Equilibrium Constants for Ionisation and Enolisation of 2-Phenylacetylfuran

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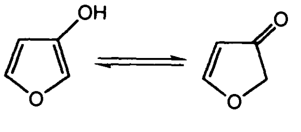
The equilibrium constant for keto–enol tautomerism of 2-phenylacetylfuran K_E = [enol]/[ketone] has been measured as 1.32×10^{-6} ($pK_E = 5.88$) by combining rate constants for enolisation and ketonisation. Rates of enolisation were measured by iodination and of ketonisation by quenching the enolate anion into acidic buffers and monitoring relaxation of the initially formed enol to its keto tautomer by stopped-flow. The pK_a for ionisation of 2-phenylacetyl furan was measured spectrophotometrically as 14.38. Combining this with pK_E gives $pK_a^{EH} = 8.5$ for the enol tautomer. Comparison with deoxybenzoin ($pK_E = 5.15$, $pK_a^{EH} = 9.6$) shows a mild influence of the oxygen of the furan ring (*a*) in enhancing the acidity of the enol and (*b*) in stabilising the keto relative to enol tautomer. Phenylacetylfuran shows a high pH-independent rate for the tautomerisation reaction which prevents observation of metal-ion catalysis. A Brønsted exponent $\alpha = 0.35$ has been measured and is compared with values for related substrates with pK_as in the range 18 to −11. Values of pK_a and pK_T for acetylfuran are estimated.

In the past ten years equilibrium constants have been measured for keto–enol tautomerism and ionisation in basic solution of a wide range of carbonyl compounds[1–3] including heterocyclic ketones containing pyridyl[4] and pyrazyl[5] substituents. 'Keto–phenol' tautomerism of hydroxy-furans, -thiophenes, -pyrroles and their benzo derivatives, *e.g.*, $1 \rightleftharpoons 2$, has also been investigated by Capon and co-workers.[3] However, despite recent interest in rates of enolisation of acetyl derivatives of furan, thiophene and pyrrole,[6] there appear to have been no studies of the effect of these 'π-excessive' heterocycles as simple carbonyl substituents upon keto–enol equilibria. In this paper we report such a study for 2-phenylacetylfuran 3.



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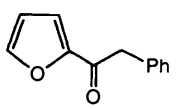

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The choice of phenylacetylfuran was prompted partly by the observation that enolisation of acetylfuran is subject to catalysis by metal ions.[6] It was thought that for phenylacetylfuran it would be possible to measure equilibrium and binding constants as well as rate constants for this catalysis. In practice, no catalysis by metal ions was observed for reasons discussed below. However, tautomeric and ionisation constants could be measured, and the effect of the furanyl group on these equilibria is described.

Results

2-Phenylacetylfuran is just acidic enough for its pK_a to be determined from direct spectrophotometric measurements in aqueous sodium hydroxide. Appearance of an absorption peak at 340 nm is consistent with formation of an enolate anion. From absorbance measurements in the concentration range 0.1–2.3 mol dm^{-3} NaOH a value of $pK_a^{KH} = 14.38$ at 25 °C was obtained.

Rate constants for ketonisation were measured by quenching a solution of the enolate anion in 0.5 mol dm^{-3} NaOH into acidic or buffer solutions and monitoring relaxation of the enol so generated to its more stable keto tautomer by stopped-flow spectrophotometry. The reaction was subject to buffer catalysis as well as catalysis by OH^- and H^+ ions and also showed a pH-independent reaction. At a single pH, the dependence of observed first-order rate constants (k_{obs}) upon the concentration of buffer base (B) at constant buffer ratio ($[BH^+]/[B]$) is described by eqn. (1) in which k and k_0 represent the slope and intercept of the plot.

$$k_{obs} = k_0 + k[B] \quad (1)$$

Values of k and k_0 for borate, lutidine, phosphate, cacodylate, acetate and chloroacetate buffers at different buffer ratios and 1 mol dm^{-3} ionic strength are shown in Table 1. In principle, the buffer catalysis could represent contributions from the acid or base component of the buffer as shown in eqn. (2), where k_{GB} and k_{GA} are rate constants for general-base and general-acid catalysis, respectively. In practice, apart from H_3O^+, a small contribution from acid catalysis was found only for the strongest carboxylic acids used, namely chloroacetic and cyanoacetic. Values of k_{GA} and k_{GB} were derived from values of k [eqn. (1)] as described previously[4] and are also listed in Table 1.

$$k = k_{GB}[B] + k_{GA}[A] \quad (2)$$

Rates of reaction in solutions of HCl showed a linear dependence on $[H^+]$ with rate constant $k_H = 4.1$ dm^3 mol^{-1} s^{-1} and a well-defined intercept corresponding to a pH-independent reaction with rate constant $k_{H_2O} = 0.30$ s^{-1}. Measured first-order rate constants (k_{obs}/s^{-1} at 25 °C) at different concentrations of HCl (mol dm^{-3}) were as follows: 0.29 (0.01); 0.39 (0.02); 0.53 (0.05); 0.72 (0.1); 1.23 (0.2) and 2.32 (0.5). Measurements in aqueous sodium hydroxide showed a base-independent reaction with first-order rate constants (k_{obs}/s^{-1}) at different concentrations of hydroxide ion (mol dm^{-3}): 30.4 (0.05); 32.6 (0.01); 31.1 (0.1); 31.0 (0.4).

