Keto–enol tautomerism and hydration of 9-acylfluorenes

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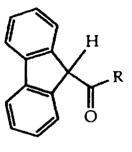
Keto–enol tautomeric constants and ionisation constants have been measured for the keto and enol tautomers of 9-formyl-, 9-acetyl- and 9-benzoyl-fluorene in aqueous solution at 25 °C. Values of pK_E (K_E = [enol]/[ketone] and p$K_E = -\log K_E$) are -1.22, 2.28 and 1.91, respectively, and the corresponding pK_as for enolate anion formation are 6.19, 9.94 and 9.44 for the keto tautomers and 7.41, 7.66 and 7.53 for the enols. The measurements demonstrate the effectiveness of the fluorenyl group in increasing enol stability and ketone acidity. For 9-formylfluorene, for which the enol is the stable tautomer, K_E is increased by a factor of more than 10^7 and the acidity of the keto tautomer by more than 10^9 relative to acetaldehyde (pK_E = 6.17, pK_a = 16.73). For 9-acetyl- and 9-benzoyl-fluorenes tautomeric constants were determined kinetically by combining rate constants for ketonisation measured spectrophotometrically following quenching of their enolate anions in carboxylic acid buffers with rate constants for enolisation measured by halogen trapping under the same conditions. For 9-formylfluorene rate constants for enolisation were measured by generating its unstable aldehyde tautomer from an ethanethiol hemithioacetal by reaction with iodine. Combining these rate constants with rate constants for ketonisation from trapping the aldehyde with bisulfite ion gave the tautomeric constant. In aqueous solution the aldehyde tautomer of 9-formylfluorene is appreciably hydrated and an equilibrium constant K_h = [hydrate]/[aldehyde] = 5.6 was derived from measurements of the (slower) equilibration of enol and hydrate following enolisation in acetic acid buffers. In aqueous solution therefore the enol (71%) and hydrate (24%) are the principal species. log k–pH profiles for enolisation, ketonisation and hydration reactions are reported. Intrinsic reactivities of the three enolate anions towards protonation by H_3O^+ and carboxylic acids are compared within an extended Brønsted plot of log k *versus* ΔpK with measurements by Kresge for the corresponding enolate anions derived from fluorene-9-carboxylic acid and its methyl, methylthio and methylthione esters. Surprisingly, not only are the thio and thione esters less acidic than the oxygen ester, but intrinsically less reactive.

Although normally of higher energy than their keto tautomers enols can be stabilised by intramolecular hydrogen bonding and resonance effects of α-keto substituents or by resonance[1,2] and steric effects[2,3] of α-aryl groups. An extreme example of α-aryl stabilisation not involving steric effects occurs with the 9-acylfluorenes (**1**), and for 9-formylfluorene indeed in aqueous solution the enol **3** is more stable than its keto tautomer **2**.[4,5]


1 R = H, Me, Ph


2 **3**

Isolation of 9-formylfluorene in α- and β-forms and assignment of enol and aldehyde structures was reported by Wisliscenus and Waldmuller in 1909.[6] The tautomers are acidic enough to dissolve in dilute aqueous sodium hydroxide, and precipitation by acidification at not too low temperatures produces predominantly the α-form as a yellow oil, whereas the β-form is obtained as a white solid from evaporation of solutions in CCl_4 and $CHCl_3$.[7] NMR spectra coupled with UV measurements confirm that in CCl_4 and $CHCl_3$ 9-formylfluorene is present predominantly as the aldehyde whereas in polar solvents such as methanol, acetonitrile and water (and even dioxane and ether) the enol is exclusively present. The preference for enol over the keto form in polar solvents is typical of enols lacking intramolecular hydrogen bonding.[8]

The greater stability of the enol than aldehyde form of 9-formylfluorene poses problems for determining the tautomeric constant K_E = [enol]/[aldehyde] by the commonly used kinetic method of combining rate constants for ketonisation and enolisation. Rates of enolisation cannot be measured by the halogen trapping method applicable when the enol is the unstable tautomer: it is necessary to generate a stoichiometric concentration of aldehyde and monitor its relaxation to enol directly. Similarly, instead of generating an unstable enol and measuring its relaxation to the keto tautomer, ketonisation must be stimulated by trapping the unstable aldehyde product.[4,5]

At first, it appeared that relaxation of the enol could be observed by direct neutralisation of the enolate anion in acidic or buffer solutions, since this led to a 30% drop in intensity of the initially observed enol absorbance. However, in the less polar solvent methanol, in which there must be more aldehyde than in water, NMR spectra showed only the presence of enol, and it became apparent that the predominant reaction being observed was not ketonisation but formation of the hydrate of the aldehyde, which indeed is the major non-enolic species present in aqueous solution.

This conclusion was confirmed by direct measurements of rates of ketonisation using bisulfite ion to trap the 9-formylfluorene as fast as it was formed.[5] These rates were considerably faster than those for relaxation of the enol, which should therefore represent formation of the hydrate of the aldehyde. If Chieng, Kresge and Krogh's[9] study of diphenylacetaldehyde is taken as a guide, their measurement of K_h = [hydrate]/[aldehyde] = 4.7 implies that the dominant equilibrium for 9-formylfluorene should be between enol and hydrate rather than enol and aldehyde.

Measurements of rates of ketonisation of 9-formylfluorene by trapping the aldehyde with bisulfite ion, and of equilibrium constants for reaction of the enol to hydrate, have been described already.[5] In this paper we consider (*a*) generation of the aldehyde from reaction of its hemithioacetal with iodine and measurement of rates and equilibria for its subsequent enolisation, and (*b*) measurement of rate and equilibrium

Table 1 Slopes (k) and intercepts (k_o) of plots of measured first-order rate constants against concentration of buffer base for ketonisation of 9-acetylfluorene enol and enolisation of 9-formylfluorene in aqueous solution at 25 °C ± 0.1 °C and constant buffer ratio

			FlC=C(CH$_3$)OH[b]		FlCHCHO[c]	
Buffer	Ratio[a]	pH	k/dm^3 mol^{-1} s^{-1}	k_o/s^{-1}	k^G/dm^3 mol^{-1} s^{-1}	k^G_o/s^{-1}
Cyanoacetic	1	2.37	1.93	0.25	—	—
Chloroacetic	1	2.73	4.03	0.26	4.35	4.62
Glycolic	1	3.69	11.8	0.22	7.29	3.02
Acetic	1	4.65	31.8	0.25	16.77	3.36
	4	5.20	30.2	0.37	15.88	2.77
Propionic	1	4.79	37.1	0.36	—	—
Lutidine	1	6.73	27.1	0.97	—	—
	2	7.01	28.5	1.36	—	—
	3	7.20	32.2	1.55	—	—

[a] Ratio of buffer base to buffer acid concentrations. [b] Ketonisation; ionic strength 0.1 mol dm^{-3} with NaCl. [c] Enolisation; ionic strength 0.2 mol dm^{-3} with NaCl; includes competing hydration and a contribution from reverse ketonisation.

constants for hydration of the aldehyde. In addition, the more straightforward evaluation of tautomeric constants for 9-acetyl- and 9-benzoyl-fluorenes is described.

Results

UV Spectra and pK_as

The UV spectrum of 9-formylfluorene in methanol and water shows a long wavelength absorption with λ_{max} = 315 nm closely resembling that of its enol methyl ether (λ_{max} = 315 nm), which is consistent with the presence of a significant concentration of enol. In basic solutions there is a shift of this peak to 334 nm consistent with formation of an enolate anion. Quantitative measurements of peak intensities as a function of pH lead to an apparent pK_a = 7.55. The pK_a is apparent because it corresponds to ionisation of a mixture of enol, aldehyde and hydrated aldehyde forms of the substrate.[5]

Measurements of spectra of 9-acetylfluorene and 9-benzoylfluorene show the characteristic fluorene chromophore with no sign of an enol tautomer. Acetylfluorene undergoes ionisation in dilute sodium hydroxide to an anion with λ_{max} = 365 nm, assumed to be the enolate anion: measurements in phenol buffers give pK_a = 9.94 ± 0.05. Benzoylfluorene behaves similarly, yielding an anion with λ_{max} = 370 nm and pK_a = 9.45 ± 0.03 based on measurements in phenol buffers.

Keto–enol tautomerism of acetyl- and benzoyl-fluorenes

The relatively low values of the pK_as for acetyl and benzoylfluorene allowed kinetic measurements of ketonisation to be made by quenching solutions of the enolate anions in dilute sodium hydroxide into acidic or buffer solutions at pHs below their pK_as to form the enols. For acetylfluorene, measurements were made in acetic, chloroacetic, hydroxyacetic, cyanoacetic, propanoic and 2,6-lutidine buffers as well as HCl solutions. First-order rate constants (k_{obs}) were measured by stopped-flow spectrophotometry as a function of buffer concentration at constant buffer ratio, and the dependence of k_{obs} upon the concentration of the basic component of the buffer (B) was found to be described by eqn. (1), in which k and k_o are buffer

$$k_{obs} = k_o + k[B] \qquad (1)$$

dependent and buffer independent rate constants, respectively. Values of k_o and k for different buffers and buffer ratios are shown in Table 1. In practice no catalysis by buffer acids or even hydrogen ions was observed.

