Keto–enol interconversion of 2-phenylacetylthiophene

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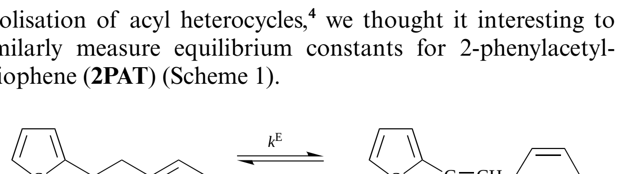
The equilibrium constant for keto–enol tautomerism of 2-phenylacetylthiophene (2PAT) K_T = [enol]/[ketone] has been determined as 3.55 × 10^{-7} (pK_T 6.45) by combining rate constants for enolisation and ketonisation. The pK_a^{KH} for ionisation of 2PAT has been measured spectrophotometrically as 14.60. Combining this with pK_T gives pK_a^{EH} 8.15 for the enol form of 2PAT. Comparison of these values with those previously reported for 2-phenylacetylfuran and deoxybenzoin shows a significant influence of both five-membered heterocyclic rings (*a*) in increasing the acidity of the enol and (*b*) in stabilising the keto relative to the enol tautomer. Micelles from a cationic surfactant (CTABr) strongly decrease the rate of ketonisation of the enolate of 2PAT and increase the apparent acidity of the keto form.

Tautomeric constants (K_T) for aldehydes and ketones can be measured kinetically by combining rates of enolisation (k^E) with reverse rates of ketonisation (k^K).[1] Rates of enolisation can be determined by the well established 'halogen trapping'[2] procedure. In favourable cases rates of ketonisation can be determined by 'stopped flow' upon quenching a solution of the corresponding enolates into acidic or buffer solutions. The initial reaction that will occur on neutralisation is the protonation of the enolate, resulting in a solution containing enol far in excess of its equilibrium concentration. The kinetics associated with the return to the equilibrium position can then be monitored. The above methods have been recently applied to the tautomerisation reaction of 2-phenylacetylfuran.[3]

In view of the fact that 2-phenylacetylfuran appears[3] to fall out of a sequence of similar ketones in terms of the magnitude of its tautomeric constant and our interest in the rates of enolisation of acyl heterocycles,[4] we thought it interesting to similarly measure equilibrium constants for 2-phenylacetylthiophene (**2PAT**) (Scheme 1).



2PAT
keto form (**KH**)

2PAT
enol form (**EH**)

Scheme 1

The addition of relatively concentrated NaOH (about 0.5 mol dm^{-3}) provides a way of perturbing the tautomeric equilibrium of **2PAT**, since the species formed in base is the enolate. **2PAT** is just acidic enough to be about 20% ionised in 0.5 mol dm^{-3} NaOH. With this work we show that relatively high concentrations of the enolate can be produced in less concentrated NaOH solutions in the presence of micelles from cationic surfactants. This might hopefully uncover new possibilities of utilising enolates as nucleophiles in aqueous media for synthetic purposes.

Experimental

Materials

All inorganic salts (KCl, NaCl, KI, KH_2PO_4, Na_2HPO_4), cetyltrimethylammonium bromide (CTABr), iodine and buffer acids [$CNCH_2COOH$, $ClCH_2COOH$, $HOCH_2COOH$, CH_3COOH, $(CH_3)_2AsO_2H$, H_3BO_3] were commercial samples of Analar grade (Aldrich, Merck or Carlo Erba) and were used without further purification except CTABr, which was recrystallised from acetone.

2-Phenylacetylthiophene (2PAT)

This was prepared by the general method described in refs. 5 and 6. Recently distilled $SnCl_4$ (3.4 ml, 0.029 mol) was added to a mixture of thiophene (3.4 g, 0.040 mol) and phenylacetyl chloride (5.28 ml, 0.040 mol) in 50 ml dry benzene cooled to 0 °C (ice bath). The greenish blue reaction mixture was stirred for 1 h. The intermediate obtained was hydrolysed by the slow addition of a mixture of 18 ml of water and 20 ml of concentrated hydrochloric acid and stirring was continued as the two phases separated. The organic layer was dried over sodium sulfate and the solvent removed to yield a yellow oil. Chromatography on silica gel with cyclohexane–diethyl ether [4:1 (v/v)] as the eluent gave white crystals of **2PAT**, mp 49–50 °C (lit.,[6] 49–50 °C); δ_H(300 MHz; $CDCl_3$) 4.20 (s, 2 H, CH_2), 7.13 (dd, 1 H, 4-H of thiophene $J_{4,5}$ 4.9, $J_{3,4}$ 3.8), 7.33 (m, 5 H, Ph), 7.64 (dd, 1 H, 5-H of thiophene $J_{4,5}$ 4.9, $J_{4,3}$ 1.1), 7.78 (dd, 1 H, 3-H of thiophene $J_{3,4}$ 3.8, $J_{3,5}$ 1.1).†