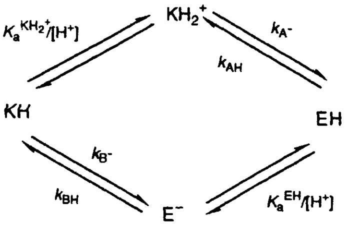
The observation of acid- and base-catalysed reactions is consistent with the usual mechanisms for keto–enol tautomerism[1,2,7] shown in the upper (acid) and lower (base) pathways of Scheme 1. In this Scheme KH, EH, KH_2^+ and E^- represent keto and enol forms of 2-phenylacetylfuran and their conjugate acid and base respectively. Also shown are acid dissociation constants for the enol (pK_a^{EH}) and the conjugate acid of the

Table 1 Slopes k and intercepts k_0 for plots of measured first-order rate constants (k_{obs}/s^{-1}) against concentration of buffer base in aqueous solution at 25 °C and ionic strength 1 mol dm^{-3}

Base	R[a]	pH[b]	k_0/s^{-1}	$k/dm^3\ mol^{-1}\ s^{-1}$	$k_{GB}/dm^3\ mol^{-1}\ s^{-1}$	$k_{GA}/dm^3\ mol^{-1}\ s^{-1}$
H_2O		2–5	0.27	4.1	0.27/55.5	4.1
$CNCH_2COO^-$	0.25	1.66	0.35	2.80		
	1.0	2.27	0.28	2.18		
	4.0	2.87	0.27	2.14	2.0	0.20
$ClCH_2COO^-$	0.25	2.06	0.29	5.62		
	1.0	2.67	0.34	4.80		
	4.0	3.27	0.29	4.60	4.5	0.28
$HOCH_2COO^-$	0.25	3.02	0.15	16.0		
	1.0	3.67	0.38	13.7		
	4.0	4.23	—	16.7	15.3	
CH_3COO^-	1.0	4.55	—	66.4		
	4.0	5.15	—	69.8	68.1	
Cacodylate	1.0	6.07	—	5300	5300	
HPO_4^{2-}	0.25	6.39	(1.4)[c]	317		
	1.0	6.99	5.7	428		
	4.75	7.67	7.0	399	400	
Lutidine	1.0	6.93	—	2270	2270	
$H_2BO_3^-$	0.2	8.33	20.6	462		
	1.0	9.03	17.1	236		
	4.0	9.63	25.2	185	60	172[d]

[a] Buffer ratio [B]/[BH$^+$]. [b] pH calculated with correction to ionic strength 1 mol dm^{-3}. [c] Based on two measurements only. [d] From protonation of enolate anion by $H_2BO_3^-$.

ketone (p$K_a^{KH_2^+}$), together with rate constants for protonation of the enol (k_{AH}) and enolate anion (k_{BH}), and for deprotonation of the ketone (k_{B^-}) and its conjugate acid (k_{A^-}) in the acid and base pathways, respectively.



Scheme 1

To convert measured values of k_{GA} and k_{GB} into the rate constants of Scheme 1 it is necessary to know the ionisation constants pK_a^{EH} and p$K_a^{KH_2^+}$ and also the tautomeric constant K_E = [enol]/[ketone] for keto and enol forms of phenylacetylfuran. The tautomeric constant was determined by combining rate constants for ketonisation (k^K, Table 1) with corresponding values (k^E) for enolisation measured under the same conditions by the usual iodine trapping method.[1,6–9] Thus measurements in acetate buffers (buffer ratio = 4) gave $k^E = k^E_{GB}$ = 9.23×10^{-5} dm^3 mol^{-1} s^{-1} for enolisation, and combining this with k^K_{GB} = 69.8 for ketonisation in the same buffers gave K_E = 1.30×10^{-6} (pK_E = 5.88). This value of pK_E can be combined with the measurement of the acid dissociation constant of the ketone pK_a^{KH} = 14.38 to obtain the pK_a of the enol as pK_a^{EH} = pK_a^{KH} − pK_E = 8.5.

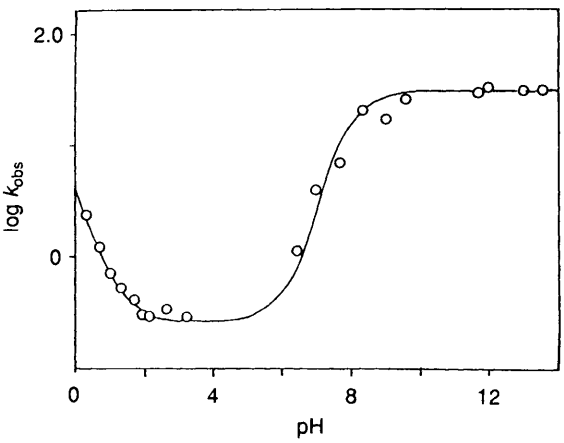


Fig. 1 pH profile for the ketonisation of phenylacetylfuran enol

In principle, the pK_a of the enol may also be determined from the pH-profile for the ketonisation reaction. This profile is shown in Fig. 1 as a plot of values of log k_0 from Table 1 and of log k_{obs} for ketonisation in aqueous HCl or NaOH solutions against pH. The profile shows pH regions for H$^+$ and OH$^-$ catalysis together with two regions in which the reaction is pH-independent. The pH-independent region at lower pH (2–5) is sensibly interpreted as an uncatalysed (water) reaction in which the enol initially ionises to an enolate anion and H_3O^+ which then recombine to form ketone and H_2O.[10] For the reaction at high pH, the reactant is the enolate anion rather than enol and this is protonated by H_2O to form the ketone. The 'break' in the pH-profile near pH 8 then represents the change in reactant from the enolate anion at high pH to enol at lower pH.[11] The point of inflection corresponds to the pK_a of the enol, below which the reaction becomes base-catalysed. A value of pK_a^{EH} = 8.1 may be obtained from a best fit of experimental rate constants to eqn. (3), in which k_H = 4.1 dm^3 mol^{-1} s^{-1}, k_{OH} = 2.5×10^7 dm^3 mol^{-1} s^{-1} and k_{H_2O} = 0.30 s^{-1} are rate constants for H$^+$ catalysed, OH$^-$ catalysed and uncatalysed ketonisations, respectively, and are also chosen to provide a best fit to the experimental values.