In acetic acid buffers rates of enolisation of 9-acetylfluorene were measured using trapping by I_3^- under zero-order conditions[2,10] and by Br_2 (and Br_3^-) under first-order conditions.[11] Second-order rate constants for catalysis by acetate ion in 1:1 buffers at ionic strength 0.1 were 0.162 dm^3 mol^{-1} s^{-1} and 0.139 dm^3 mol^{-1} s^{-1} for bromine and iodine, respectively. The value for bromine was preferred because under first-order conditions, unlike zero-order conditions, it is not necessary to know the concentrations of halogen or substrate. Bromination measurements are also less susceptible than iodination to reversibility at mildly acidic pHs. Oxidation of solutions of all the acylfluorenes to fluorenone occurred readily despite the precaution of bubbling nitrogen or argon through the solutions before each measurement.

The measurements of rate constants for enolisation and ketonisation allowed evaluation of a tautomeric constant, K_E, for the keto–enol equilibrium. Combining the rate constant for bromination with a value of 31.0 dm^3 mol^{-1} s^{-1} for acetate catalysis of ketonisation in 4:1 and 1:1 acetic acid buffers gave K_E = [enol]/[ketone] = 0.162/31.0 = 5.23 × 10^{-3} (pK_E = 2.28). This is close to a less precise value based on the intercept k_o = 1.6 × 10^{-3} s^{-1} [eqn. (1)] from bromination and the corresponding rate constant (0.27 s^{-1}) for buffer-independent ketonisation giving K_E = 1.6 × 10^{-3}/0.27 = 6 × 10^{-3}.

Combining the tautomeric and ionisation constants for acetylfluorene with the rate constants for buffer base catalyses of ketonisation from Table 1, 'molecular' rate constants k_{B^-} for proton abstraction from the ketone by buffer base and values of k_{BH} for the reverse protonation of the enolate anion by buffer acid can be obtained from the relationships $k_{B^-} = kK_E$ and $k_{BH} = kK_aK_E/K_a^{KH}$ (where K_a is the ionisation constant of the buffer acid and K_a^{KH} that of the ketone) which is based on eqn. (1) and expressions for k implied by the reaction scheme of eqn. (2). Values of k_{BH} and kB^- for the buffers studied are listed in Table 2.

$$EH + B^- \underset{}{\overset{K_a^{KH}/K_aK_E}{\rightleftharpoons}} E^- + BH \underset{k_{B^-}}{\overset{k_{BH}}{\rightleftharpoons}} KH \qquad (2)$$

The buffer-independent rate constants k_o from Table 1 may be combined with measurements of first-order rate constants for reaction in HCl solutions to yield a pH–profile for ketonisation. Measured rate constants for the reaction (k_{obs}/s^{-1} at 25 °C) at different concentrations of HCl (mol dm^{-3}) were as follows: 0.25 (0.055), 0.24 (0.095), 0.26 (0.245), 0.27 (0.495). These are sensibly pH-independent with an average rate constant k_{H_2O} = 0.25 s^{-1}. However inspection of values of k_o from measurements in lutidine buffers showed the appearance of a hydroxide-catalysed ketonisation with rate constant ~9 × 10^6 dm^3 mol^{-1} s^{-1} which may be interpreted as rate-determining protonation of the enolate anion by a water molecule. These values yield rate constants k_{BH} for attack of H_3O^+ and H_2O on enolate anion as in eqn. (2) and k_{B^-} for the reverse proton abstraction from the ketone by H_2O and OH^- which are also listed in Table 2.

Table 2 Second-order rate constants ($dm^3\ mol^{-1}\ s^{-1}$) for deprotonation (k_B) of 9-acylfluorenes (FlCHCOR) and protonation (k_{BH}) of their enolate anions in aqueous solution at 25 °C (ionic strength 0.20 mol dm^{-3})

		R = CH_3		R = Ph		R = H	
Acid	pK_a	k_{BH}	k_{B^-}	k_{BH}	k_{B^-}	k_{BH}	k_B
H_3O^+	−1.74	1.1×10^7	1.3×10^{-3}	6.61×10^6	2.40×10^{-3}	4.0×10^5	0.254
$CNCH_2COOH$	2.43	3.3×10^5	0.0101				
$ClCH_2COOH$	2.86	2.5×10^5	0.0211			6.09×10^3	2.85
$HOCH_2COOH$	3.83	8.0×10^4	0.0619			1.39×10^3	5.67
CH_3COOH	4.75	2.52×10^4	0.163	3.46×10^3	7.1×10^{-2}	4.04×10^2	14.7
CH_3CH_2COOH	4.90	2.13×10^4	0.194				
2,6-Lutidinium	6.77	230	0.16				
H_2O	15.74	4.0	1.1×10^4			6.25×10^{-2}	4.0×10^6

Table 3 Dependence upon iodide and acetate ion concentrations of first-order rate constants for reaction of the ethanethiol hemicetal of 9-formylfluorene with triiodide ion in aqueous solution at 25 °C[a]

	k/s^{-1}	
[KI]/mol dm^{-3}	$[CH_3COO^-]$ = 0.05 mol dm^{-3}	$[CH_3COO^-]$ = 0.01 mol dm^{-3}
0.15	4.95	2.80
0.12	5.95	
0.09	8.7	
0.06	15.1	

[a] Ionic strength 0.2 mol dm^{-3} with NaCl; concentration of hemithioacetal is *ca.* 5.8×10^{-5} mol dm^{-3}; concentration of I_3^- + I_2 is 1.8×10^{-5} mol dm^{-3}.

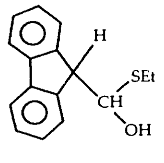
Kinetic results for benzoylfluorene were similar to those for acetylfluorene but the measurements are more limited. Ketonisation rate constants were obtained by quenching the enolate anion in 1 : 1 acetic acid buffers (pH, 4.65) and gave $k = 5.75\ dm^3\ mol^{-1}\ s^{-1}$ for buffer catalysis and a buffer-independent rate constant $k_o = 1.94\ s^{-1}$.

A rate constant for enolisation of 9-benzoylfluorene was also measured from bromination in 1 : 1 acetic acid buffers. However the brominated product precipitated from water and the measurements were made in water containing 20% methanol. Measurements in 30% and 40% aqueous methanol showed no systematic trend in rate constants with solvent composition and it was assumed that the values in 20% methanol were unchanged from water itself. The rate constants were not sufficiently accurate to separate values of k and k_o from the slope and intercept of a buffer plot and $K_E = 1.22 \times 10^{-2}$ was evaluated from ratios of rate constants (k_{obs}) for ketonisation and enolisation measured at the same buffer concentrations. This value of K_E then allowed evaluation of $k = 7.2 \times 10^{-2}\ dm^3\ mol^{-1}\ s^{-1}$ for the buffer-independent reaction for enolisation from the corresponding values of k and k_o for ketonisation. These rate constants then gave values of k_{B^-} and k_{BH} for acetic acid and H_3O^+ catalysis based on eqn. (2) and are listed with those for 9-acetylfluorene in Table 2.

Enolisation of 9-formylfluorene

Reaction of 9-formylfluorene to form its more stable enol tautomer required generation of the aldehyde from a hemithioacetal. In 1 : 1 acetic acid buffers it was possible to choose conditions in which the disappearance of the iodine was at least ten times faster than appearance of the spectrum of the enol. The overall reaction is shown in Scheme 1 including the ultimate equilibration of the enol with hydrate.

Rate constants for reaction of iodine with 9-formylfluorene hemithioacetal are shown in Table 3. The reaction was not studied in detail but the rate showed an inverse dependence upon $[I^-]^2$ consistent with rapid formation of an iodosulfonium intermediate as in the oxidation of sulfides,[12] reaction of iodine with thioacetals[13] and iodine-promoted opening of the thiazolidine ring.[14] A single measurement indicated catalysis by acetate ion which may act as a base catalyst in expelling an ethyl sulfenyl iodide leaving group, if the reverse attack of weakly basic thiolate ions upon a carbonyl group may be taken as a guide.[15,16]



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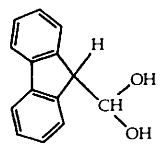


5

$$4 + I_3^- \xrightarrow{\text{fast}} \text{Aldehyde} \overset{\text{slow}}{\rightleftharpoons} \text{Enol} \overset{\text{v. slow}}{\rightleftharpoons}$$
$$\text{Hydrate} + \text{EtSI} + H^+ + 2I^-$$

Scheme 1

The slower appearance of the spectrum of the enol of 9-formylfluorene following formation of the aldehyde was studied in carboxylic acid buffers and showed catalysis by buffer base only, as expected from the previous measurements for 9-acetyl- and 9-benzoyl-fluorene. Rate constants k and k_o based on eqn. (1) are listed in Table 1. Values of log k_o are plotted as filled circles in Fig. 1 against pH to yield a pH profile. It can be seen that log k_o is pH independent in the pH range of acetic buffers as it was for 9-acetylfluorene.