Kinetic measurements

Rates of ketonisation of **2PAT** were measured by quenching a freshly prepared solution of the enolate anion in 0.5 mol dm^{-3} aqueous NaOH with 0.5 mol dm^{-3} HCl plus an appropriate concentration of HCl or buffer (in the case of the OH^- catalysed reaction NaOH was only partially neutralised) and by monitoring the relaxation of the enol at λ_{max} 347 nm to the more stable keto form. The stopped-flow spectrophotometer was a Model VI Tri-tech Dynamic Instruments.

The enolisation reactions were followed by halogen-trapping as previously described[4] using a Varian Cary 1E UV–VIS spectrophotometer.

All kinetic measurements were made at 25.0 ± 0.1 °C and at an ionic strength (*I*) of 1.0 mol dm^{-3} (KCl or NaCl).

Ionisation constants

The pK_a^{KH} of **2PAT** was determined spectrophotometrically by monitoring the appearance of the enolate in solutions of

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† *J* values are given in Hz.

Table 1 Catalytic constants for the enolisation of **2PAT** at 25 °C and ionic strength 1.0 mol dm^{-3} (KCl)

Catalyst	r	k/10^{-6} dm^3 mol^{-1} s^{-1}
Hydronium ion[a]		4.28 (±0.04)
Glycolate	1	11.5 (±0.3)
	5	14.0 (±0.6)
Acetate	1	55.2 (±1.2)
	5	51.1 (±2.7)
Phosphate	1	376 (±17)
	5	378 (±5)

[a] From the intercept of the catalytic plot a value of 2.17 (±0.02) × 10^{-7} s^{-1} for the water catalysed reaction was estimated.

increasing concentration of sodium hydroxide. An average value of pK_b = −0.35 was obtained from absorbance measurements at constant 5 × 10^{-5} mol dm^{-3} substrate concentration in the range (of partial dissociation of **2PAT**) 0.1–3 mol dm^{-3} NaOH using eqn. (1), where A, A_o (0.0018) and A_{max} (0.5783)

$$K_b = \frac{(A_{max} - A)\,[OH^-]}{(A - A_o)} \qquad (1)$$

are absorbances at λ 353 nm at the specified [OH$^-$], in water and for the fully ionised ketone, respectively. As observed for pK_as in acid solution by Long and Paul[7] it is commonly assumed[8,3] that the dependence of log K_b on [OH$^-$] becomes linear below *ca.* 2 mol dm^{-3}. A thermodynamic pK_a^{KH} value of 14.60 (±0.03) was obtained by extrapolation to zero [OH$^-$] of a linear plot of pK_a^{KH} *vs.* [OH$^-$].

The p$K_a^{KH_2^+}$ value of **2PAT** was determined spectrophotometrically (λ 350 nm) in concentrated aqueous solutions of H_2SO_4 (4.0–18.2 mol dm^{-3}). In UV–VIS pK_{BH^+} determinations in concentrated acid solutions corrections are usually required[9] to estimate how much of the absorbance change for B or BH$^+$ is due to conversion into its conjugate species and how much is due to a lateral medium shift of λ_{max}. For the present purpose we have adopted the simple graphical correction proposed by Johnson and Katritzky.[10] Both the excess acidity[11a] and Hammett acidity function[11b] (H_o) methods were used giving a mean value of −6.13 (p$K_a^{KH_2^+}$ −6.10, m^* 1.0; p$K_a^{KH_2^+}$ −6.15, m 0.98).