$$k_{\mathrm{obs}} = k_{\mathrm{H}}[\mathrm{H}^+] + k_{\mathrm{H_2O}} + \frac{k_{\mathrm{OH}}[\mathrm{OH}^-]}{1 + K_a^{\mathrm{EH}}/[\mathrm{H}^+]} \qquad (3)$$

Agreement between the value of 8.1 for pK_a^{EH} from the pH-profile and 8.5 from $pK_a^{KH} - pK_T$ is not particularly good. However, the downward break in the pH-profile is defined only by intercepts (k_0) for phosphate buffers which are subject to a relatively large uncertainty with formal errors of ±30% at pH 7.0 and 7.7, respectively, and an unknown error at pH 6.4, where k_0 is extrapolated from only two rate measurements. Thus a value of pK_a^{EH} based on these measurements is subject to considerable uncertainty.

The same is true of a further value of pK_a^{EH} obtainable from the pH-dependence of the slopes k for apparent catalysis by buffer base in eqn. (1) when the pH is close to the pK_a of the enol. In close analogy with the last term of eqn. (3) the relationship between k and K_a^{EH} is given by eqn. (4) in which k_{GB} is the rate constant for general-base catalysis with the enol as reactant.[12]

$$k = k_{\mathrm{GB}}/(1 + K_a^{\mathrm{EH}}/[\mathrm{H}^+]) \qquad (4)$$

In Table 1 it can be seen that values of k for the three borate buffers and two phosphate buffers which have pH closest to the pK_a of the enol are dependent on pH. A best fit of these values to eqn. (4) is achieved with $pK_a \sim 9.0$, $k_{GB} = 500$ dm^3 mol^{-1} s^{-1} for borate ion and $k_{GB} = 400$ dm^3 mol^{-1} s^{-1} for HPO_4^{2-} (neglecting k for the phosphate buffer at pH 6.39 in Table 1). This value is probably no more accurate than $pK_a^{EH} = 8.1$ from the pH-profile, but it is satisfactory that the best value of 8.5, based on pK_E, is the average of the other two. It is used to calculate specific rate constants based on Scheme 1 from the measurements in Table 1 and values of k_{OH} and k_{H_2O} for the HO^- and water reactions from fitting eqn. (3) to the pH-profile.

In practice, not all the rate constants in Scheme 1 can be evaluated because the pK_a for *O*-protonation of phenylacetylfuran is not known and its measurement is hindered by decomposition of the substrate in strongly acidic solutions where protonation occurs. However, rate constants for the basic pathway (k_B and k_{BH}) can be derived using measured values of k_{GB} for ketonisation. Except in the case of borate and phosphate buffers [*cf.*, eqn. (4)] the latter are equal to values of k in Table 1 provided allowance is made for a small correction for the acid reaction of cyanoacetate and chloroacetate buffers. The values are substituted into eqns. (5) and (6) in which K_a is the ionisation constant of the buffer acid.

$$k_{\mathrm{BH}} = (K_a/K_a^{\mathrm{EH}})k_{\mathrm{GB}} \qquad (5)$$

$$k_{\mathrm{B}} = K_{\mathrm{E}}k_{\mathrm{GB}} \qquad (6)$$

Values of k_{BH} and k_B are listed in Table 2. For the acid pathway in Scheme 1 only k_{AH} (= k_{GA}) for the ketonisation can be evaluated. For the acids H_3O^+, cyanoacetic and chloroacetic, for which acid catalysis can be detected, $k_{AH} = 4.8$, 0.20 and 0.155, dm^3 mol^{-1} s^{-1}, respectively. As already noted, calculation of k_{A^-} would require a knowledge of $pK_a^{KH_2^+}$.

Values of k_{BH} are shown plotted as log k *versus* pK_a in the form of a Brønsted correlation in Fig. 2. A straight line ($\log k = 7.25 + \alpha \log K_a$) is drawn through the points for the carboxylic acids. Rate constants for H_3O^+ and lutidinium ion also fall on this line but cacodylic acid shows a small positive deviation and $H_2PO_4^-$, $B(OH)_3$ and H_2O all deviate negatively. Of the negative deviations, those for boric acid and water are commonly observed in Brønsted plots and that for $H_2PO_4^-$ is probably due to electrostatic repulsion between the negatively charged acid and enolate anion in the transition state.

Table 2 Rate constant (dm^3 mol^{-1} s^{-1}) for reaction of 2- phenylacetylfuran, its enolate anion and enol with oxygen and nitrogen acids and bases in aqueous solution at 25 °C and ionic strength 1 mol dm^{-3}

Acid	pK_a	k_{BH}[a]	k_{B^-}[b]	k_{AH}[c]
H_3O^+	−1.74	8.7 × 10^7	3.6 × 10^{-7}/55.5	4.1
$CNCH_2COOH$	2.40	2.5 × 10^6	2.5 × 10^{-6}	0.20
$ClCH_2COOH$	2.86	2.0 × 10^6	5.7 × 10^{-6}	0.155
$HOCH_2COOH$	3.83	1.05 × 10^6	2.0 × 10^{-5}	
CH_3COOH	4.76	3.8 × 10^5	8.6 × 10^{-5}	
Cacodylic	6.27	9.0 × 10^5	6.7 × 10^{-3}	
2,6-Lutidinium	6.69	1.22 × 10^5	2.85 × 10^{-3}	
HPO_4^{2-}	7.20	2.00 × 10^3	5.0 × 10^{-4}	
Boric	9.24	82	5.7 × 10^{-4}	
H_2O	15.74	32/55.5	13.0	

[a] Rate constants for protonation of enolate anion. [b] Rate constants for deprotonation of ketone. [c] Rate constants for protonation of enol.

