \gg k_2$ ,  $k_f = k_{\text{H}_2\text{O}} k_2/k_{-1}[\text{H}^+]$  and the rate is inversely proportional to  $[\text{H}^+]$ ; and when  $k_2 \gg k_{-1}[\text{H}^+]$ ,  $k_f = k_{\text{H}_2\text{O}}$  and a limiting value is obtained.

\* Superscripts are used to indicate overall rate constants and subscripts fundamental rate constants.

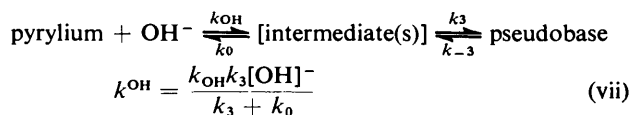
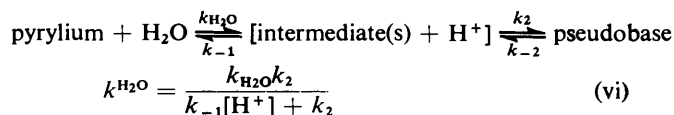
Table 6. Kinetic and thermodynamic data for the pyrylium ion (7)

$\text{p}K'_a$	$5.07 \pm 0.02$
$\text{p}K_c$	10.7
$k_{\text{H}_2\text{O}}$	$4.3 \times 10^{-3} \text{ s}^{-1}$
$k_{-2}$	$2.64 \times 10^{-3} \text{ s}^{-1}$
$k''$	$2.14 \times 10^3 \text{ s}^{-1}$
$K'$	$5.97 \times 10^4$

Table 7. Effect of pH on the conversion of pseudobase (12) into the pyrylium ion (7)

pH	$10^3 k_{\text{obs}}/\text{s}^{-1}$	$10^3 k_f/\text{s}^{-1}^a$	$10^3 k_r/\text{s}^{-1}^{b,c}$	$K^d$	$A_\infty$
1.13	$2.62 \pm 0.02$		2.62		0.735
2.19	$2.61 \pm 0.01$		2.61		0.738
3.05	$2.65 \pm 0.01$		2.65	0.038	0.711
3.99	$2.95 \pm 0.01$	0.29	2.66	0.110	0.666
4.82	$3.14 \pm 0.05$	1.15	1.99	0.580	0.474

<sup>a</sup> Conversion of pyrylium ion into pseudobase. <sup>b</sup> Conversion of pseudobase into pyrylium ion. <sup>c</sup>  $k_{\text{obs}} = k_r$  when  $K < 0.1$ . <sup>d</sup>  $K = (0.737 - A_\infty)/(A_\infty - 0.020)$ .



$$k_f = \frac{k_{\text{H}_2\text{O}}k_2}{k_{-1}[\text{H}^+] + k_2} + \frac{k_{\text{OH}}k_3[\text{OH}^-]}{k_3 + k_0} \quad (\text{viii})$$

The hydrogen ion concentration at which these two rates become equal is then given by equations (ix) and (x).

$$k^{\text{H}_2\text{O}} = \frac{k_{\text{H}_2\text{O}}k_2}{k_{-1}[\text{H}^+]} \quad (\text{ix})$$

$$[\text{H}^+] = \frac{k_2}{k_{-1}} = \frac{1}{K'} \quad (\text{x})$$

In a previous kinetic analysis of this type of reaction, a mathematically equivalent kinetic expression was obtained.<sup>5</sup> It is now proposed that the constant  $K_a$  obtained previously<sup>5</sup> and attributed to the pyrylium-2*H*-pyran equilibrium in a recent review<sup>19</sup> is  $k_2/k_{-1}$ . The observed pH-rate profile in agreement with the previous<sup>5</sup> study, indicated the presence of at least one intermediate prior to the formation of acyclic pseudobase.