Results

Enolisation reactions

The rates of iodination of **2PAT** (concentration about 2.0 × 10^{-4} mol dm^{-3}) were measured in dilute hydrochloric acid, in acetate, glycolate and phosphate buffers. All reactions were strictly zero order with respect to halogen concentration, with the rate-determining step being the formation of the enol. There was no evidence of reversibility of the iodination reaction under the adopted experimental conditions. In acidic solutions relatively low concentrations (2–5 × 10^{-3} mol dm^{-3}) of iodide ion were used to avoid reversibility and corrections for dissociation of I_3^- to I_2 and I^- were properly made.[12]

The H_3O^+ catalysed rate constant was measured with HCl concentrations in the range 5.0 × 10^{-3}–0.1 mol dm^{-3}. General base catalysed rate constants were determined at buffer ratios (r = [A$^-$]/[HA]) 1 and 5.

The experimental results are collected in Table 1.

Ketonisation reaction in dilute hydrochloric acid

Reaction rates were measured with **2PAT** concentration about 2.5 × 10^{-4} mol dm^{-3} and HCl concentrations in the range 0.01–0.8 mol dm^{-3}. The observed rate law was given by eqn. (2) with k_e being the experimental pseudo-first order rate constant.

$$k_e = k_o + k_H\,[H^+] \qquad (2)$$

Table 2 Pseudo-first order rate constants for the H_3O^+ catalysed ketonisation reaction of **2PAT** at 25.0 ± 0.1 °C and ionic strength 1.0 mol dm^{-3} (NaCl)

[HCl]/mol dm^{-3}	k_e/s^{-1}
0.01	0.717
0.02	0.758
0.05	0.883[a]
0.10	1.38[a]
0.20	2.11[a]
0.30	3.18[a]
0.40	4.18[a]
0.50	4.73[a]
0.60	5.68[a]
0.70	6.61[a]
0.80	7.56[a]

[a] Values used in the pH-profile (see Fig. 1).

The slope value, k_H, of a plot of k_e *vs.* [H$^+$], represents the H_3O^+ catalysed rate constant [k_H = 8.69 (±0.12) dm^3 mol^{-1} s^{-1}] while the intercept [k_o = 0.52 (±0.05) s^{-1}] represents the ‘spontaneous’ (water catalysed) rate constant. The experimental data are collected in Table 2.

Ketonisation reaction in buffer solutions

Reaction rates were measured in chloroacetate, cyanoacetate, glycolate, acetate, cacodylate, borate and phosphate buffers with **2PAT** (concentration about 2.5 × 10^{-4} mol dm^{-3}). The observed rate constant, k_e, was of the form shown in eqn. (3), in which B represents the basic component of the buffer.

$$k_e = k_o + k\,[B] \qquad (3)$$

Eqn. (3) is a simplified form of eqn. (4) where catalysis is

$$k = k_{GB}\,[B] + k_{GA}\,[A] \qquad (4)$$

dissected into the two possible contributions k_{GB} and k_{GA}, by the basic, B, and acid, A, components of the buffer.

This treatment of the kinetic results in buffer solutions was previously introduced by More O’Ferrall and co-workers[3,13] and his same symbolism is adopted herein. However no acid catalysis by the buffer acid was detected for the ketonisation reaction of **2PAT** enol under the adopted experimental conditions. The values of k_{GB} were calculated as previously described[3,13] from k values obtained by performing different series of kinetic experiments, each at constant buffer ratio r.

In solution of cacodylate, phosphate and borate buffers, where pH is close to the pK_a^{EH} of the enol, rate constants, k, at the different buffer ratios are related to the pH of the solution by eqn. (5).

$$k = k_{GB}\,[1 + (K_a^{EH}/[H^+])]^{-1} \qquad (5)$$

Best fit of eqn. (5) gives the values of k_{GB} for the above three buffer systems. The range of buffer concentrations, buffer ratios and the values of k_o, k and k_{GB} for the different buffers are reported in Table 3.

Ketonisation reaction in dilute sodium hydroxide

Reaction rates were measured with **2PAT** concentration about 2.5 × 10^{-4} mol dm^{-3}. A value of k'_o = 54.2 (±2.4) s^{-1} was calculated as an average among the following experimental rate constants, determined at four different NaOH concentrations (in parentheses): 50.8 (0.005), 54.3 (0.01), 55.3 (0.05) and 56.4 (0.1). The rate constant, k'_o, is apparently independent of [OH$^-$] as the base catalysis is brought about by ionisation of the enol to the much more reactive enolate ion followed by ketonisation of the latter through a rate-determining proton transfer to the enolate carbon atom. Under the above experimental conditions base catalysis becomes saturated (see Fig. 1 below)