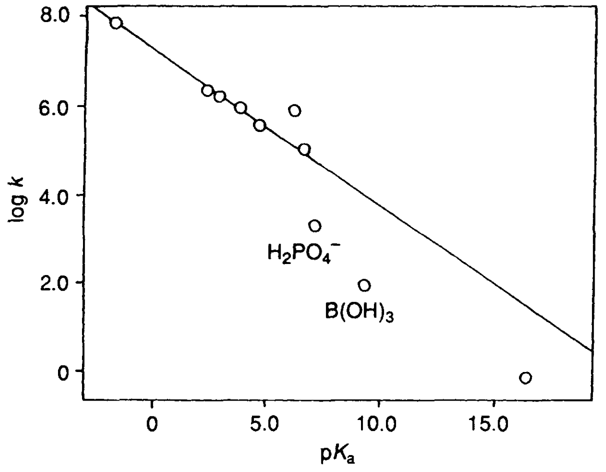
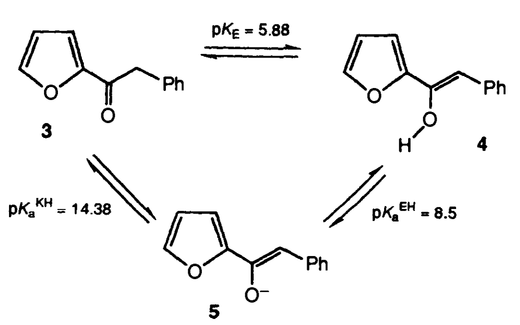


Fig. 2 Brønsted plot of log k versus pK_a for ketonisation of 2-phenylacetylfuran enol

Discussion

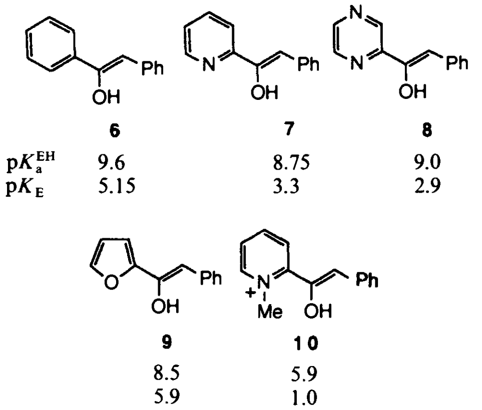
Equilibrium constants for ionisation and tautomerisation of 2-phenylacetylfuran are summarised as their pK values ($-\log K$) in Scheme 2. Phenylacetylfuran is just acidic enough for its basic ionisation constant to be measured in aqueous sodium hydroxide ($pK_a = 14.38$) and this means that rates of ketonisation can be measured by quenching the enolate anion in acidic or buffer solutions to generate the enol. These rates are slow enough to measure by stopped-flow despite the low equilibrium concentration (one part in 10^6) and hence instability (and high reactivity) of the enol tautomer.



Scheme 2

When the pK values in Scheme 2 are compared with those of other simple ketones it is noticeable that the pK_a of the enol (8.5) is significantly smaller than that of acetone[13] (10.96), acetophenone[14] (10.34) or acetaldehyde (10.50).[15] The most likely explanation of this is that it reflects the electronegativity of the oxygen atom in the furanyl ring. Data showing the influence of α-substituents upon enol pK_a are scarce but a hint of the importance of electronegativity effects is provided by the slightly lower acidity of the enol of acetone (with an α-methyl substituent) than of acetophenone or acetaldehyde (with α-phenyl or hydrogen substituents) and still lower acidity[16] ($pK_a^{EH} = 11.55$) of the enol of the pyruvate anion which has a negatively charged α-carboxylate substituent [$CH_2{=}C(OH)COO^-$].

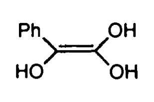
Further evidence of the influence of α-substituents is provided by a comparison of **4** with enols of other phenylacetyl ketones.[5,17] The pK_a of a number of these, including the enols of phenylacetyl pyrazine (**8**), 2-phenylacetylpyridine (**7**) and the *N*-methyl derivative of the latter (**10**),[17] are shown under their respective structures (**6**–**10**) in Scheme 3. It can be seen that an α-phenyl substituent increases the acidity of the enol by one unit and that this is part of the reason for the greater acidity of the enol of phenylacetyl furan than those of acetaldehyde or acetophenone. However, it can also be seen that the acidity increases with changing α-substituent, from $pK_a^{EH} = 9.6$ for the enol of deoxybenzoin (**6**)* to $pK_a^{EH} = 5.9$ for the enol of *N*-methyl-2-phenylacetylpyridinium ion, in the order α-phenyl < pyrazyl < pyridyl < furanyl < pyridinium passing from left to right in the scheme. This order is not quite that expected in so far as the pyrazine enol shows a higher pK_a than that of the pyridine (9.0 compared with 8.75) which is the reverse order of their electronegativities, but the overall trend seems clear and the greater electronegativity implied for a furanyl than pyridyl substituent is probably consistent with their Hammett σ constants.[18]



Scheme 3

In principle a clearer indication of the influence of an oxygen substituent upon enol acidity should be provided by measurements for enols of carboxylic acids and esters. Thus Kresge has shown that the enols of mandelic acid (**11**)[19] and its methyl ester[20] are highly acidic with $pK_a^{EH} = 6.82$ and 6.45, respectively. However this may be partly a result of the presence of a β-hydroxy group capable of stabilising the enolate anion by hydrogen bonding (**12**).

