Kinetics of ionisation of 3-phenylcoumaran-2-one and reprotonation of the resulting carbanion

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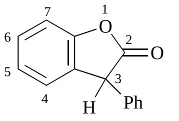
The kinetics of the reversible ionisation of 3-phenylcoumaran-2-one ($pK_a = 8.9$), to form a carbanion, are reported in 50% (v/v) water–dioxane mixtures at 25 °C. Proton abstraction is catalysed by hydroxide ion, water and general bases which generate a Brønsted β_B of 0.52 indicative of a fairly symmetrical transition state. Rate limiting proton abstraction by hydroxide ion is confirmed by a primary kinetic isotope effect, k_H/k_D, of 3.81. Protonation of the enolate carbanion occurs by the hydronium ion and general acids but not by water. In acidic solution, below pH 5, O-protonation occurs initially to generate the neutral enol and ketonisation occurs by C-protonation of the minor enolate anion species in an overall pH independent step. The pK_a of the enol is 6.0 and the pK_E is calculated to be 2.9. The intrinsic rate constant, log (k_o/dm^3 mol^{-1} s^{-1}), of 2.60 is similar to those of other carbon acids of pK_a *ca.* 9, suggesting that a relatively small amount of molecular and solvent reorganisation is required in order to stabilise the generated charge in the transition state. A rate–equilibrium correlation for proton transfer to hydroxide ion from carbon acids activated by a mono carbonyl group has been extended in the thermodynamically favourable direction to cover pK_a units with no signs of significant curvature in the direction predicted by Marcus theory.

Introduction

Coumaran-2-ones† are carbon acids which readily ionise at high pH, forming an enolate anion especially when the molecule is activated by, for example, π acceptor substituents such as 5-nitro[1] or 3-phenyl[2] (**1**).



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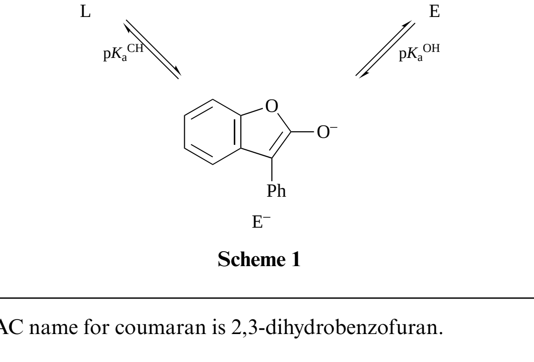
For 3-phenylcoumaran-2-one (**1**), it was found[2] that a relatively stable enolate anion is generated upon 3-H ionisation. The enol tautomer, however, could not be detected in neutral solution using standard spectroscopic techniques, despite the fact that enolisation results in the formation of an aromatic benzofuran type system. The lactone (L), is in equilibrium with the enol (E) and enolate (E$^-$) according to Scheme 1. The pK_a^{CH} of 3-phenylcoumaran-2-one is 8.39 in water[2] and, assuming that less than 1% exists as the enol (E), $pK_E > 2$, the pK_a^{OH} must be less than 6.39. We thought the pK_E could be measured indirectly by determining pK_a^{OH} for the enol from the kinetics of protonation of the enolate carbanion (E$^-$). At pH values below the pK_a^{OH}, O-protonation should occur faster than C-protonation. Herein, we report that this is the case giving a novel kinetic method of determining the enol content.



Scheme 1

Studies into the carbon acidity of activated compounds and the kinetics of their ionisation provide information about the mechanism of such reactions and the conditions controlling them. Deprotonation of strong carbon acids is usually catalysed by general bases (B) and Brønsted β_B values (d log k^B/d log K_a^{BH}) are thought to provide the best indication of the extent of proton transfer in the transition state,[3,4] based on the assumption that little or no resonance or solvational effects distort this value. When compared with the Brønsted α_{CH} value (d log k^B/d log K_a^{CH}), an indication of the amount of molecular and solvent reorganisation undergone by the system in the transition state can be obtained. Such imbalanced transition states can also be characterised by the intrinsic barrier ΔG_o, or more conveniently, the related intrinsic rate constant k_o of Marcus theory[4] which is the approach taken in this study. High intrinsic energy barriers usually imply a large degree of molecular and solvational reorganisation to produce planar,[5] delocalised and solvated carbanions. The effect of solvent content (Me_2SO) on rate constants such as k_o has been reported in several cases, as k_o often reflects the stabilising influences experienced by the carbon acid in the transition state during proton transfer.[6–8]

Results and discussion

Carbon acid acidity

Carbanion (E$^-$) formation from 3-phenylcoumaran-2-one (**1**) in basic solution (Scheme 1) was demonstrated in a previous paper.[2] The pK_a^{CH} of the lactone **1** in water is 8.4 whereas that for the unsubstituted coumaran-2-one in water is 12.2.[2] These low

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† IUPAC name for coumaran is 2,3-dihydrobenzofuran.