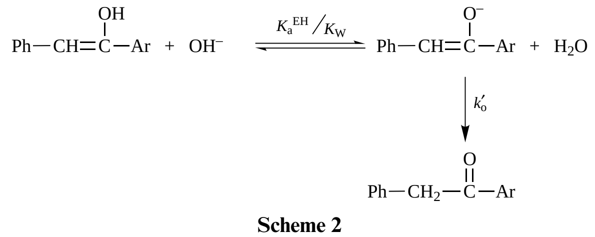
Table 3 Slopes k and intercepts k_o from the plot of the experimental pseudo-first order rate constants (k_e/s^{-1}) against concentration of buffer base, B, in aqueous solution at 25 °C and ionic strength 1.0 mol dm^{-3} (NaCl), buffer ratios r, range of buffer concentrations and rate constants for general base catalysis k_{GB}

Base	r	pH	k_o/s^{-1}	k/dm^3 mol^{-1} s^{-1}	k_{GB}/dm^3 mol^{-1} s^{-1}
$CNCH_2COO^-$	0.3^{a}	1.74	0.72 (±0.06)^{r}	5.61 (±0.21)	
	0.5^{a}	1.96	0.73 (±0.02)	5.59 (±0.08)	
	1^{a}	2.27	0.55 (±0.03)^{r}	6.16 (±0.12)	
	2^{a}	2.57	0.59 (±0.01)^{r}	6.12 (±0.05)	
	4^{b}	2.87	0.54 (±0.01)	5.86 (±0.08)	5.99 (±0.14)
$ClCH_2COO^-$	0.3^{a}	2.14	0.92 (±0.13)	9.07 (±0.48)	
	0.5^{a}	2.36	0.66 (±0.08)	10.1 (±0.3)	
	1^{a}	2.67	0.60 (±0.13)^{r}	11.2 (±0.5)	
	2^{c}	2.97	0.56 (±0.08)^{r}	11.2 (±0.3)	
	4^{a}	3.27	0.32 (±0.06)	11.6 (±0.2)	11.4 (±0.5)
$HOCH_2COO^-$	0.4^{d}	3.23	0.93 (±0.19)	39.3 (±1.2)	
	1^{e}	3.63	0.67 (±0.26)^{r}	45.1 (±1.0)	
	2^{e}	3.93	0.72 (±0.26)	46.8 (±1.0)	
	4^{e}	4.23	0.58 (±0.54)^{r}	47.0 (±2.0)	
	5^{e}	4.32	0.50 (±0.35)^{r}	45.3 (±1.3)	46.8 (±0.8)
CH_3COO^-	0.3^{f}	4.03	5.0 (±1.7)	148 (±8)	
	0.5^{g}	4.25	3.1 (±1.8)	174 (±9)	
	1^{a}	4.56	—	184 (±7)	
	2^{g}	4.86	—	187 (±6)	
	4^{g}	5.16	—	213 (±9)	212 (±8)
$(CH_3)_2AsO_2^-$	0.7^{h}	5.76	76 (±21)	2330 (±1610)	
	1^{i}	6.07	28 (±4)	4280 (±220)	
	2^{j}	6.37	48 (±1)	1230 (±30)	3840 (±490)
HPO_4^{2-}	0.3^{k}	6.47	59 (±2)	369 (±29)	
	0.5^{l}	6.69	36 (±2)	642 (±38)	
	1^{m}	6.99	6.0 (±2.4)^{r}	1070 (±30)	
	3^{m}	7.47	15 (±4)^{r}	110 (±50)	
	5^{n}	7.69	36 (±2)^{r}	763 (±31)	1410 (±80)
$B(OH)_4^-$	0.3^{p}	8.51	62 (±1)	317 (±26)	
	0.5^{q}	8.73	53 (±3)^{r}	686 (±32)	
	1^{q}	9.03	57 (±3)^{r}	474 (±50)	
	2.5^{q}	9.43	55 (±2)^{r}	492 (±26)	11400 (±1500)