Also of interest is the magnitude of the tautomeric constant of phenylacetylfuran. Values of pK_E are included in Scheme 3 and it can be seen that again these generally decrease from left to right, from $pK_E = 5.15$ for deoxybenzoin (**6**)[21] to $pK_E = 1.0$ for the *N*-methylpyridinium ion (**10**). There can be little doubt that this is principally a consequence of the unfavourable effect of an electronegative substituent directly bound to the carbonyl group upon the stability of the keto tautomer.[2,22] However, now phenylacetylfuran appears to fall out of sequence, and indeed shows the smallest enol content ($pK_E = 5.9$) despite furan being one of the most electronegative substituents in the series.



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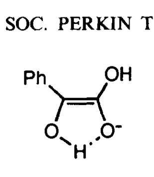

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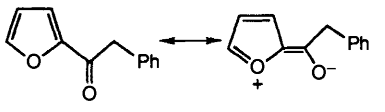

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This behaviour is understandable if we recognise that as a result of the 'π-excessive' character of furan phenylacetyl furan is formally a vinylogous ester, so the carbonyl group is stabilised by π-conjugation with the lone pair of electrons on the oxygen atom (**13**). It is not surprising that the conjugative effect here overrides the unfavourable σ-electron withdrawing effect of oxygen because there is no charge developed in the keto–enol equilibrium. By contrast 2-furoic acid ($pK_a = 3.16$) is a stronger acid than benzoic acid ($pK_a = 4.20$) because σ-inductive stabilisation of the negative charge on the carboxylate group overrides π-conjugative stabilisation of the acid.†

Comparison with Acetylfuran: Absence of Metal-ion Catalysis.—The data for phenylacetylfuran may be used to estimate approximate ionisation constants and an enol content for acetylfuran, for which direct measurements are lacking. We suppose that replacing a phenyl group by a furanyl group in acetophenone has the same effect as it has in deoxybenzoin. Then, from $pK_E = 7.90$ and $pK_a^{EH} = 10.34$ for acetophenone[14] and the difference in pK_E and pK_a between deoxybenzoin and phenylacetylfuran in Scheme 3, we predict for 2-acetylfuran $pK_E = 8.7$ and $pK_a^{EH} = 9.1$. From the sum of these values pK_a^{KH} for the ketone is 17.8 (compared with 18.2 for acetophenone).

An alternative estimate of pK_a^{KH} for acetylfuran comes from a correlation between log k and pK_a for reactions of simple ketones with hydroxide ion reported by Keefe and Kresge.[1] This correlation is described by eqn. (7), in which p is a statistical factor taking account of the presence of equivalent reacting hydrogens in the ketone. Phenylacetylfuran shows a small deviation from the correlation, but combining k_{OH} from Table 2 with $pK_a^{KH} = 14.38$ for phenylacetylfuran and $k_{OH} = 0.41$ for acetylfuran,[6] gives $pK_a^{KH} = 18.1$ for acetylfuran, which is in reasonable agreement with the value of 17.8 deduced above, especially as k_{OH} for phenylacetylfuran was measured at 1 mol dm^{-3} ionic strength and is probably a little high.

$$\log (k_{OH}/p) = 0.4 \log (K_a^{KH}/p) + 6.47 \qquad (7)$$

Rate constants for enolisation of phenylacetylfuran and acetylfuran[6] are compared in Table 3. It can be seen that there is little difference in their H^+ rate constants ($k_H = 3.4$ and 5.3×10^{-6} dm^3 mol^{-1} s^{-1}, respectively) consistent with the observation[23] that these values are rather invariant from ketone to ketone and commonly close to 10^{-5} (with possibly a weak dependence on enol content).[24] On the other hand for the water and hydroxide reactions, which yield an enolate anion as an intermediate, the greater acidity of phenylacetyl- than acetylfuran is reflected in substantially larger rate constants for the former. A consequence is that the ratio of acid-catalysed to pH-independent rate constants is significantly smaller for phenyl-

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* The pK_a of the enol of deoxybenzoin is estimated, *cf.*, ref. 4.

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

acetyl- than acetyl-furan. Although this does not prevent observation of an H^+-catalysed reaction, it does prevent observation of metal-ion catalysis even though this is readily detectable for acetylfuran. The acidity of the ketone indeed is an important factor in determining whether acid or metal-ion catalysis is observable. For the more acidic β-diketones metal catalysis is detectable because the additional carbonyl group acts as a second coordination site but acid catalysis is either very weak or not observed at all.[25]

Brønsted Exponent.—A Brønsted exponent, $\alpha = 0.35$, may be derived from the measurements for the reactions of carboxylic acids with the phenylacetyl enolate anion in Table 2. This corresponds to $\beta = 0.65$ for the more commonly studied reverse enolisation reaction catalysed by carboxylate anions.[26] Values of α have been compiled previously as a function of the pK_a of the conjugate acid of the reacting carbon base for ketones and other carbon acids.[27,28] In Table 4 further data are shown from recent studies[9,29–32] spanning a range of pK_as and including the highly acidic non-ketonic carbon acid, the α-phenethyl carbocation (**14**), for which Jencks and Richard[33] found $pK_a = -11.2$ and $\alpha = 0.86$.