In Table 1 and Fig. 1 the rate constants for appearance of enol from 9-formylfluorene are designated k^G to indicate that they were measured by 'generating' the aldehyde tautomer (from reaction of its hemithioacetal with iodine). Strictly speaking they do not correspond to the rate constant k_E for enolisation because they need to be corrected for contributions from the reverse ketonisation reaction (k_K), and from competing hydration (k_h) as well as the reverse dehydration reaction (k_d) as shown in eqn. (3). However we shall see that these corrections are quite small.

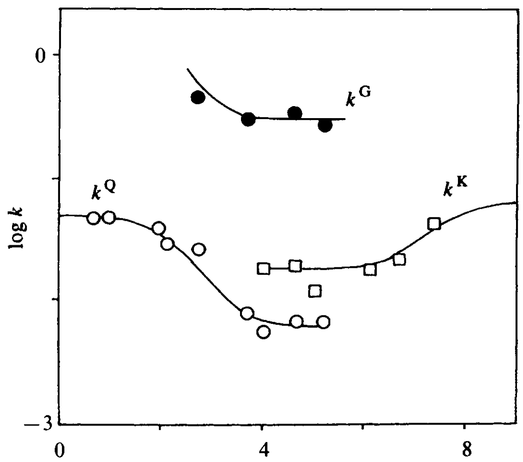


Fig. 1 log k–pH Profiles for 9-formylfluorene: (○) hydration of enol; (□) ketonisation of enol from trapping aldehyde with bisulfite ion; (●) enolisation of aldehyde from hemithioacetal (**4**)

$$k^G = k_E + k_K + k_h + k_d \qquad (3)$$

Ketonisation of 9-formylfluorene

Measurements of rate constants for buffer-catalysed ketonisation of the enol of 9-formylfluorene by trapping the aldehyde as its bisulfite complex have been described.[5] There is no influence of hydration on this reaction because the enol is formed stoichiometrically in the buffer by 'quenching' a solution of enolate anion at sufficiently high concentration of bisulfite ion that hydration does not compete with trapping of the aldehyde intermediate.

Buffer-independent rate constants (k_K^o) for the ketonisation reaction are plotted as a pH profile in the range pH 3–pH 7 in Fig. 1 (squares). These data are not recorded in ref. 5 and values ($k_o/10^{-2}$ s^{-1}) at different pHs (in parentheses) at ionic strength 0.2 were: 1.84 (4.0), 1.85 (4.6), 1.20 (5.0), 1.74 (6.07), 2.23 (6.69) and 4.31 (7.35). The reaction shows pH-independent and base-catalysed regions consistent with attack of H_3O^+ and H_2O, respectively, upon an enolate anion intermediate as shown in Scheme 2. The behaviour is similar to that for ketonisation of the enol of 9-acetylfluorene except that in Fig. 1 there is some sign of saturation of the hydroxide rate as the pK_a of the enol (7.55) is approached whereas saturation was not observed for the less acidic enol of 9-acetylfluorene.

$$\mathrm{EH} \xrightleftharpoons{K_a^{\mathrm{EH}}/[\mathrm{H^+}]} \mathrm{E^-} \xrightarrow{k_H[\mathrm{H^+}] + k_{\mathrm{H_2O}}} \mathrm{KH}$$

Scheme 2

The ketonisation rate constants can be combined with k_G to give a preliminary value of the keto–enol equilibrium constant $K_E \sim k^G/k_K = 16.3/0.88 = 18.5$ (from rate constants for acetate catalysis), but a more accurate value is obtained by correcting k^G for the contribution from hydration as indicated in eqn. (3).

Hydration of 9-formylfluorene

For kinetic measurements of the hydration of 9-formylfluorene we return to generation of the aldehyde tautomer from reaction of the hemithioacetal with iodine. The subsequent conversion of aldehyde into enol is followed by a slower relaxation of the absorption of the enol to about 70% of its initial intensity. This is the same process as is observed upon quenching of the enolate anion into acid or acidic buffers and may be interpreted as equilibration of enol and hydrate as shown in Scheme 1.

In 1 : 1 acetic acid buffers the decrease in enol concentration showed good first-order kinetics and gave rate constants designated k^Q_{obs}. The superscript Q indicates the experimental origin of the rate constants in the quenching reaction. However the process to which they refer is hydration of the enol with the aldehyde as a reactive intermediate. The relaxation of the enol occurs one hundred times more slowly than enolisation, and correction of the measured enolisation rate constant (k^G) for its influence is too small to be significant. However, direct hydration of the *aldehyde* (not shown in Scheme 1) is a faster process which competes with the initial enolisation as shown in eqn. (3). Moreover, as expected, the hydration reaction is acid-catalysed whereas enolisation is pH-independent. This means that the influence of hydration becomes greater at lower pH.

Returning to the slower hydration of the *enol*, in carboxylic acid buffers this process shows catalysis by both buffer acids and buffer bases. Slopes and intercepts [k and k_o based on eqn. (1)] from plots of k^Q_{obs} against buffer base concentration for acetic, glycolic and chloroacetic acids are shown in Table 4. The catalysis by buffer acid as well as buffer base is apparent from the dependence of k for the acetic acid buffers on the buffer ratio ($[CH_3COO^-]/[CH_3COOH]$) and the small difference in values of k for 1 : 1 buffers of acids with different pK_as.

Values of the intercepts of the buffer plots in Table 4 are plotted as log k^Q_o against pH in Fig. 1 to provide a pH profile for the hydration reaction (unfilled circles). Also included are the following rate constants (k^Q_{obs}/s^{-1}) measured at different molarities (mol dm^{-3}) of HCl; 2.79 (0.008), 3.87 (0.01), 4.74 (0.1), 4.73 (0.2). It can be seen that the profile shows a pH-independent reaction above pH 4 and an acid-catalysed reaction as the pH decreases. However in HCl solutions, below pH 2, saturation of the acid catalysis is observed. This must mean that the acid-catalysed hydration reaction becomes faster than reaction of the enol to form aldehyde which is not subject to acid catalysis and so becomes rate-determining, rendering the overall reaction again pH-independent.

Measured rate constants k^Q may be expressed in terms of the rate constant for tautomerisation and hydration as in eqn. (4).

$$k^Q = \frac{k_h k_K + k_d k_E}{k_h + k_E} \qquad (4)$$

This equation is based on Scheme 3 in which EH, KH and Hyd represent the enol, its keto tautomer (aldehyde) and the hydrate, respectively. The approximation is made that in the enol-to-hydrate conversion the aldehyde is present at a low steady-state concentration. The two terms in the equation represent forward and reverse reactions. As implied by the large amount of enol present at equilibrium (*ca.* 70%) the reverse (dehydration) reaction is the dominant one.

$$\mathrm{EH} \underset{k_E}{\overset{k_K}{\rightleftharpoons}} \mathrm{KH} \underset{k_d}{\overset{k_h}{\rightleftharpoons}} \mathrm{Hyd}$$

Scheme 3

In principle, all four rate constants k_h, k_d, k_E and k_K, can be determined by combining a measurement of k^Q with values of k^G [*cf.* eqn. (3)], k_K and one further independently measured rate or equilibrium constant. In practice the extra measurement is provided by the equilibrium constant for the enol hydration reaction, which may be obtained from measurements of initial and final absorbances accompanying quenching of the enolate anion in acidic solutions.[5]

Indeed two equilibrium measurements are possible depending on whether the initial absorbance reflects a stoichiometric or equilibrium concentration of enol. As already mentioned, in solutions of HCl but not in acetic acid buffers, the enol is equilibrated with the aldehyde more rapidly than it is converted into hydrate. If the final absorbance from relaxation of the enol is A_∞ and initial absorbances in acetic acid buffers and HCl, respectively, are A_0 and A'_0 then the relationships between initial and final absorbances from quenching enolate anion in the two acidic solutions are as shown in eqns. (5) and (6).

$$\frac{A_0 - A_\infty}{A_\infty} = \frac{[\mathrm{Hyd}] + [\mathrm{KH}]}{[\mathrm{EH}]} = 0.399 \qquad (5)$$

$$\frac{A'_0 - A_\infty}{A_\infty} = \frac{[\mathrm{Hyd}]}{[\mathrm{EH}] + [\mathrm{KH}]} = 0.309 \qquad (6)$$

The concentrations of species shown in these equations are equilibrium values and in principle they may be used to obtain equilibrium constants for hydration (K_h) and enolisation (K_E) of the aldehyde from the relationships of eqns. (7) and (8). Thus

$$K_h = k_h/k_d = [\mathrm{Hyd}]/[\mathrm{KH}] \qquad (7)$$

$$K_E = k_E/k_K = [\mathrm{EH}]/[\mathrm{KH}] \qquad (8)$$

eqns. (5) and (6) can be transformed into simultaneous equations involving enolisation and hydration equilibrium constants which can be solved to give $K_E = 15$ and $K_h = 5$.