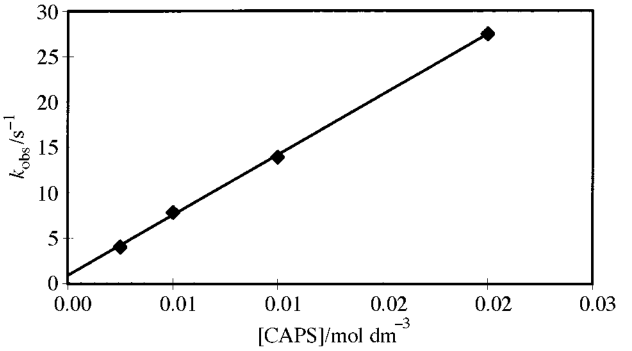
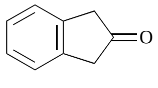


Fig. 1 Observed pseudo first order rate constants for ionisation of 3-phenylcoumaran-2-one (1×10^{-4} mol dm^{-3}) as a function of buffer concentration. CAPS buffer in 50% (v/v) dioxane–water at pH 10.93. $I = 0.05$ mol dm^{-3} (NaCl), $T = 25$ °C.

values are attributed to delocalisation in the aromatic benzofuran type enolate and the 3-phenyl substituent in **1**. The value of 12.2 for coumaran-2-one may be compared with the same value of 12.2 for indan-2-one (**2**) in water[9,10] which is acknowledged to be a remarkably low value for a monofunctional ketone bearing neither a heteroatom nor aromatic activating substituents.



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The favourable influence of the α- phenyl substituent on enolate carbanion stability is interesting because it is larger than expected. The pK_a values of CH_3CHO, $PhCH_2CHO$ and Ph_2CHCHO in water are 16.7, 13.1 and 10.4 respectively.[11] The first phenyl substituent thus lowers the pK_a by 3.6 units, whereas the second is attenuated by 2.7 pK_a units. The enolate anion of coumaran-2-one is stabilised by the adjacent benzene ring and the potential aromaticity of the benzofuran system. Perhaps the initial surprise is the same pK_a^{CH} of coumaran-2-one and indan-2-one.[9] Presumably, the gain in resonance stabilisation of the aromatic benzofuran system is compensated for by the loss of ester/lactone resonance in the keto form. Nonetheless, the reduction in pK_a of 3.8 on going from coumaran-2-one to 3-phenylcoumaran-2-one is substantial.

Deprotonation by bases

In aqueous dioxane solutions (50:50 v/v) at high pH, 3-phenylcoumaran-2-one derivatives were found to ionise, resulting in a rapid and reversible formation of a chromophore at around 300 nm in the ultraviolet region of the spectrum, due to formation of the corresponding enolate anion as a result of proton loss from 3-H.[2] The pK_a of the lactone **1** is 8.86 in 50:50 (v/v) dioxane–water at 25 °C and was determined from the sigmoidal dependence of the absorbance at 300 nm as a function of pH. The rate of formation of this chromophore was measured in 50:50 (v/v) H_2O–dioxane mixtures at 25 °C and constant ionic strength of 0.05 mol dm^{-3} (KCl) using stopped flow spectrometry.

The rate of formation of the chromophore followed an exponential form as the concentration of the sodium hydroxide or buffer was in large excess of that of the lactone (1×10^{-4} mol dm^{-3}). The apparent associated first order rate constants were determined as a function of buffer concentration and pH. The pseudo first order rate constants showed a first order dependence on hydroxide ion concentration and gave a second order rate constant, k_{OH}, for CH deprotonation of 1.85×10^4 dm^3 mol^{-1} s^{-1}. Deprotonation is buffer catalysed and, for example, the dependence of the first order rate constant on the concentration of an aminosulfonic acid is shown in Fig. 1. The slopes of these lines, k_{cat}, were plotted against the fraction of free base in the buffer to generate the second order rate constant, k_B, for each buffer species (Fig. 2).

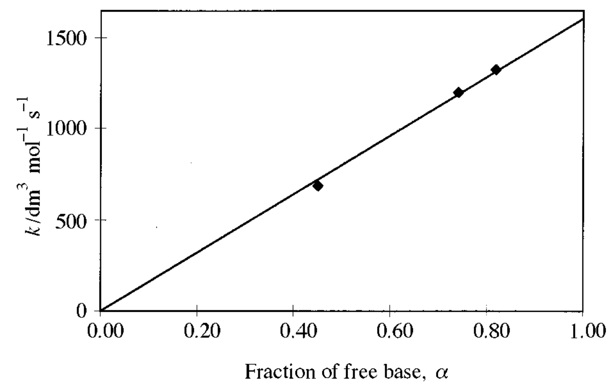


Fig. 2 Catalytic second order rate constants for ionisation of 3-phenylcoumaran-2-one as a function of fraction of free base of CAPS buffer in 50% (v/v) dioxane–water at pH 10.93. $I = 0.05$ mol dm^{-3} (NaCl), $T = 25$ °C.