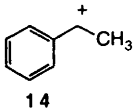

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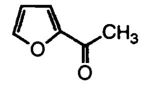
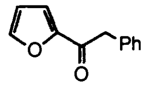
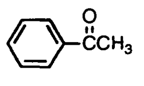
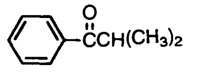
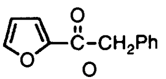
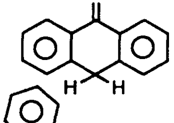
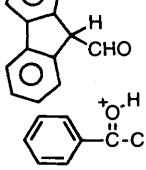
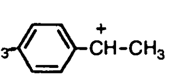
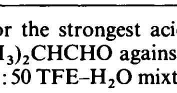
Table 3 Comparison of rate constants[a] for enolisation of acetylfuran and phenylacetyl furan

Acid	Base		
H_3O^+		3.35×10^{-6}	5.2×10^{-6}
	H_2O	$6.7 \times 10^{-9}/55.5$	$3.6 \times 10^{-7}/55.5$
	CH_3COO^-	1.1×10^{-6}	8.6×10^{-5}
	HO^-	0.41	13

[a] Units $dm^3\ mol^{-1}\ s^{-1}$; values for 2-acetylfuran from ref. 6; those for phenylacetylfuran refer to 1 mol dm^{-3} ionic strength.

It can be seen that there is a trend in α-values down the table from 0.32 for acetophenone to 0.86 for **14**. This is consistent with an inverse relationship between reactivity and selectivity and with interpretation of α as a measure of proton transfer in the transition state, as has been discussed extensively elsewhere.[28,32–36] Only brief further comment is called for. Firstly, it is noticeable that rate constants of the exothermic proton transfer reactions for the largest and smallest values of α fall well short of diffusion rates so that variations of α from this source do not arise. Secondly, it can be seen that there is a considerable clustering of α values with little change in acidity of the substrate in the pK_a range 10–18. This partly reflects the examples chosen, and Kresge's systematic study of vinyl ethers[34] giving α values from 0.58–0.84 fall in the reactivity range (and almost certainly range of pK_a) between the last two entries in the table for protonated acetophenone ($\alpha = 0.50$) and the α-phenethyl carbocation ($\alpha = 0.86$). However, it is also true that individual structural changes, such as from acetophenone to isobutyrophenone, produce changes in α (from 0.32 to 0.37) without an accompanying change in pK_a or reactivity. Such effects have been analysed by Bunting and Stefanidis[28] using a Marcus treatment with variable intrinsic barrier, and have been interpreted in terms of 'imbalance' of C–H bond making and localisation of anionic charge in the proton-transfer transition state.[36] They add a degree of 'noise' to simple correlations of α with pK_a which tends to obscure trends in α unless large changes in acidity are examined. This is especially true as the accessible range of α values is normally limited to 0.15–0.85 by the encroachment of diffusion for fast reactions. Nevertheless, the result for phenylacetylfuran and other new data in Table 4 are useful in providing values of α

Table 4 Brønsted exponents, pK_a and acetic acid rate constants ($dm^3\ mol^{-1}\ s^{-1}$) for proton transfer between carboxylic acids and selected carbon bases in aqueous solution at 25 °C

Carbon acid	Ref.	k_{AcO^-}	k_{AcOH}	pK_a	α
	9	5.7×10^{-8}	2.0×10^{6a}	18.31	0.32
	23	2.45×10^{-8}	7.73×10^{5}	18.26	0.37
$(CH_3)_2CHCHO$	32	3.55×10^{-6}	1.91×10^{5}	15.49	0.39^b
	—[c]	8.6×10^{-5}	3.8×10^{5}	14.4	0.35
	28	1.9×10^{-3}	3.34×10^{2}	10.0	0.37
	29	2.44×10^{2}	6.57×10^{3}	6.2	0.51
	10	0.50	4.53	−4.0	0.50
	33	5.8×10^{6}	6.4×10^{-10}	-11.2^d	0.86

[a] For the strongest acid used to determine α ($CNCH_2COOH$) the rate constant is $4.5 \times 10^7\ dm^3\ mol^{-1}\ s^{-1}$. [b] Based on a plot of log *k* for $(CH_3)_2CHCHO$ against log *k* for isobutyrophenone for CH_3COOH, HCOOH and H_3O^+ catalysts to evaluate relative values of α. [c] This work. [d] 50:50 TFE–H_2O mixtures: pK_a in H_2O estimated as −12.1.

over a range of pK_a for which there have been rather few previous measurements.

Experimental

Instruments used in this work included Varian 300 MHz FT and JNM-PMX 60 MHz continuous wave NMR spectrometers, a Durrum-110 stopped-flow spectrometer equipped with a transient recorder and an Apple-2 microcomputer for data analysis, a Philips 8600 single-beam UV–VIS spectrometer and Radiometer pH meter.