In practice, however, care needs to be exercised to extract optimum values of rate and equilibrium constants from the experimental measurements. Thus better values of K_E and K_h may be obtained by combining the equilibrium measurements with measurements of rate constants for enolisation, ketonisation and hydration (k^G, k_K and k^Q) from acetic acid buffers by using eqns. (3) and (4) above.

Evaluation of rate and equilibrium constants for enolisation and hydration

Best values of the desired rate constants are obtained from experimental measurements (k^G, k^Q and k_K) by iteration using eqns. (3)–(8). The fact that all of the measured values either correspond directly to simple processes (*e.g.* k_K) or require only small corrections before they do so makes this task relatively easy. Thus for the hydration of the enol described in Scheme 3 and eqn. (4) the dominant term, as noted above, is the reverse dehydration reaction. This can be corrected for the contribution of the forward reaction using the initial value of the equilibrium constant K_h from eqns. (7) and (8) to obtain values of k_h and k_d. These in turn may be used to correct k^G in eqn. (3) for the minor contribution from hydration to yield $k_E + k_K$. Finally combination of $k_E + k_K$ with k_K from ref. 5 gives k_E and K_E. The cycle is then repeated (twice) until there is no further change in values.

Since dehydration is the most important term in the rate expression for enol to hydrate conversion it is appropriate to express k^Q in eqn. (4) in terms of k_d and a correction term. If we replace k_h by k_dK_h and k_E by k_KK_E we obtain eqn. (9) in which

$$k^Q = \frac{k_d(K + 1)}{k_d(K/k_K) + 1} \qquad (9)$$

$K = K_h/K_E$ is the equilibrium constant for the overall reaction of enol to hydrate. The value of this can be obtained as $K = 0.33$ from eqns. (7) and (8) and is relatively insensitive to and more reliable than the individual values of K_h and K_e.

Table 4 Slopes (k^Q) and intercepts (k^Q_o) of plots of measured first-order rate constants against concentration of buffer base for quenching solutions of 9-formylfluorene enolate anion in aqueous carboxylic acid buffers at 25 °C and 0.2 mol dm^{-3} ionic strength

Buffer	R[a]	pH	k^Q/dm^3 mol^{-1} s^{-1}	k^Q_o/s^{-1}
Chloroacetic	1	2.73	0.253	0.026
Glycolic	1	3.67	0.216	0.0079
Acetic	0.25	4.00	0.442	0.0054
Acetic	1	4.64	0.168	0.0067
Acetic	4.0	5.21	0.091	0.0066

[a] Ratio of buffer base to buffer acid concentrations [RCOO]$^-$/[RCOOH].

In acetic acid buffers hydration (quenching) of the enol is subject to both acid and base catalysis. The slopes ($k = k^Q$) of plots of observed first-order rate constants against buffer base concentrations [eqn. (1)] at constant buffer ratio (R = [CH$_3$COO$^-$]/[CH$_3$COOH]) recorded in Table 4 should then be expressed in terms of contributions from catalysis of dehydration by acetic acid and acetate ion with rate constants $k_d^{\mathrm{AcOH}} + k_d^{\mathrm{AcO^-}}$, respectively as in eqn. (10). In this expression

$$k^Q = \frac{(K + 1)[k_d^{\mathrm{AcO^-}} + k_d^{\mathrm{AcOH}}/R]}{(k_d^{\mathrm{AcO^-}} + k_d^{\mathrm{AcOH}}/\mathrm{R})(K/k_K^{\mathrm{AcO^-}}) + 1} \qquad (10)$$

the rate constant $k_K^{\mathrm{AcO^-}}$ refers to acetate catalysis of ketonisation of 9-formylfluorene determined previously[5] (which does not include a contribution from acid catalysis).

Eqn. (10) can be rearranged to express $k_d^{\mathrm{AcO^-}}$ and k_d^{AcOH} in terms of k^Q as in eqn. (11), and it can be seen that the right-hand

$$k_d^{\mathrm{AcO^-}} + k_d^{\mathrm{AcOH}}/R = \frac{k^Q}{(1 + K) - (K/k_K^{\mathrm{AcO^-}})k^Q} \qquad (11)$$

side of this equation has the form $k_Q/(a - bk^Q)$ where $a = (1 + K)$ and $b = K/k_K^{\mathrm{AcO^-}}$, and that $k_d^{\mathrm{AcO^-}}$ and k_d^{AcOH} may be separated as slope and intercept of a plot of $k^Q/(a - bk^Q)$ for values of k^Q at different buffer ratios (R) against $1/R$. Taking $k_K^{\mathrm{AcO^-}} = 0.88$ from ref. 5 and $K = 0.33$ (to obtain a and b), values of k^Q from Table 4 at buffer ratios 4.0, 1.0 and 0.25 yield $k_d^{\mathrm{AcO^-}} = 0.050$ dm^3 mol^{-1} s^{-1} and $k_d^{\mathrm{AcOH}} = 0.083$ dm^3 mol^{-1} s^{-1}.

We are now in a position to evaluate an enolisation rate constant from the rate measurements following generation of the aldehyde from the 9-formylfluorene hemithioacetal by reaction with iodine using eqn. (3) for k_G. In this equation the hydration rate constant k_h can be replaced by $k_dK_h = k_dKk_E/k_K$ where, as before, $K = K_h/K_E = 0.33$. This yields eqn. (12).

$$k^G = k_E(1 + k_dK/k_K) + k_d + k_K \qquad (12)$$

Eqn. (12) may be rearranged to give $k_E^{\mathrm{AcO^-}}$ for acetate catalysis in terms of the measurements of k^G as the slopes of plots of k_{obs} against acetate ion concentration at different buffer ratios from Table 1 as in eqn. (13).

$$k_E^{\mathrm{AcO^-}} = \frac{k^G - ({k_d}^{\mathrm{AcO^-}} + k_d^{\mathrm{AcOH}}/R) - k_K^{\mathrm{AcO^-}}}{[1 + (k_d^{\mathrm{AcO^-}} + k_d^{\mathrm{AcOH}}/R)K/k_K^{\mathrm{AcO^-}}]} \qquad (13)$$

From values of k^G at buffer ratios 1:1 and 1:4 in Table 1 rate constants $k_E^{\mathrm{AcO^-}} = 15.0$ and 14.5 dm^3 mol^{-1} s^{-1}, respectively are calculated. Combining the average of these, 14.8 dm^3 mol^{-1} s^{-1}, with 0.88 dm^3 mol^{-1} s^{-1} for $k_K^{\mathrm{AcO^-}}$, the ketonisation rate constant, yields $K_E = 14.8/0.88 = 16.8$. Finally insertion of this value into eqns. (5) and (6) gives an average value of 5.6 for K_h. This leaves $K_h/K_E = K = 0.33$ for the enol–hydrate equilibrium unchanged, and therefore there is no need to recalculate a dehydration rate constant using an improved value of K in eqn. (11).

Water reactions

An independent value of K_E can be obtained by combining rate constants for the buffer-independent water reactions k^{H_2O} in a similar manner to those for catalysis by acetate ion, k^{AcO^-}. The values may be derived from the pH-independent ranges of the pH profiles in Fig. 1. Thus the pH-independent values of k_o^K and k_o^G may be expressed in terms of forward and reverse rate constants for uncatalysed hydration and enolisation reactions as in eqns. (14) and (15). Eqn. (15) is based on eqn. (12) (with $K = K_h/K_E$); the numerical values are averages of measurements from Fig. 1.

$$k_o^K = k_K^{H_2O} = 0.0170 \qquad (14)$$

$$k_o^G = k_E^{H_2O}(1 + k_d^{H_2O}K/k_K^{H_2O}) + k_d^{H_2O} + k_K^{H_2O} = 0.30 \qquad (15)$$

For hydration of the enol (k^Q) there are two pH-independent reactions, one at low and one at high pH. At high pH enolisation is much faster than hydration so that in Scheme 3 $k_h \ll k_E$. Under these conditions EH and KH may be assumed to be in rapid equilibrium (which is a superior assumption to the previous one that KH is at a steady state). Eqn. (16) is then obtained for k_o^Q with the numerical value again taken from an average of measurements in Fig. 1 (and Table 4).

$$k_o^Q = k_d^{H_2O}[1 + K_h/(1 + K_E)] = 0.0067 \qquad (16)$$

If in eqn. (6) [Hyd]/[KH] is replaced by K_h and [EH]/[KH] by K_E, $K_h/(1 + K_E) = 0.309$ is obtained which, when substituted in eqn. (16), gives $k_d^{H_2O} = 5.1 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}. Combining this value with $K = 0.33$ and $k_K^{H_2O} = 0.0170$ [from eqn. (14)] and substituting into eqn. (15) then gives $k_E^{H_2O} = 0.253$, whence $K_E = k_E^{H_2O}/k_K^{H_2O} = 14.9$. Considering that the intercepts of buffer plots on which this K_E is based are considerably less reliable than the slopes of the plots for acetic acid buffers on which $K_E = 16.8$ was based, the agreement between the two values is quite satisfactory.

pH Profiles

The pH-dependences of the experimental rate constants in Fig. 1 may be calculated from the rate constants for the water reactions evaluated above if these are combined with rate constants for H$^+$ catalyses and the pK_a of the enol form of 9-formylfluorene.