*Conversion of the Pseudobase (12) into the Pyrylium Ion (7).*—The <sup>13</sup>C and <sup>1</sup>H n.m.r. spectra of reaction mixtures at alkaline pH (<10) indicated the complete conversion of the pyrylium ion (7) into its acyclic pseudobase. Solutions of (12) were then used to study the conversion of pseudobase into pyrylium ion. It was thus possible to obtain values of  $k_{\text{obs}}$  at low pH which could not be determined easily starting with the cation (7) (Table 7). Figure 3 shows the pH-rate profile for conversion of pseudobase (12) into (7) ( $k_r$ ). The rate constants for the reverse reaction obeyed the theoretical equation (xi).

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

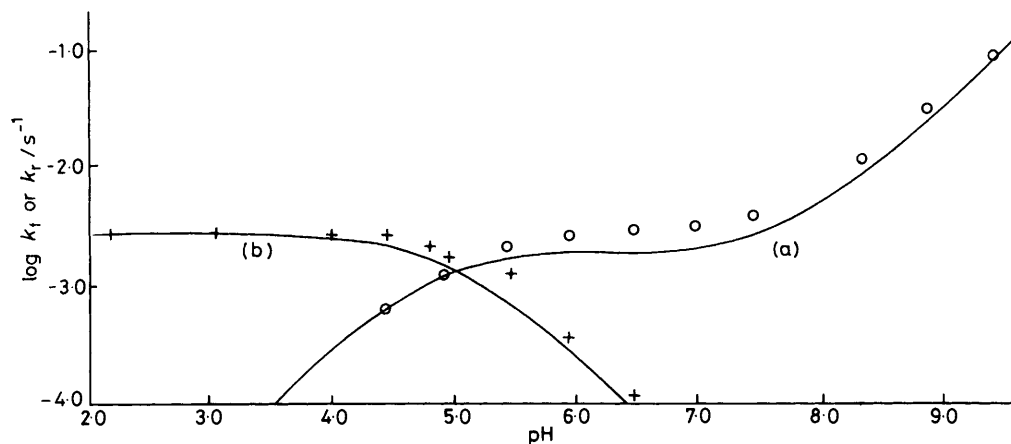
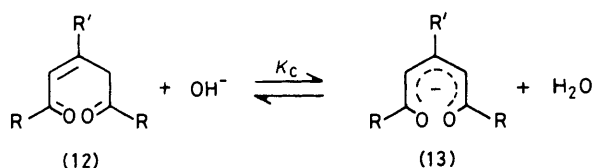
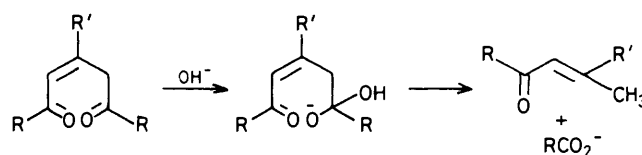


Figure 3. (a)  $\log k_t$  versus pH; solid line from equation (iv) and Table 6; kinetic data from Table 4; (b)  $\log k$  versus pH; solid line from equation (xi) and Table 6; kinetic data from Tables 4 and 7



Scheme 6.



Scheme 7.

A similar pH-rate profile has been reported for the conversion of 1,3,5-triphenylpent-2-ene-1,5-dione into (1a) in alcohol-water.<sup>28</sup> Here too, the apparent titration step is a consequence of the steady state expression for  $k_t$ : when  $k_{-1}[\text{H}^+] \gg k_2$ ,  $k_r = k_{-2}$ ; and when  $k_2 \gg k_{-1}[\text{H}^+]$ ,  $k_r = k_{-1}k_{-2}[\text{H}^+]/k_2$ . The  $[\text{H}^+]$  value where both rates are equal is also  $k_2/k_{-1}$ ; a similar value ( $1.02 \times 10^{-5}$ ) was found.

The proposal<sup>28,32,33</sup> that the rate-determining step in the conversion of pseudobase into pyrylium ion is the enolisation of the 2-ene-1,5-dione will be supported in the following sections.