2-Phenylacetyl furan was prepared from 2-furfural *via* the oxime and nitrile using an adaptation of a previously described Grignard reaction[37] of the nitrile in the final step. An attempt to prepare furonitrile directly from furfural[38] gave the oxime which was converted into the nitrile by reaction with dimethylaminopyridine and thionyl chloride as described by Arrieta and Palomo.[39]

2-Phenylacetylfuran.—2-Furonitrile (7.05 g, 0.076 mol) in 80 cm^3 anhydrous diethyl ether was added over 1 h to benzylmagnesium chloride (0.076 mol) causing precipitation of a yellow solid. The reaction mixture was stirred overnight at room temperature, 20 g of ammonium chloride in 80 cm^3 H_2O were added and stirring was continued for 1 h as the phases separated. The ether layer was dried over sodium sulfate and the solvent was removed to yield 12.6 g of a dark yellow viscous oil which was purified by column chromatography (eluent: benzene–ethyl acetate, 9 : 1) to give an oil which crystallised from *n*-pentane as brown flakes with a low m.p., *ca.* 40 °C (lit.,[40] 47 °C) (Found: C, 77.8; H, 5.6; $C_{12}H_{10}O_2$ requires C, 77.4; H, 5.41%); $\delta_H(CDCl_3)$ 4.11 (s, 2 H, CH_2), 6.51 (dd, 1 H + imp., 4-H of furan J_{34} = 3.5 Hz, $J_{4,5}$ = 1.7 Hz), 7.21 (d, 1 H, 3-H of furan $J_{3,4}$ = 3.5 Hz), 7.3 (m, 5 H, Ph) and 7.58 (d, 1 H, 5-H of furan $J_{4,5}$ = 1.7 Hz); $\delta_C(CDCl_3)$ 187.2 (C), 152.9 (C), 147.2 (CH), 134.7 (C), 130.1 (2 CH), 129.2 (2 CH), 127.6 (CH), 118.5 (CH), 113.0 (CH) and 46.0 (CH_2).

Ionisation Constant.—In concentrated solutions of NaOH 2-phenylacetylfuran (λ_{max} = 280 nm) undergoes a change in UV spectrum consistent with formation of an enolate anion (λ_{max} = 340 nm), ionisation to which is complete in 5 mol dm^{-3} base. A value of pK_b = −0.38 was obtained from absorbance measurements at constant substrate concentration in the range 0.1–3 mol dm^{-3} NaOH using eqn. (8), in which A and A_{max} are absorbances at 340 nm measured at the specified [OH$^-$] and in the high base concentration limit (5 mol dm^{-3}), respectively, and log K_b is obtained from extrapolation to zero base concentration of a plot of log K against [OH$^-$] assuming that this dependence becomes linear below *ca.* 2 mol dm^{-3},[41] as observed for pK_as in acid solution by Long and Paul.[42] As implied by eqn. (8) there is no contribution to the measured absorbance at 340 nm from unionised phenylacetyl furan.

$$K_b = \frac{(A_{max} - A)\,[OH^-]}{A} \qquad (8)$$

Kinetic Measurements.—Rates of ketonisation of phenylacetylfuran were measured by stopped-flow kinetics. Freshly prepared solutions of enolate anion in 0.5 mol dm^{-3} aqueous NaOH were placed in one of the drive syringes and 0.5 mol dm^{-3} HCl plus an appropriate concentration of buffer and sodium chloride to ensure that the ionic strength after mixing was 1 mol dm^{-3} in the other. In 0.5 mol dm^{-3} NaOH phenylacetylfuran is about 20% ionised. For the buffer measurements pH values were calculated at 1 mol dm^{-3} ionic strength using eqn. (9)[43] in which I is the ionic strength, K_a is the ionisation constant and R is the ratio of base to acid concentrations of the buffer.

$$\mathrm{pH} = \mathrm{p}K_a + \log R + [0.51\, I\surd(1 + 1.5\surd I)] \qquad (9)$$

The rate constants measured were not corrected for ionic strength. Since ionic strength effects should not substantially affect pK_E the kinetically determined tautomeric constant should correspond to the thermodynamic value (for water). Since the pK_a for phenylacetylfuran was extrapolated to zero sodium hydoxide concentration, this and pK_a^{EH} for the enol should also be thermodynamic values. The same is not true of a value of pK_a^{EH} determined from the pH-profile of Fig. 1 which is based on a pH calculated for 1 mol dm^{-3} ionic strength. For anionic buffers the ionic strength correction cancels between the buffer and the substrate so that the pK_a would properly be defined in the borate buffers principally used for the pK_a measurement by a calculated pH without ionic strength corrections. However, as discussed above the pH-profile is not expected to yield an accurate value of the pK_a so no attempt was made further to correct experimental values even where corrections would be significant.

Measurements of rates of iodination of phenylacetylfuran were carried out as described previously[6,12] using zero-order conditions and 4 : 1 ([AcO$^-$]/[AcOH]) acetic acid buffers. The concentration of iodide ion was maintained at 0.01 mol dm^{-3} with the usual correction applied for dissociation of I_3^- to I_2 + I^-.[8] As for ketonisation measurements the ionic strength was maintained at 1.0 mol dm^{-3}.