Acid catalysis of hydration of the enol arises from catalysis by H$^+$ of the hydration of the aldehyde itself (and of the reverse reaction) and may be expressed by modifying eqn. (16) to eqn. (17). In this equation k_d^H is the rate constant for acid catalysis of the *de*hydration reaction and is evaluated from a best fit of the calculated to experimental pH profile as shown below.

$$k_o^Q = (k_d^{H_2O} + k_d^H[H^+])[1 + K_h/(1 + K_E)] \qquad (17)$$

At low pH the acid-catalysis of the hydration reaction becomes saturated and a second pH-independent reaction is observed. This should correspond to the acid-catalysed hydration of the aldehyde becoming faster than ketonisation of the enol. If it is assumed that $k_h \gg k_E$ in Scheme 3 and, again, that the aldehyde and hydrate are in rapid equilibrium, eqn. (18) can be written for this reaction.

$$k_o^Q = k_K^{H_2O}[1 + K_E/(1 + K_h)] \qquad (18)$$

With the assumption that the transition between H$^+$-catalysed and pH-independent reactions of eqns. (18) and (19) corresponds to the change between rate-determining hydration and rate-determining enolisation as described, eqns. (16)–(18) may be combined to yield eqn. (19) as the expression for the overall pH profile for the hydration reaction. The expression is simplified by replacing $[1 + K_E/(1 + K_h)]$ by m and $[1 + K_h/(1 + K_E)]$ by n.

$$k_o^Q = \frac{mnk_K^{H_2O}(k_d^{H_2O} + k_d^H[H^+])}{mk_K^{H_2O} + n(k_d^{H_2O} + k_d^H[H^+])} \qquad (19)$$

The line drawn through the experimental points in Fig. 1 is based on eqn. (19) with values of $k_{H_2O}^d$ [eqn. (16)], k_d^H [eqn. (17)] and $k_K^{H_2O}$ chosen to give a best fit to the experimental data. The value of m is derived from eqn. (6) as described under eqn. (16) and n is similarly obtained from eqn. (5) making use of the relationships in eqns. (7) and (8). The value of $k_K^{H_2O} = 0.0143$ s^{-1} represents an independent measurement of this rate constant which is in fair agreement with the directly determined value of 0.017 s^{-1} [eqn. (4)].

If the pH profile for hydration of 9-formylfluorene is compared with that for acetaldehyde[17] it is noticeable that there is a less pronounced pH-independent reaction for the latter. This presumably reflects a lower rate constant for H$^+$ catalysis in the case of 9-formylfluorene ($k_H = 70$ compared with 570 dm^3 mol^{-1} s^{-1}) and higher uncatalysed rate constant (0.5 s^{-1} compared with 2.9×10^{-2} s^{-1}). As no rate contribution from hydroxide catalysis is observed below pH 5 there is apparently no compensating increase from a hydroxide-catalysed reaction (for acetaldehyde $k_{OH} = 1.7 \times 10^4$ dm^3 mol^{-1} s^{-1}).

We may use the value of $k_d^H = 12.5$ obtained from the pH profile to evaluate the relative contributions of the competing acid-catalysed hydration and pH-independent enolisation of the aldehyde following its generation by iodination from the thiomethyl hemiacetal (k_o^G). Replacing $k_d^{H_2O}$ by $k_d^{H_2O} + k_d^H[H^+]$ in eqn. (15) [derived from eqn. (3)] adds the term $(1 + K_h)k_d^H[H^+]$ and the modified equation may be written in simplified form as eqn. (20).

$$k_o^G = k_K^{H_2O}(1 + K_E) + (k_d^{h_2O} + k_d^H[H^+])(1 + K_h) \qquad (20)$$

The line through the points for the enolisation reaction (k_o^G) in Fig. 1 is based on eqn. (20), with $k_K^{H_2O}$ taken from the rate profile for ketonisation, $K_E(= k_E^{H_2O}/k_K^{H_2O})$ chosen to give a best fit of the pH-independent reaction to the experimental measurements as described in the discussion of eqns. (15) and (16) above and $K_h = KK_E$. It can be seen that the value for k_d^H adequately represents the small increase in rate below pH 3 and is consistent with the incursion of the hydration reaction. Rate constants were not measured at lower pHs because of the interference between the hydration and enolisation reactions.

Above pH 6 the pH-independent reaction for ketonisation of the enol, $k_o^K = k_K^{H_2O}$ [eqn. (14)], becomes sensitive to protonation of the enolate anion intermediate by H$_2$O rather than by H$_3$O$^+$, as shown in Scheme 2. The reaction then exhibits catalysis by hydroxide ion, which should be quickly saturated by stoichiometric conversion of the enol into enolate anion. The reaction cannot be studied over the full range of this transition because ionisation of the bisulfite ion in the same pH range renders trapping of the aldehyde inefficient. The 'expected' behaviour is described by eqn. (21) based on Scheme 2. In this equation K_a^{EH} is the ionisation constant of the enol and $k_K^{H_2O}$ and k_K^{OH} are rate constants for the pH-independent and hydroxide-catalysed ketonisation reactions.

$$k_o^K = \frac{(k_K^{H_2O} + k_K^{OH}[OH^-])}{(1 + K_a^{EH}/[H^+])} \qquad (21)$$

The line drawn through the points for the ketonisation pH profile is based on this eqn. (21) with $k_K^{OH} = 2.5 \times 10^5$ and $k_K^{H_2O} = 0.0170$ chosen to provide a best fit to the data and K_a^{EH}

taken as its independently measured value ($pK_a^{EH} = 7.40$) based on $pK_a^{app} = 7.55$ for the ionisation of 9-formylfluorene and the tautomeric and hydration constants K_E and K_h, *i.e.*, $K_a^{EH} = K_a^{app}(1 + 1/K_E + K_h/K_E)$.[5]

Molecular rate constants

Rate constants for ketonisaton and enolisation in carboxylic acid buffers other than acetic acid can be derived from measurements of k_Q and k_G at the same buffer ratio. First $k_d^{RCOO^-} + k_d^{RCOOH}/R$ is evaluated from the slope of a plot of measured hydration rate constants against carboxylate anion concentration (k^Q) based on eqn. (11) with $RCOO^-$ and RCOOH replacing AcO^- and AcOH or, as shown in eqn. (22), with

$$k_d = \frac{k^Q}{(1 + K) - (K/k_K^{RCOO^-})k^Q} \qquad (22)$$

$k_d^{RCOO^-} + k_d^{RCOOH}/R$ denoted k_d. Although the value of $k_K^{RCOO^-}$ in eqn. (22) is not directly available (because kinetic measurements for bisulfite trapping were confined to acetate buffers) its value may be guessed from the measured value of $k_K^{AcO^-}$ and use of the Brønsted relationship with $\alpha = 0.5$. Then $k_E^{RCOO^-}$ is derived from the counterpart of eqn. (13) shown as eqn. (23) with k_d again written for $k_d^{RCOO^-} + k_d^{RCOOH}/R$.

$$k_E^{RCOO^-} = \frac{k_G - k_d - k_K^{RCOO^-}}{1 + k_d K/k_K^{RCOO^-}} \qquad (23)$$

Finally a better value of $k_K^{RCOO^-}$ is obtained from the relationship $k_K^{RCOO^-} = k_E^{RCOO^-}/K_E$ and this is used in eqn. (13) to re-evaluate k_d ($= k_d^{RCOO^-} + k_d^{RCOOH}/R$) and hence a corrected value of $k_E^{RCOO^-}$ from eqn. (23).

The enolisation rate constants $k_E^{RCOO^-}$ for catalysis by carboxylate anions and $k_E^{H_2O}$ for reaction with H_2O correspond to the rate constant k_{B^-} in eqn. (2) for attack of base on the aldehyde. These rate constants are listed in Table 2 together with values of k_{BH} for the reverse protonation of the enolate anion by acid obtained as $k_{BH} = k_{B^-}K_a/K_a^{KH}$ where K_a and K_a^{KH} are the ionisation constants of the carboxylic acid and of the aldehyde form of 9-formylfluorene, respectively. For the water reactions k_{B^-} corresponds to $k_E^{H_2O}$, with units s^{-1}, and k_{BH} to the reverse protonation of the enolate anion by H_3O^+ ($k_E^{H_2O}/K_a^{KH}$). The value of K_a^{KH} for ionisation of the aldehyde tautomer of 9-formylfluorene can be derived from the apparent equilibrium constant K_a^{app} for ionisation of an equilibrium mixture of aldehyde, enol and hydrate to enolate anion[5] as $K_a^{KH} = (K_E + K_h + 1)K_a^{app}$ from which $pK_a^{KH} = 6.2$. The values of k_{BH} and k_{B^-} are based on $k_K^{H_2O} = 0.0152$ and $k_E^{H_2O} = 0.254$ which are averages of values obtained from measurements of rate constants for ketonisation (k^K and k^Q) and enolisation (k^G).