**Reaction of the Pyrylium Ion (7) at  $\text{pH} \geq 10$ .**—The pyrylium ion (7) disappears within 10 s at  $\text{pH} \geq 10$ , to give an absorbance spectrum characteristic of pseudobase (12) and its anion (13),<sup>23,26,29,38</sup> which absorbs at 487 nm.<sup>19,21,24</sup>

The  $\text{p}K_c$  value was determined spectrophotometrically<sup>35</sup> to be 10.7 for this equilibrium. Solutions of the anion at  $\text{pH} < 10$  were unstable with respect to pseudobase. At higher pH, it still decomposes, but, at  $\text{pH} 10$ – $11.5$  values of  $A_\infty$  were constant for at least 30 s and hence were used to determine  $\text{p}K_c$ .

The anion band at 487 nm disappeared in a biphasic process which was separated into two pseudo-first-order components. A new species which absorbed at 330 nm was observed. No pyrylium ion was formed when solutions containing this species were acidified with HCl. The  $^{13}\text{C}$  n.m.r. spectrum ( $\text{H}_2\text{O}-\text{D}_2\text{O}$ ) of the reaction mixture at  $\text{pH} \text{ ca. } 12$  indicated cleavage of pseudobase (12),<sup>18,20,38</sup> showing characteristic peaks for carboxylate (174.7),  $\text{CH}_3$  (26.5), and  $\text{CH}_2\text{D}$  (25.9 p.p.m.).

The presence of two methoxy signals in the  $^{13}\text{C}$  n.m.r. spectrum indicated the reaction was more complex than shown in Scheme 7.<sup>23,24</sup> Similar results obtained under argon eliminated the possibility of autoxidation.<sup>18</sup>

The cleavage reaction was the slower of the two processes

which consumed the anion (13). In the next section the faster process will be discussed.

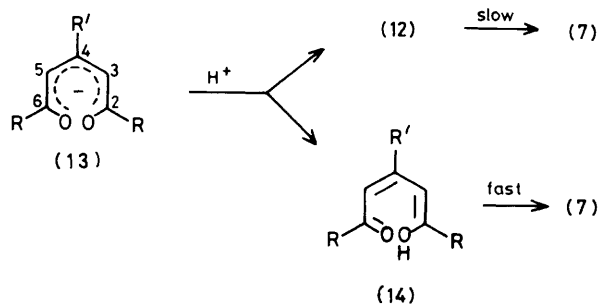
**Conversion of the Anion (13) into the Pyrylium Ion (7).**—Acidification of solutions of the anion of (12) gave the pyrylium ion (7) in a biphasic manner. The immediate formation of (7) was followed by a slower reaction which also gave the cation.

Enolisation of the pseudobase to the oxo-dienol was proposed as the rate-determining step in the acid-catalysed conversion of pseudobase into cation.<sup>28,32,33</sup> In agreement, protonation of the anion (13) on oxygen led directly to the oxo-dienol (14), which rapidly cyclised to the pyrylium ion (7); whereas protonation on carbon gave the pseudobase (12) which affords (7) more slowly. When solutions containing the anion (13) were acidified to  $\text{pH} 4.80$ , the rate ( $3.03 \times 10^{-3} \text{ s}^{-1}$ ) of the slow formation of pyrylium ion (7) was close to that obtained starting with pseudobase ( $3.23 \times 10^{-3} \text{ s}^{-1}$ ) at the same pH. If the rate-determining step occurs after enolisation, the rates of formation of pyrylium cation from the two tautomers should be similar.