[a] $0.020 \leqslant [B] \leqslant 0.492$ mol dm^{-3}. [b] $0.020 \leqslant [B] \leqslant 0.300$ mol dm^{-3}. [c] $0.010 \leqslant [B] \leqslant 0.500$ mol dm^{-3}. [d] $0.016 \leqslant [B] \leqslant 0.300$ mol dm^{-3}. [e] $0.020 \leqslant [B] \leqslant 0.480$ mol dm^{-3}. [f] $0.030 \leqslant [B] \leqslant 0.400$ mol dm^{-3}. [g] $0.010 \leqslant [B] \leqslant 0.400$ mol dm^{-3}. [h] $0.005 \leqslant [B] \leqslant 0.020$ mol dm^{-3}. [i] $0.005 \leqslant [B] \leqslant 0.030$ mol dm^{-3}. [j] $0.005 \leqslant [B] \leqslant 0.050$ mol dm^{-3}. [k] $0.010 \leqslant [B] \leqslant 0.100$ mol dm^{-3}. [l] $0.020 \leqslant [B] \leqslant 0.096$ mol dm^{-3}. [m] $0.025 \leqslant [B] \leqslant 0.125$ mol dm^{-3}. [n] $0.010 \leqslant [B] \leqslant 0.125$ mol dm^{-3}. [p] $0.006 \leqslant [B] \leqslant 0.048$ mol dm^{-3}. [q] $0.012 \leqslant [B] \leqslant 0.120$ mol dm^{-3}. [r] Value used in the pH-profile (see later).

because the ionisation equilibrium is shifted completely to the formation of the enolate and further formation of the more reactive species is no longer possible.

The prime index in k'_o refers to the spontaneous catalysis for the ketonisation reaction of the enolate form and is related to the kinetically indistinguishable OH$^-$ catalysed ketonisation of the enol, k_{OH}, by the expression: $k'_o = k_{OH}\, K_W/K_a^{EH}$ (Scheme 2).



Scheme 2

Calculation of the tautomeric constant, K_T

The tautomeric constant, K_T = [enol]/[ketone], was calculated as the ratio of the second order rate constants for the enolisation and the ketonisation reactions, measured under the same conditions. The value of pK_T 6.45 (±0.12) is an average of the experimental values determined under the following different conditions: dilute hydrochloric acid, glycolate buffer (r = 1 and 5), acetate buffer (r = 1) and phosphate buffer (r = 1 and 5). The enolisation and ketonisation rate constants measured were not corrected for 1.0 mol dm^{-3} ionic strength. Since ionic strength effects should not substantially affect K_T values the kinetically determined tautomeric constant should correspond to the thermodynamic value.

pH-Profile

A pH-profile for the ketonisation reaction (Fig. 1) was drawn by plotting log k [the value of log k_e for the reaction in hydrochloric acid (Table 2), log k_o determined in the different buffers (Table 3) and log k_e = log k'_o in sodium hydroxide solutions (see above)] against pH. The profile shows a pH region for H_3O^+ catalysis ($0 < \text{pH} \leqslant 2$), a pH region for OH$^-$ catalysis ($6 \leqslant \text{pH} \leqslant 8$) and two regions where the reaction is pH-independent. The pH-independent region at lower pH corresponds to the 'water' reaction of the enol,[14] while the pH-independent region at higher pH is due to the complete ionisation of the enol to the enolate anion and its subsequent protonation by water to form the ketone. The point of inflection that occurs in the pH-profile at pH near eight represents the change in reactant from enol (at lower pH) to enolate (at high pH). A value of enol acidity constant pK_a^{EH} 8.03 (±0.04) can be obtained from a best fit of experimental data to eqn. (6),

$$k_e = k_H\,[H^+] + k_o + \frac{(k'_o K_a^{EH}/K_W)[OH^-]}{1 + (K_a^{EH}/[H^+])} \qquad (6)$$

in which k_H = 8.69 dm^3 mol^{-1} s^{-1}, k_o = 0.52 s^{-1} and k'_o = 54.2 s^{-1}.

The two values of pK_a^{EH} obtained from eqn. (6) and from the equation: pK_a^{EH} = pK_a^{KH} − pK_T = 8.15, are in quite good agreement, especially taking into consideration that only the former is a thermodynamic value as [H$^+$] in eqn. (6) are calculated from pH values allowing for activity coefficients, $\gamma_\pm$, at 1.0 mol dm^{-3} ionic strength, I, in terms of eqn. (7).[15]