The rate constants k_{B^-} and k_{BH} for HO^- and H_2O can also be obtained from the rate constant for the hydroxide-catalysed ketonisation reaction k_K^{OH} obtainable from the pH profile for ketonisation *via* eqn. (21). The relationships between k_{BH} and k_{B^-} and k_K^{OH}, based on eqn. (2), are $k_{BH}/s^{-1} = k_K^{OH}Kw/K_a^{EH}$ and $k_{B^-} = k_{BH}Kw/K_a^{KH}$. The values of k_{BH} and k_{B^-} for OH^- are 6.25×10^{-2} and 4.0×10^6 dm^3 mol^{-1} s^{-1}, respectively.

Evaluation of the rate constants k_d for dehydration of formylfluorene hydrate catalysed by acetic acid and acetate ion has been described. The corresponding hydration rate constants are obtained as $k_h = K_h k_d$ and give $k_h^{AcO^-} = 0.28$ and $k_h^{AcOH} = 0.465$ dm^3 mol^{-1} s^{-1}. Values for the other carboxylic acids studied cannot be separated into acid and base contributions because measurements were made at only one buffer ratio. However, rate constants for H_3O^+ catalysis and the uncatalysed reaction are available from the pH profile for hydration as $k_d^{H_2O} = 5.1 \times 10^{-3}$ and $k_d^H = 12.5$ dm^3 mol^{-1} s^{-1} from eqn. (19) for k_o^Q. Conversion into hydration rate constants as before then gives $k_h^{H_2O} = 2.86 \times 10^{-2}$ and $k_h^H = 70$. These rate constants are summarised in Table 5. Their relative magnitudes are comparable to those reported for acetaldehyde by Sørensen and Jencks[17] and suggest no change from the mechanisms of hydration proposed for this aldehyde.

Table 5 Second-order rate constants (l dm^3 mol^{-1} s^{-1}) for hydration and dehydration of 9-formylfluorene

Catalyst	H^+	CH_3COO^-	CH_3COOH	H_2O
Hydration	70	0.28	0.465	$2.86 \times 10^{-2}/55.5$
Dehydration	12.5	0.050	0.083	$6.7 \times 10^{-3}/55.5$

Discussion

9-Acetyl- and 9-benzoyl-fluorenes are ketones of high enol content and high acidity. There is thus no difficulty in measuring their ionisation and tautomeric constants.[1,2] Their enolate anions are formed in dilute sodium hydroxide and quenching in acid or acidic buffers yields enols, relaxation of which to the stable ketone tautomers can be monitored spectrophotometrically.[18] The combination of rate constants for ketonisation and enolisation (measured by halogenation) gives the tautomeric constant K_E = [enol]/[ketone].

For 9-formylfluorene the situation is very different. Not only is the enol the stable tautomer but the aldehyde is extensively hydrated, so the predominant equilibrium in aqueous solution is between enol and hydrate. In principle, kinetic evaluation of a tautomeric constant requires generation of the unstable aldehyde and measurement of a rate constant for its enolisation, which may then be combined with the previously described measurements of a rate constant for the reverse ketonisation based on trapping the aldehyde formed from the enol with bisulfite ion.[5] In practice, however, the measured rates of enolisation of the aldehyde need to be corrected for the competing hydration reaction.

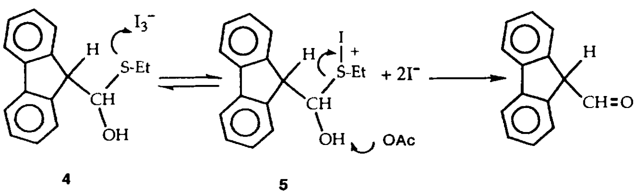
Rate constants for hydration (and dehydration) may be obtained from measurements of rates and equilibria for the reaction of enol to hydrate. However if they are to refer to the aldehyde rather than enol as reactant a knowledge of the keto–enol tautomeric constant is required! Fortunately the hydration correction to the enolisation rate constant for hydration is quite small so that the tautomeric constant and hydration correction can be evaluated iteratively.

Enolisation of 9-formylfluorene

Generation of 9-formylfluorene in its aldehyde form was attempted using a number of adducts of the aldehyde as precursors. For the bisulfite complex and for carbinolamines derived from addition of hydrazine and hydroxylamine, formation of the aldehyde was too slow for the subsequent enolisation reaction to be observed.[19] However a faster reaction was achieved using a thiohemiacetal adduct.

The ethanethiol hemiacetal of 9-formylfluorene was prepared by stirring freshly distilled 9-formylfluorene with ethanethiol for 2 h and was isolated as an easily decomposed white solid. Reactions of this adduct in acid or acidic buffers gave 9-formylfluorene. The reaction was again too slow for measurement of the rate of the subsequent enolisation. However, addition of triiodide ion led to a rapid consumption of iodine followed by a slower appearance of the 9-formylfluorene enol tautomer.

The iodination reaction was monitored spectrophotometrically from the disappearance of I_3^-. It was first order in I_3^-, was catalysed by base and showed an inverse second-order dependence on concentration of iodide ion consistent with reaction *via* the iodosulfonium ion intermediate (**5**) as shown in Scheme 4.

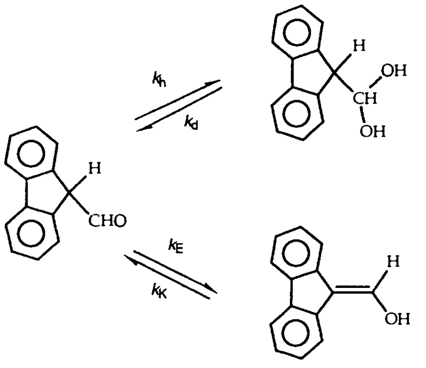


Scheme 4

Reaction of equimolar concentrations of iodine and substrate in acetic acid buffers showed that the iodine disappeared at least ten times more rapidly than the subsequent appearance of the UV spectrum of the enol, the rate of formation of which from the aldehyde could then be measured.

As already noted, the aldehyde formed from the hemithioacetal is subject to two competing reactions, enolisation and hydration. However, in acetic acid buffers at not too low pH, enolisation is considerably faster than hydration which is observed principally as a subsequent reaction leading to a slow decrease in the initial enol absorbance by about 30%. Typically, enolisation was measured by stopped flow and hydration by conventional spectrophotometry.

The hydration and enolisation reactions are shown in Scheme 5 with rate constants for enolisation and ketonisation denoted k_E and k_K and for hydration and dehydration k_h and k_d. Insofar as both forward and backward rates of enolisation and hydration need to be considered Scheme 5 represents potentially complex kinetic behaviour requiring analysis as a series of first-order reactions. However, because the rates of enolisation and hydration differ substantially both processes show good first-order kinetics and the initial enolisation is well approximated by the sum of rate constants $k_E + k_K + k_h + k_d$, of which the contribution from the enolisation constant k_E amounts to approximately 90%. Thus correction for $k_h + k_d$ as described below yields the sum of rate constants $k_E + k_K$, and combination of this with k_K from bisulfite trapping allows separation of k_E and evaluation of the tautomeric constant $K_E = k_E/k_K$.



Scheme 5

Hydration of 9-formylfluorene

The slow hydration reaction following stoichiometric formation of the enol from aldehyde or enolate anion precursors is represented by Scheme 5 if the enol is considered as reactant. Since enolisation is much faster than hydration the effective rate constant for conversion of enol into hydrate combines the rate constant k for hydration of the aldehyde and equilibrium constant for tautomerisation of enol to aldehyde, *i.e.*, $k = k_h/K_E$.

Table 6 Equilibrium constants ($dm^3\ mol^{-1}$) for adduct formation K = [adduct]/[aldehyde][addend] to 9-formylfluorene (FlCHO), *p*-chlorobenzaldehyde (Cl–PhCHO) and acetaldehyde in aqueous solutions at 25 °C

Addend	FlCHO	Cl–PhCHO	CH_3CHO
H_2O	5.6/55.5	0.016/55.5[a]	1.2/55.5
NH_2NH_2	330	7.0[b]	2.5×10^3[c]
HONHMe	205	6.6[e]	
$HONH_2$	480	24[d]	
HSO_3^-	3.5×10^4	1.14×10^4[b]	(8×10^3)[f]
HCN	—	300[b]	7100[g]

[a] Based on γ-scale of E. G. Sander and W. P. Jencks, *J. Am. Chem. Soc.*, 1968, **90**, 6154. [b] Sander and Jencks, *loc. cit.* [c] J. Fastrez, *J. Am. Chem. Soc.*, 1977, **99**, 7004. [d] S. Kelly, Ph.D. Thesis, National University of Ireland, 1991; [e] J. E. Reimann and W. P. Jencks, *J. Am. Chem. Soc.*, 1966, **82**, 3973. [f] Reported by T. H. Lowry and K. S. Richardson in *Mechanism and Theory of Organic Chemistry*, Harper and Row, New York, 2nd edn., p. 614, as calculated from literature data for 50% EtOH at 0 °C. Comparison with other values in the table suggests this may be in error.