As already discussed, ketonisation of the oxo-dienol (14) to give the 2-ene-1,5-dione (12) should be the rate-determining step in the conversion of the pyrylium ion (7) into the pseudobase (12). This implies that the oxo-dienol (14) is an intermediate in the formation of (12) and, indeed such an intermediate was isolated by Basselier<sup>24</sup> in the hydrolysis of 2,3,5,6-tetraphenylpyrylium ion and shown to cyclise faster than the 1,5-dienone.<sup>33</sup>

Anion formation was fast on mixing the pyrylium ion (7) with the appropriate buffer ( $\text{pH} \geq 10$ ). In comparison, the rate constant for formation of the anion (13) from the pseudobase (12) was  $2.70 \times 10^{-2} \text{ s}^{-1}$  at  $\text{pH} 11.01$ . These results indicated that the cation (7) and the pseudobase (12) gave the anion (13) by two distinct routes.

The pyrylium ion (7) reacts quickly with  $\text{OH}^-$  to form the



Scheme 8.

oxo-dienol (14), which is rapidly deprotonated to yield the anion (13). In this metastable state the concentration of anion (13) is higher than its equilibrium value ( $K_e$ ). The fast process in the biphasic disappearance of (13) is the establishment of equilibrium between anion (13) and pseudobase (12). In the fast process the anion absorbance drops to essentially the same value as obtained from the pseudobase at the same pH. The pseudobase (12) is a carbon acid and proton transfer would be expected to be slower.<sup>39</sup>

### Conclusion and Implications

The oxo-dienol (14) is the only intermediate present to any significant extent in equilibrium with the pyrylium ion (7) and pseudobase (12). 2*H*-Pyran intermediates ring open very rapidly and only when ring opening is structurally hindered are they isolated.<sup>16</sup> This postulate can explain the observed pH-rate profiles (for  $k_f$  and  $k_r$ ).

Sulphonic acid groups confer water solubility on both the pyrylium ion (7) and its acyclic pseudobase (12), but do not affect the pH dependence of either the forward<sup>5</sup> or the reverse rate<sup>33</sup> (Figure 3).

The apparent equilibrium constant  $K_a'$  raises the  $pK_a'$  value for (7) two units over that for 2,4,6-triphenylpyrylium ion. For 2,4,6-trimethylpyrylium ion the pseudobase was greatly favoured at all pH values studied.<sup>5</sup> The pyrylium (7) will thus be present over a larger pH range than other previously studied pyrylium ions;<sup>5</sup> this pH range is particularly useful synthetically.

There are few previous studies of cation-pseudobase equilibria in completely aqueous media. This makes it difficult to compare many of the data in the literature.<sup>19</sup> Introduction of hydrophilic groups (such as the sulphonic acid group) provides a new possible means of studying these reactions in water.

The reactions of this new water-soluble pyrylium ion with amines are described in the following paper.

### Experimental

I.r. spectra were taken with a Perkin-Elmer 283 B and u.v. spectra with Perkin-Elmer 330 and Pye Unicam 8-200 spectrometers. A Varian EM 360 instrument was used for recording <sup>1</sup>H n.m.r. spectra and a JEOL FX 100 instrument for <sup>13</sup>C spectra. Elemental analyses were carried out by Atlantic Microlab Inc., Atlanta, Georgia. M.p.s were taken with a Bristolscope microscopic hot stage and are uncorrected. The u.v. and <sup>1</sup>H and <sup>13</sup>C n.m.r. data for the compounds under study are summarised in Tables 1–3 and in the body of this paper.

*Sodium 3-Formyl-6-methoxybenzenesulphonate.*—*p*-Anisaldehyde (12 g, 0.088 mol) was added dropwise to fuming