$$-\log \gamma_\pm = 0.512\,\sqrt{I}(1 + 1.5\,\sqrt{I}) - 1 \qquad (7)$$

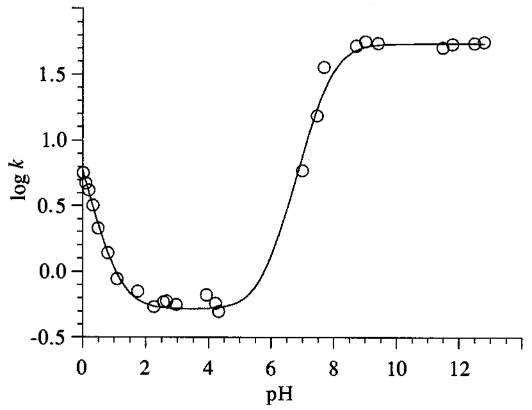


Fig. 1 pH-Profile for the ketonisation reaction of **2PAT**. For the significance of log k see the 'pH-profile' section in the text.

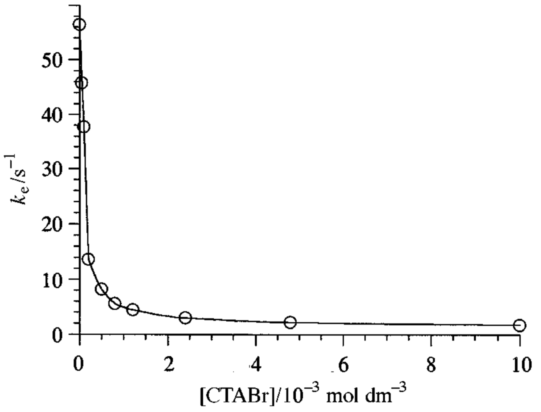


Fig. 2 Effect of the addition of CTABr on the rate of ketonisation of the enolate of **2PAT** in aqueous NaOH (0.1 mol dm^{-3}), ionic strength 1.0 mol dm^{-3} (NaCl), at 25.0 ± 0.1 °C. The line is drawn as a visual guide. The reported[16] c.m.c. value in water of CTABr is 9.2×10^{-4} mol dm^{-3}.

Measurements in the presence of CTABr

An apparent pK_a^{KH} of 12.35 (±0.01) for [**2PAT**] = 5.0×10^{-5} mol dm^{-3} in the presence of CTABr 0.02 mol dm^{-3} was determined by varying the concentration of NaOH in the range 0.0002–3.0 mol dm^{-3} at λ 383 nm (A_o 0.0026 and A_{max} 0.7487) by the same procedure adopted in the absence of CTABr (see Experimental section).

The enolate rate of ketonisation, k_e, is strongly depressed by the presence of CTABr micelles as can be seen in Fig. 2. It is quite surprising that CTABr depresses k_e even at concentrations lower than the critical micelle concentration (c.m.c.[16] = 9.2×10^{-4} mol dm^{-3} in pure water).† However the c.m.c. of ionic surfactants is usually lowered by salts and the presence of organic compounds is also lowering c.m.c. This is frequently observed when comparing c.m.c. measured by solubility with values obtained by conductivity, surface tension, or other non-invasive techniques. Moreover it is not unusual to observe premicellar effects,[17] depending upon the binding of the substrates.

Micellar effects upon ketonisation reactions under the adopted experimental conditions can be treated[18–21] quantitatively in terms of an equilibrium distribution of the enolate, E, between water and micelles as distinct reaction regions (Scheme 3). In this pseudophase model, K_S^E is an association constant with respect to micellised surfactant, CTABr, and k'_o and k'_M are first order rate constants in aqueous and micellar pseudophases respectively which give eqn. (8).

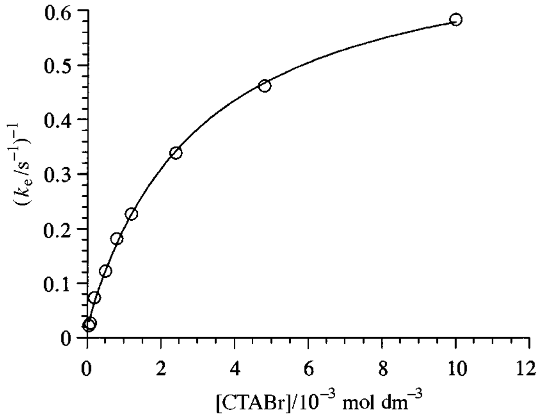
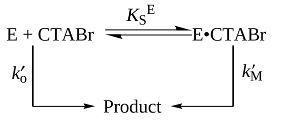