In practice, because hydration occurs only to the extent of 30%, the measured rate constant is also a sum of forward and reverse contributions $k_h/K_E + k_d$, with the latter the more important. The two contributions may be separated by combining the measured rate constant with a measurement of the enol–hydrate equilibrium constant, evaluated from the fractional drop in absorbance of the enol accompanying the hydration reaction.

In acetic acid buffers this drop in absorbance follows rapid equilibration of the enol and aldehyde tautomers. However, the hydration reaction is acid-catalysed whereas keto–enol tautomerisation is not, and in HCl solutions, in contrast to acetic acid buffers, hydration is significantly faster than ketonisation. The drop in absorbance then reflects an initial absorbance which is due to enol only. By combining the two measurements the required equilibrium constant K = [Hyd]/[EH] = 0.33 is obtained from eqns. (5) and (6).[5]

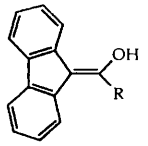
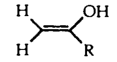
From the value of k_h/K_E we can obtain k_h in acidic buffers by using the measurement of K_E based on the rate constants for enolisation and ketonisation (from trapping the aldehyde with bisulfite ions). As we have seen the enolisation rate constant requires correction for competing hydration. But because this correction is small initially an uncorrected value of k_E can be used to derive K_E and k_h and the three constants can then be refined iteratively.

From the value of K = [Hyd]/[EH] and K_E = [EH]/[KH] we can also obtain the value of the equilibrium constant for hydration of 9-formylfluorene K_h = [Hyd]/[KH] = KK_E = 5.6. This value is significantly larger than $K_h = 1.2$ for acetaldehyde but comparable to $K_h = 4.7$ for diphenylacetaldehyde.[9] In Table 6 equilibrium constants for hydration are compared with values for addition of bisulfite ion and the α-effect amines, NH_2OH, CH_3NHOH and NH_2NH_2 for 9-formylfluorene,[5,19,20] acetaldehyde[21] and *p*-chlorobenzaldehyde.[20,22]

Tautomeric and ionisation constants

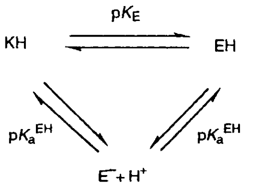
After correction of the rate constant for enolisation in 1 : 1 acetic acid buffers for the competing hydration reaction the value of K_E = [enol]/[aldehyde] for 9-formylfluorene in aqueous solution at 25 °C is obtained as 16.8, thus providing a quantitative measure of the unusual stability of this enol relative to its aldehyde tautomer. Combination of K_E with $K_h = 5.6$ gives as percentages of enol, hydrate and aldehyde at equilibrium in aqueous solution at 25 °C, 71.8, 23.9 and 4.2%, respectively.

Table 7 Comparison of tautomeric and ionisation constants of 9-acylfluorenes with those of acetaldehyde, acetone and acetophenone in water at 25 °C[a]

						
R	pK_E	pK_a^E	pK_a^K	pK_E	pK_a^E	pK_a^K
H	−1.22	7.41	6.19	6.23	10.50	16.73
Me	2.28	7.66	9.94	8.33	10.94	19.27
Ph	1.91	7.53	9.44	7.96	10.34	18.31

[a] Other than for the acylfluorenes data are taken from ref. 2.

Expressed in the usual logarithmic form the tautomeric constant becomes $pK_E = -1.22$. Combining this with $pK_a^{EH} = 7.41$ for ionisation of the enol[5] then yields $pK_a^{KH} = 6.19$ for the aldehyde based on the thermodynamic cycle of Scheme 6.

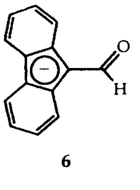


Scheme 6

The measurements of pK_E and of pK_a for the more stable keto forms of 9-acetyl- and 9-benzoyl-fluorenes may also be used to derive pK_as for the corresponding enols based on Scheme 6. These constants and values for 9-formylfluorene are summarised in Table 7.

For comparison, Table 7 also includes keto–enol tautomeric and ionisation constants for acetaldehyde[2,23] acetone[2,24] and acetophenone.[2,25] The positive sign of all the pK_Es save that for 9-formylfluorene indicates that this aldehyde provides the only example of an enol more stable than its keto tautomer. As expected, the methyl and phenyl substituents in 9-acetyl- and 9-benzoyl-fluorene decrease the enol content ($pK_E = 2.28$ and 1.91, respectively). The effect is slightly greater than for the same substituents in acetaldehyde, perhaps because of a steric interaction between the substituents and the aromatic rings of the fluorenyl group, but the difference is not large.

The dominant influence of the fluorenyl group is to increase the enol content of acetaldehyde by a factor of more than 10^7. As noted earlier[5] this effect is much greater than upon the acidity of the enol (*ca.* 10^3) despite the capacity of the fluorenyl group for stabilising a negative charge through resonance structures possessing the aromatic dibenzocyclopentadienyl anion structure (**6**).[5]



6

A further comparison with symetrically substituted aldehyde enols,[2,9,23,26] is shown in Table 8. Resonance stabilisation of the enol by phenyl substituents is apparent from the 10^5-fold greater enol content of diphenylacetaldehyde than acetaldehyde.[9] Interestingly the effect of changing from two phenyl groups to the fluorenyl group upon enol content and enol acidity is about the same (a little over 100-fold).

Table 8 Comparison of pK_E, pK_a^E and pK_a^K for symmetrically substituted enols of aldehydes and phenols at 25 °C

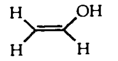
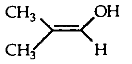
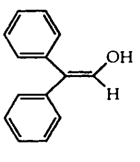
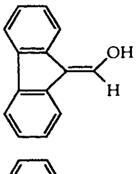
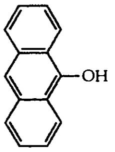
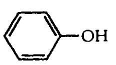
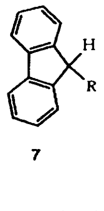
Enol/phenol	pK_E	pK_a^E	pK_a^K	Ref.
	6.23	10.50	16.73	2, 23
	3.86	11.63	15.49	26
	0.98	9.4	10.42	9
	−1.22	7.41	6.19	This work
	2.10	7.90	10.00	28
	−13.0	9.95	0	27

Table 8 also includes data for phenol[27] and anthrol.[28] These are not strictly comparable to the aldehyde enols and differ from each other in that tautomerisation of anthrol involves a 1,5-hydrogen shift to form anthrone whereas phenol involves a 1,3-hydrogen shift to give cyclohexa-2,4-dienol. Nevertheless the much greater stability of the phenol than anthrol relative to its ketone reflects the very unfavourable effect of dibenzoannellation on aromatic stabilisation of the enol. This is presumably also a factor in the rather weak effect of α-fluorenyl substitution upon the acidity of the enol of acetaldehyde.

Brønsted relationship

The kinetic measurements for ketonisation of the enols of 9-formylfluorene and 9-acetylfluorene in carboxylic acid buffers yield Brønsted plots with slopes $\alpha = 0.62 \pm 0.02$ (based on three points only) and $\alpha = 0.50 \pm 0.02$, respectively, for reaction of the carboxylic acids with the enolate anions. The results are shown in Fig. 2 as plots of log *k* against Δp*K*, the difference in pK_a between the fluorene substrate and carboxylic acid (unfilled circles). Also included are rate constants for reaction with H_3O^+ (filled circles), which show no deviation from the carboxylic acid plot, together with rate constants for reaction of acetic acid and H_3O^+ with 9-benzoylfluorene.



a R = COOH
b R = COOMe
c R = COSMe
d R = CSOMe

7

In addition, rate constants measured by Chiang, Jones and

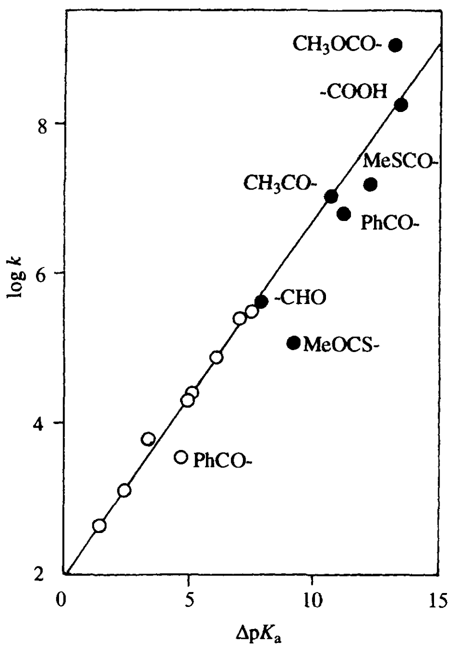


Fig. 2 Plot of log k against ΔpK_a for the protonation of 9-substituted fluorenyl anions by H_3O^+ (●) or carboxylic acids (○)