sulphuric acid (20 ml; 30% oleum) at 0 °C with stirring. The mixture was warmed to 25 °C for 30 min and the product was precipitated by pouring the purple-red oil into brine (120 ml). The precipitate crystallised from water (as plates) on cooling to 5 °C and was dried over P<sub>2</sub>O<sub>5</sub> to give the salt (6.5 g, 31%), m.p. > 350 °C (Found: C, 40.2; H, 3.0; S, 13.4. C<sub>8</sub>H<sub>7</sub>NaO<sub>5</sub>S requires C, 40.3; H, 3.0; S, 13.5%);  $\nu_{\text{max}}$  (CHBr<sub>3</sub> mull) 1 700, 1 600, 1 490, 1 260, and 1 200 cm<sup>-1</sup>;  $\delta$  (D<sub>2</sub>O) 4.0 (3 H, s), 6.9 (1 H, d, *J* 9 Hz), 7.6 (1 H, dd, *J* 9 and 2 Hz), 7.95 (1 H, d, *J* 2 Hz), and 9.45 (1 H, s, CHO).

*4-(4-Methoxy-3-sulphophenyl)-2,6-bis-(4-sulphophenyl)pyrylium Perchlorate.*—Sodium 4-acetylbenzenesulphonate (8.9 g, 40.0 mmol), sodium 3-formyl-6-methoxybenzenesulphonate (5.5 g, 20.0 mmol), and perchloric acid (16 g, 70%) were heated at 100–105 °C for 75 min with constant stirring. Acetone (200 ml) was added to the hot black oil, and the precipitate was washed with acetone (2 × 20 ml) and filtered off. Acetone (160 ml) after 60 min precipitated the pure pyrylium salt (microprisms), which was dried at 80 °C and 1 mmHg over P<sub>2</sub>O<sub>5</sub> (yield 3.22 g, 47%), m.p. > 350 °C (Found: C, 42.2; H, 3.0; S, 14.1. C<sub>24</sub>H<sub>19</sub>ClO<sub>15</sub>S<sub>3</sub> requires: C, 42.4; H, 2.8; S, 14.2%);  $\nu_{\text{max}}$  (CHBr<sub>3</sub>) 3 700–3 180br, 1 630, 1 590, 1 490, 1 190–1 240, and 1 090 cm<sup>-1</sup>.

*Kinetic Method.*—A 0.005 58M-solution of the pyrylium ion (7) was prepared in 0.1M-HCl. Reactions were initiated by injecting 10  $\mu$ l of this solution with a Hamilton syringe into a thermostatted (25.0  $\pm$  0.1 °C) u.v. cell containing 3.0 ml of buffer (*I* = 0.01). Reactions were followed by monitoring the disappearance or appearance of the characteristic absorbance at 407 nm of the pyrylium ion (7). Pseudo-first-order rate constants were obtained from the slope of the straight line obtained from a plot of  $\ln(A - A_\infty)$  vs. time (s) ( $r \geq 0.9995$ ).

### References

- 1 A. R. Katritzky, *Tetrahedron*, 1980, **36**, 679.
- 2 A. R. Katritzky and S. S. Thind, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1895.
- 3 A. R. Katritzky, N. E. Grzeskowiak, N. F. Eweiss, and E. A. Elsherbini, *J. Chem. Soc., Perkin Trans. 1*, 1983, 497.
- 4 Unpublished work from our laboratories.
- 5 A. Williams, *J. Am. Chem. Soc.*, 1971, **93**, 2733.
- 6 A. T. Balaban and C. D. Nenitzescu, *Liebigs Ann. Chem.*, 1959, **625**, 74.
- 7 A. N. Narkevich, G. N. Dorofeenko, and Yu. A. Zhdanov, *Dokl. Akad. Nauk. SSSR*, 1967, **176**, 103 (*Chem. Abs.*, 1968, **68**, 78605z).
- 8 C. Toma and A. T. Balaban, *Tetrahedron*, Suppl., 1966, **7**, 27.
- 9 Yu. A. Zhdanov, G. N. Dorofeenko, and A. N. Narkevich, *Zh. Obshch. Khim.*, 1963, **33**, 2418 (*Chem. Abs.*, 1963, **59**, 14105b).
- 10 M. H. O'Leary and G. A. Samberg, *J. Am. Chem. Soc.*, 1971, **93**, 3530.
- 11 A. Dinculescu and A. T. Balaban, *Rev. Roum. Chim.*, 1980, **25**, 1505 (*Chem. Abs.*, 1981, **95**, 203696r).
- 12 A. R. Katritzky, Y. K. Yang, J. Ellison, and J. Marquet, following paper (Part 6).
- 13 A. R. Katritzky, M. F. Abdel-Megeed, G. Lhomme, and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, 1979, 426.
- 14 A. R. Katritzky, J. Adamson, E. M. Elisseou, G. Musumarra, R. C. Patel, K. Sakizadeh, and W. K. Yeung, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1041.
- 15 A. T. Balaban, W. Schroth, and G. Fischer, *Adv. Heterocycl. Chem.*, 1969, **14**, 111.
- 16 A. T. Balaban, A. Dinculescu, G. N. Dorofeenko, G. W. Fischer, A. V. Koblik, V. V. Mezheritskii, and W. Shroth, 'Pyrylium Salts, Part II,' Academic Press, New York, 1982.
- 17 A. R. Katritzky, R. T. C. Brownlee, and G. Musumarra, *Tetrahedron*, 1980, **36**, 1643.
- 18 W. Dilthey and T. Böttler, *Ber.*, 1919, **52**, 2040.