Fig. 3 Plot of the experimental first order rate constants for ketonisation of the enolate of **2PAT** in NaOH (0.1 mol dm^{-3}) against the stoichiometric concentration of CTABr, fitted into eqn. (9) (solid line)



Scheme 3

$$k_e = \frac{k'_o + k'_M K_S^E [\mathrm{CTABr}]}{1 + K_S^E [\mathrm{CTABr}]} \tag{8}$$

Eqn. (8) in turn can be expressed as eqn. (9).

$$\frac{1}{k_e} = \frac{(1/k'_o) + (K_S^E[\mathrm{CTABr}]/k'_o)}{1 + (k'_M K_S^E [\mathrm{CTABr}]/k'_o)} \tag{9}$$

A multiple regression analysis of eqn. (9) by using experimental k_e, k'_o and [CTABr] values (Fig. 3) affords the following results: K_S^E = 14 000 (±500) dm^3 mol^{-1}; k'_M = 1.34 (±0.03) s^{-1}.

The value of K_S^E can also be measured directly by UV–VIS spectroscopy, as the association with CTABr causes a bathochromic shift of λ_{max} of the enolate from 347 to 383 nm. The change in absorbance at λ 383 nm was measured ‡ as a function of the concentration of the surfactant in 1.0 mol dm^{-3} NaOH assuming that both the free and the associated enolate contribute to the observed absorbance, A.

Eqn. (10) was derived accordingly, where [**2PAT**]$_i$ is the initial

$$A = \frac{[\mathbf{2PAT}]_i K_S^E [\mathrm{CTABr}]}{1 + K_S^E [\mathrm{CTABr}]} \varepsilon_{\mathrm{E\cdot CTABr}} + \frac{[\mathbf{2PAT}]_i}{1 + K_S^E [\mathrm{CTABr}]} \varepsilon_{\mathrm{E}} \tag{10}$$

concentration of the substrate and $\varepsilon_{\mathrm{E\cdot CTABr}}$ (15 954 dm^3 mol^{-1} cm^{-1}) and ε_{E} (1854 dm^3 mol^{-1} cm^{-1}) are the molar absorptivities of the associated and free enolate respectively.

From a best fit of experimental A values to eqn. (10) a value of K_S^E may be obtained: K_S^E = 13 000 (±1000) dm^3 mol^{-1}.

The binding constant, K_S^{KH} = 173 (±20) dm^3 mol^{-1} of the keto form (KH) with the surfactant was similarly determined in aqueous solution of CTABr at λ 305 nm although the spectral difference between the associated and the free ketone was considerably smaller.

Discussion

Equilibrium constants for ionisation and tautomerisation of **2PAT** are summarised in Scheme 4 as their pK values.

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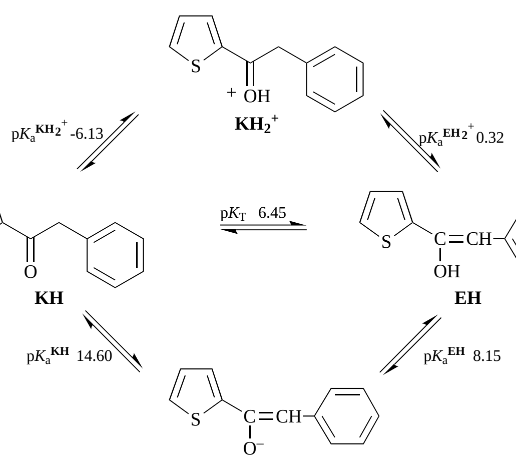
† We thank a referee for drawing our attention to this.

‡ The value of K_S^E is not affected significantly by the change of λ.



KH_2^+

KH

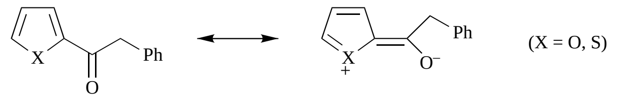
EH

E

Scheme 4

As expected[3] the pK_a^{EH} of the enol of **2PAT** (8.15) is considerably lower than that of acetone[22a] (10.96) or acetophenone[22b] (10.34) and is of the order expected from other aryl benzyl ketones[3] (Scheme 5). Although there can be little doubt that electronegativity of the α-substituent is an important factor in determining the observed acidity trend it has previously been pointed out[3] that pyrazine and pyridine enols show pK_a^{EH} values which are in the reverse order of their electronegativities. The same inversion applies to furan and thiophene enols herein. In fact, *e.g.* 2-furoic acid (pK_a 3.16)[23] is a stronger acid than thiophene-2-carboxylic acid (pK_a 3.51)[24] and σ-values[25] for 2-furyl and 2-thienyl groups are 1.10 and 0.66, respectively.