Kresge[29] for reaction of H_3O^+ with carbanions from fluorene-9-carboxylic acid (pK_a for C–H ionisation = 11.73), its methyl and thiomethyl esters (pK_as = 11.52 and 10.51, respectively) and *O*-methyl fluorene-9-thiocarboxylate (pK_a = 7.40), *i.e.*, **7a–d**, are included in the plot (also as filled circles). It can be seen that while the reactions of formyl and acyl fluorenes and the fluorene carboxylic acid fall on a common line, the reactions of thio and thiono esters and also of the 9-benzoylfluorene show appreciable negative deviations, while the methyl ester deviates positively. These deviations represent differences in 'intrinsic' reactivity of the carbon substrates.[30] None of the deviations are large (< tenfold in rate constant) and in the case of 9-benzoylfluorene probably arise from a small steric effect. However the intrinsically low reactivity of the thiomethyl relative to (oxy) methyl ester is noteworthy. Kresge has drawn attention to the surprisingly small difference in thermodynamic acidity of the two esters despite the reported superiority of the thioester group in activating C–H ionisation.[29] From Fig. 2 it appears that in comparison with fluorene-9-carboxylic esters the kinetic effect of even this small thermodynamic advantage is more than offset by an unfavourable difference in intrinsic reactivities.

Experimental

Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. Measurements of pH were made with a Radiometer PHM 26 pH meter using a Radiometer glass electrode (type G 202C) coupled with a Radiometer calomel electrode (type K401) as reference. Kinetic measurements were carried out using Pye Unicam SP8-400 and PU-8800 and Perkin-Elmer (Hitachi) 124 spectrophotometers. A Durrum D110 spectrometer equipped with a Datalab 901 transient recorder and Apple-II microcomputer for data analysis was used for stopped-flow measurements. Solutions for kinetic or equilibrium studies were prepared from doubly distilled and deionised water using 'AR' or 'Aristar' buffer and acid reagents. Solutions of sodium hydroxide were prepared after washing AR reagent pellets with water to remove sodium carbonate. The solutions were standardised against hydrochloric acid prepared from Merck 'Titrisol' ampoules. Kinetic and equilibrium measurements were made at 25 ± 0.1 °C.

9-Formylfluorene was prepared by the method described by Carpino.[31] Bulb-to-bulb distillation of the product (bp 150–154 °C/1 mmHg) gave a yellow oil referred to by Wisliscenus and Waldmuller as the α-form of 9-formylfluorene[6] and considered to have the enol structure. The aldehyde tautomer (β-form) was prepared using the procedure described by Wisliscenus.[6] Equivalent amounts of freshly distilled 9-formylfluorene enol (5 g) and potassium methoxide (1.8 g) were dissolved in ether (100 cm^3). The solution was stirred for 15 min after which water (100 cm^3) was added. The aqueous layer was collected, washed with light petroleum, cooled to 0 °C and acidified with ice-cold 10% hydrochloric acid (25 cm^3). The resulting precipitate was quickly collected with a minimum exposure to air and yielded a white powder which was recrystallised from carbon tetrachloride. On being heated this product reverted to the oily β-(enolic) tautomer which was also obtained from neutralisation of the enolate anion at higher temperature. A possible explanation of this surprising behaviour is that the aldehyde is the least soluble among enol, aldehyde and hydrate forms and that at low temperatures precipitation of the aldehyde following formation from the enol competes with acid-catalysed conversion into the more soluble hydrate.

The following NMR spectra were recorded: α-isomer, oil (enol); δ_H(270 MHz; $CDCl_3$) 6.2 (1 H, br, OH), 7.90 (1 H, s, =CH), 7.3–8.2 (8 H, m, aromatic); δ_H(CD_3OD) 7.89 (1 H, s, =CH), 7.15–8.2 (8 H, m, aromatic); β-isomer, white solid (aldehyde); δ_H(270 MHz; $CDCl_3$) 4.72 (1 H, d, *J* 3.4, H-9), 7.2–7.9 (8 H, aromatic), 9.15 (1 H, d, *J* 3.4, CHO).

The methyl ether of 9-formylfluorene enol was prepared by reacting the potassium enolate salt in aqueous solution with dimethyl sulfate as described by Brown and Bluestein.[32] Recrystallisation from methanol gave yellow needles mp 103–104 °C (lit., 104 °C); δ_H(60 MHz; $CDCl_3$) 4.15 (3 H, s, OCH_3), 7.4 (1 H, s, =CH), 7.25–8.30 (8 H, m, aromatic).

9-Acetylfluorene was prepared as described by Von and Wagner[33] and recrystallised from methanol to yield colourless crystals, mp 73.5–74.5 (lit.,[33] 74.5–75.5 corr.); δ_H(60 MHz; $CDCl_3$) 1.66 (3 H, s, CH_3), 4.87 (1 H, s, 9-H), 7.4–8.05 (8 H, m, aromatic). On storage the compound liquefied to an oil which then solidified to a product reported to be a dimer.[33]

9-Benzoylfluorene was prepared as described in the literature.[34] Recrystallisation from methanol gave colourless crystals, mp 135–136 °C (lit.,[33] 135 °C); δ_H(60 MHz; $CDCl_3$) 5.6 (1 H, s, 9-H), 7.2–8.0 (13 H, m, aromatic).

9-Formylfluorene ethanethiol hemithioacetal

Freshly distilled 9-formylfluorene (1 g) was stirred at 0 °C in ethanethiol (3 cm^3) for 2 h. A white precipitate formed which when exposed to air or heated decomposed to 9-formylfluorene with loss of ethanethiol. The most satisfactory method for isolating the product was achieved by precooling a Buchner funnel and flask to < 10 °C, filtering quickly and washing with cold ether (−20 °C). The product was isolated as a white powder and stored under argon at 0 °C; δ_H(270 MHz; CD_3CN) 1.13 (3 H, t, CH_3), 2.54 (2 H, q, CH_2), 3.5 (1 H, br, OH), 4.32 (1 H, d, *J* 3.5, 9-H), 5.56 (1 H, d, *J* 3.6, CH), 7.2–79 (8 H, m, aromatic) (Found: C, 74.7; H, 6.15. $C_{16}H_{16}SO$ requires C, 75.00; H, 6.25. The mass spectrum gave M^+ *m*/*z* = 238 (corresponding to loss of H_2O).

Measurements of p*K*ₐs

Measurement of a pK_a for 9-formylfluorene has been described previously.[5] Values for 9-acetyl- and 9-benzoyl-fluorene were based on absorbance measurements in phenolic buffers at λ_{max} for their enolate ions (365 and 370 nm), respectively. The pK_as were derived from eqn. (24) in which A and A^- are absorbances

$$K_a = \frac{A[\mathrm{H}^+]}{(A^- - A)} \qquad (24)$$

of the partially and fully formed anions, and the absorbance of the unionised enol was neglected. For 9-benzoylfluorene pK_a = 9.44 was based on A^- = 1.23 and the following absorbance measurements at the pHs indicated in parentheses: 0.90 (9.88); 0.84 (9.76); 0.61 (9.45); 0.26 (8.89). Similarly, for 9-acetylfluorene a pK_a = 9.94 was based on measurements of A^- = 1.86 and the following values of A at the (pHs) indicated: 1.29 (10.32); 1.02 (10.00); 0.84 (9.85); 0.75 (9.76). At each pH the recorded absorbance is the mean of two–five measurements. The ionic strength was maintained at 0.1 mol dm^{-3} with NaCl.

Kinetic measurements

Stock solutions of formylfluorene and its ethanethiol adduct were prepared in acetonitrile that had been deaerated with nitrogen or argon and were stored at 0 °C. For normal kinetic measurements 5–20 µl of stock solution were injected into 3 cm^3 of aqueous acid or buffer thermally equilibrated in a spectrophotometric cell to initiate reaction. A similar procedure was used for halogenation with the halogen added before addition of substrate from a calibrated syringe. For bromination a small correction for loss of bromine in the absence of reagent was applied. Both I_2 and Br_2 were complexed with an excess of the corresponding halide ion.

For stopped-flow measurements of ketonisation a solution of enolate anion in 0.01 mol dm^{-3} sodium hydroxide was placed in one drive syringe of the instrument and a buffer or acid solution in the other. For reaction of the ethanethiol hemithioacetal of 9-formylfluorene this substrate was contained in one syringe in the presence of 10^{-3} mol dm^{-3} HCl, to minimise its rate of hydrolysis,[16] and an approximately equimolar concentration of iodine together with an excess of buffer solution, in the other. The aqueous solutions of the hemithioacetal were prepared immediately before being used.

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