- 19 J. W. Bunting, *Adv. Heterocycl. Chem.*, 1979, **25**, 1.
- 20 J. A. Berson, *J. Am. Chem. Soc.*, 1952, **74**, 358.
- 21 R. Wizinger and P. Ulrich, *Helv. Chim. Acta*, 1956, **39**, 207.
- 22 R. Lombard and J-P. Stephan, *Bull. Soc. Chim. Fr.*, 1958, 1458.
- 23 R. Lombard and A. Kress, *Bull. Soc. Chim. Fr.*, 1960, 1528.
- 24 J. J. Basselier, *Ann. Chim. (Paris)*, 1961, **6**, 1131.
- 25 G. Rio and Y. Fellion, *Tetrahedron Lett.*, 1962, 1213.
- 26 J-P. Griot, J. Royer, and J. Dreux, *Tetrahedron Lett.*, 1969, 2195.
- 27 G. Salvadori and A. Williams, *J. Am. Chem. Soc.*, 1971, **93**, 2727.
- 28 R. Hubaut and J. Landais, *C. R. Acad. Sci., Ser. C*, 1974, **278**, 1247.
- 29 C. L. Pedersen, *Acta Chem. Scand., Ser. B*, 1975, **29**, 791.
- 30 R. A. McClelland and S. Gedge, *J. Am. Chem. Soc.*, 1980, **102**, 5838.
- 31 E. Gård, I. I. Stanoiu, A. T. Balaban, and F. Chiraleu, *Rev. Roum. Chim.*, 1969, **14**, 247.
- 32 R. Hubaut and J. Landais, *C. R. Acad. Sci., Ser. C*, 1974, **279**, 697.
- 33 R. Hubaut and J. Landais, *Bull. Soc. Chim. Fr.*, 1975, 2147.
- 34 A. R. Katritzky, J. Lloyd, and R. C. Patel, *Chem. Scr.*, 1981, **18**, 256.
- 35 A. Albert and E. P. Serjeant, 'The Determination of Ionisation Constants,' Chapman and Hall, London, 1971, ch. 4.
- 36 T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' vol. 1, Benjamin, New York, 1966, pp. 4—16.
- 37 H. H. Jaffé and M. Orchin, 'Theory and Applications of Ultraviolet Spectroscopy,' Wiley, New York, 1962, pp. 560—572.
- 38 W. Diltthey, *Ber.*, 1919, **52**, 1195.
- 39 F. Hibert, 'Comprehensive Chemical Kinetics,' vol. 8, 'Proton Transfer,' eds. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1977, pp. 113—119.

Received 29th April 1983; Paper 3/676