Also of interest is the magnitude of the tautomeric constant, pK_T, for **2PAT**. It is generally recognised[1c,3,26,27] that the relatively high enol content for aryl benzyl ketones bearing electronegative aryl groups (Scheme 5) is principally a consequence of unfavourable effects of the substituent directly bound to the carbonyl group upon the stability of the keto tautomer. However it clearly appears that benzyl ketones with 'π-excessive' five-membered heterocyclic α-substituents show a *smaller* enol content than, *e.g.* deoxybenzoin, despite the positive σ-values of the heteroaryl groups or the lower pK_a values of the corresponding carboxylic acids. External conjugation[3,28] with the lone pair of electrons on the oxygen and sulfur atoms probably stabilises the carbonyl group of the keto form.



In conclusion it appears that while the investigated five-membered heterocyclic rings behave as electron-attracting substituents in determining pK_a^{EH}, they behave as electron-donating substituents in stabilising the keto form, thus considerably increasing pK_T values with respect to deoxybenzoin. The more aromatic thiophene derivative gave a larger pK_T than the furan derivative. Probably a difference in external conjugation is more than compensated for by the effect of the greater electronegativity of the oxygen in the ring on the stability of the ketone.

A Brønsted exponent, α 0.36, may be determined from the measurements for the general acid catalysed ketonisation reaction of 2-phenylacetylthiophene enolate anion by carboxylic acids (Table S4).§ This corresponds to a β value of 0.64 (in quite good agreement with a β value of 0.66 calculated from the experimental values in acetate and glycolate buffers) for the reverse enolisation reaction catalysed by carboxylate anions. These values are very close to the corresponding values[3] (α 0.35 and β 0.65) found for 2-phenylacetylfuran and are generally consistent with an inverse relationship between reactivity and selectivity in the proton transfer reaction between carboxylic acids and selected carbon bases (see ref. 3 for a detailed discussion of this point).

From the difference of the experimental pK_a^{KH} values determined (see above) in aqueous solution in the absence and in the presence of cetyltrimethylammonium bromide (CTABr) it can be appreciated that the addition of CTABr determines a noticeable increase ($\Delta pK = 2.2$) in the acidity of the keto form. This effect should be ascribed to the stabilisation of the anionic form of **2PAT** by the CTABr micelles as it is shown by the large difference between the binding constants, K_S, of the acid and its conjugate base. This stabilisation is also apparent from the bathochromic shift in the UV–VIS spectrum of the enolate of **2PAT** upon transfer from water to CTABr micelles.

The 40-fold inhibition observed (Fig. 2) upon micellisation for the water catalysed ketonisation rate constant of the enolate anion (k_e) should probably be ascribed to a decreased water availability within the micellar aggregate.

Enolates are important intermediates in organic synthesis for C–O and C–C bond formation reactions. They are commonly obtained[29] from weakly acidic ketones using strong bases in aprotic solvents at low temperatures (*e.g.* LDA in THF or DME at −78 °C). The present results suggest a new possibility of generating significant amounts of enolates from simple ketones in aqueous micellar solutions of cationic surfactants.

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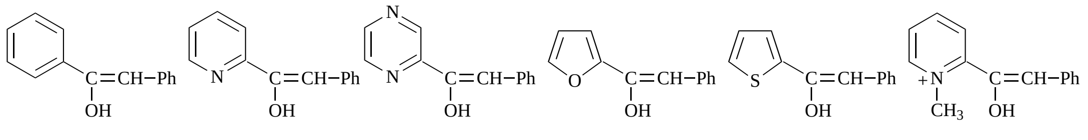

pK_a^{EH}	9.6	8.75	9.0	8.5	8.15	5.9
pK_T	5.15	3.3	2.9	5.9	6.45	1.0

Scheme 5

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§ Table S4 summarising rate constants for the general acid catalysed ketonisation reaction of 2-phenylacetylthiophene enolate anion by oxygen acid and deprotonation of the keto form by oxygen bases is available as a supplementary publication (Suppl. No. 57290, 2pp.). For details of the Supplementary Publications Scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1.

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