References

1 J. R. Keefe and A. J. Kresge in *The Chemistry of Enols*, ed. Z. Rappoport, Wiley, New York, 1990, p. 399.
2 J. Toullec in *The Chemistry of Enols*, ed. Z. Rappoport, Wiley, New York, 1990, p. 323; A. J. Kresge, *Acc. Chem. Res.*, 1990, **23**, 43.
3 B. Capon, B.-Z. Guo, F. C. Kwok, A. P. Siddharta and C. Zucco, *Acc. Chem. Res.*, 1988, **21**, 135.
4 A. R. E. Carey, S. Al-Quatami, R. A. More O'Ferrall and B. A. Murray, *J. Chem. Soc., Chem. Commun.*, 1988, 1098; A. R. E. Carey, S. Eustace, R. A. More O'Ferrall and B. A. Murray, *J. Chem. Soc., Perkin Trans. 2*, 1993, 2285.
5 A. R. E. Carey, R. A. More O'Ferrall, M. G. Murphy and B. A. Murray, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2471.
6 P. De Maria, A. Fontana, S. Frascari, F. Ferroni and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1992, 825.
7 R. P. Bell, *The Proton in Chemistry*, 2nd edn., Chapman and Hall, London, 1973.
8 G. E. Lienhard and T.-C. Wang, *J. Am. Chem. Soc.*, 1969, **91**, 1146.
9 R. P. Bell and O. M. Lidwell, *Proc. R. Soc. London, Ser. A.*, 1940, **176**, 88.
10 Y. Chiang, A. J. Kresge, J. A. Santaballa and J. Wirz, *J. Am. Chem. Soc.*, 1988, **110**, 5506.
11 Y. Chiang, A. J. Kresge and P. A. Walsh, *J. Am. Chem. Soc.*, 1986, **108**, 6314.
12 A. R. E. Carey, G. Fukata, R. A. More O'Ferrall and M. G. Murphy, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1711.
13 Y. Chiang, A. J. Kresge, Y. S. Tang and J. Wirz, *J. Am. Chem. Soc.*, 1984, **106**, 460.
14 Y. Chiang, A. J. Kresge and J. Wirz, *J. Am. Chem. Soc.*, 1984, **106**, 6392.
15 Y. Chiang, M. Hojatti, J. R. Keefe, A. J. Kresge, N. P. Schepp and J. Wirz, *J. Am. Chem. Soc.*, 1987, **109**, 4000.
16 Y. Chiang, A. J. Kresge and P. Pruszynski, *J. Am. Chem. Soc.*, 1992, **114**, 3103.
17 G. McCann, S. Eustace and R. A. More O'Ferrall, unpublished results.
18 P. Tomasik and C. D. Johnson, *Adv. Heterocycl. Chem.*, 1976, **20**, 1.
19 Y. Chiang, A. J. Kresge, P. Pruszynski, N. P. Schepp and J. Wirz, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 792.
20 Y. Chiang, A. J. Kresge, P. Pruszynski, N. P. Schepp and J. Wirz, *Angew. Chem., Int. Ed. Engl.*, **30**, 1991, **30**, 1366.
21 A. J. Kresge, personal communication.
22 A. R. E. Carey, R. A. More O'Ferrall and B. A. Murray, *J. Chem. Soc., Perkin Trans. 2*, 1993, 2297.
23 A. Argile, A. R. E. Carey, R. A. More O'Ferrall, B. A. Murray and M. G. Murphy, *J. Chem. Soc., Chem. Commun.*, 1987, 1847.

24 J. R. Keefe, A. J. Kresge and N. P. Schepp, *J. Am. Chem. Soc.*, 1990, **112**, 4862.

25 K. J. Pedersen, *Acta Chem. Scand.*, 1948, **2**, 385; M. J. Hynes, C. A. Blanco and M. T. Mooney, *J. Chem. Soc., Perkin Trans. 2*, 1991, 2055 and refs. cited therein.

26 R. P. Bell, E. Gelles and E. Moller, *Proc. R. Soc. London, Ser. A*, 1984, **106**, 460.

27 A. Argile, A. R. E. Carey, G. Fukata, M. P. Harcourt, R. A. More O'Ferrall and M. G. Murphy, *Isr. J. Chem.*, 1985, **26**, 303.

28 J. W. Bunting and D. Stefanidis, *J. Am. Chem. Soc.*, 1989, **111**, 5834.

29 G. McCann, C. McDonnell and R. A. More O'Ferrall, to be submitted to *J. Chem. Soc., Perkin Trans. 2.*

30 M. P. Harcourt and R. A. More O'Ferrall, to be submitted to *J. Chem. Soc., Perkin Trans. 2.*

31 Y. Chiang, A. J. Kresge and P. A. Walsh, *J. Am. Chem. Soc.*, 19 **108**, 6314.

32 P. Pruszynski, Y. Chiang, A. J. Kresge, N. P. Schepp and P. A. Wal *J. Phys. Chem.*, 1986, **90**, 3760.

33 J. P. Richard and W. P. Jencks, *J. Am. Chem. Soc.*, 1984, **106**, 137.

34 A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne and S. Sayatys, *J. Am. Chem. Soc.*, 1971, **93**, 413.

35 A. Williams in *The Chemistry of Enzyme Action*, ed. M. I. Page, Elsevier, Oxford, 1964, ch. 5; J. E. Leffler and E. Grunwald, *Rates and Equilibria of Organic Reactions*, Wiley, New York, 1963, p. 165.

36 C. F. Bernasconi, *Tetrahedron*, 1985, **41**, 3219; W. P. Jencks, *Chem. Rev.*, 1985, **85**, 511.

37 C. Osuch, N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, 1956, **78**, 674.

38 G. Sosnovsky, J. A. Krogh and S. G. Umhoefer, *Synthesis*, 1979, 722.

39 A. Arrieta and C. Palomo, *Synthesis*, 1983, 472.

40 W. Borsche, H. Leditschke and K. Lange, *Chem. Ber.*, 1938, **71**, 957.

41 R. A. More O'Ferrall and J. H. Ridd, *J. Chem. Soc.*, 1963, 5030.

42 F. A. Long and M. A. Paul, *Chem. Rev.*, 1957, **57**, 1.

43 A. Albert and E. P. Serjeant, *The Determination of Ionisation Constants*, 2nd edn., Chapman and Hall, London, 1971.

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