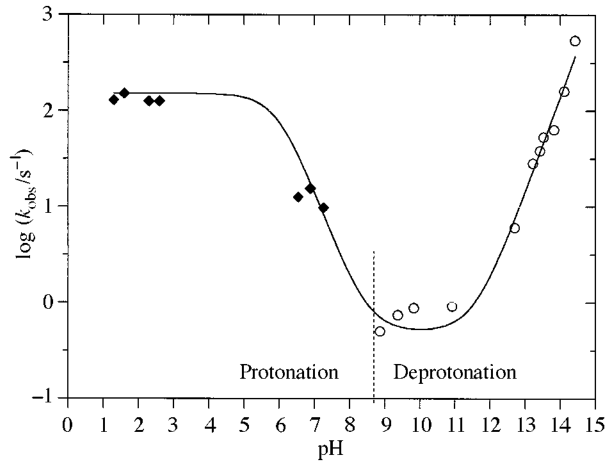


Fig. 3 Ionisation profile for 3-phenylcoumaran-2-one (**1**) in 50:50 (v/v) dioxane; $T = 25$ °C; $I = 0.05$ mol dm^{-3} (NaCl). Points corresponding to the deprotonation of **1** are shown as open circles on the right hand side of the profile, whereas those for protonation of the conjugate carbanion of **1** are shown as filled diamonds on the left hand side.

The intercepts of the buffer plots, k_{int}, (Fig. 1) gave the buffer independent rate constant and, together with the values obtained in sodium hydroxide solution, are plotted as a function of pH in the right hand side of Fig. 3. Two separate phases can be seen and represent (*i*) hydroxide ion catalysed appearance of the chromophore at high pH and (*ii*) a pH independent region with an apparent first order rate constant of 5.0×10^{-1} s^{-1}.

Overall, the observed pseudo first order rate constant for the appearance of the chromophore is given by eqn. (1). The extent

$$k_{obs} = k_{OH}[HO^-] + k_B[B] + k_{H_2O} \qquad (1)$$

of buffer catalysis dictated the accuracy to which the intercept at zero buffer concentration could be determined and probably accounts for the observed deviations of the rate constants in the apparent pH independent region of Fig. 3. The plateau is however well established over 3 pH units.

Abstraction of the proton from the lactone (L) to form the enolate (E^-) (Scheme 1) may occur by water, hydroxide ion or general base as shown in equilibria (2)–(4) with reprotonation

$$L + H_2O \xrightleftharpoons{K_a^{CH}} E^- + H_3O^+ \qquad (2)$$

$$L + {}^-OH \xrightleftharpoons{K_b} E^- + H_2O \qquad (3)$$

$$L + B \xrightleftharpoons{K_c} E^- + BH^+ \qquad (4)$$

Table 1 Rate constants for the deprotonation by hydroxide ion, k^{dp}_{OH}, and water, $k^{dp}_{H_2O}$, and subsequent reprotonation by water, $k^{p}_{H_2O}$, and by hydronium ion, k^{p}_{H}, of 3-phenylcoumaran-2-one (**1**) and its conjugate base respectively in 50:50 (v/v) dioxane–water at 25 °C[a]

k^{dp}_{OH}/dm^3 mol^{-1} s^{-1}	$k^{p}_{H_2O}$/s^{-1}	$k^{dp}_{H_2O}$/s^{-1}	k^{p}_{H}/dm^3 mol^{-1} s^{-1}
1.85×10^4	(1.30×10^{-3})[b]	5.00×10^{-1}	(3.60×10^8)

[a] $I = 0.05$ mol dm^{-3}. [b] Values in parentheses are calculated using the experimental value and the corresponding equilibrium constant (see text).

of the carbanion by hydronium ion, water or the conjugate acid of the base respectively. The equilibrium constant, K_b, in basic solution is given by K_a^{CH}/K_w, where K_w is the dissociation constant of water. In 50% dioxane the pK_w is 16.01 at 25 °C.[12] The equilibrium constant K_c is given by K_a^{CH}/K_a^{BH}, where K_a^{BH} is the acid dissociation constant of the buffer. Ionisation is reversible and the measured rate constant is the sum of the forward (k_f) and reverse (k_r) reactions as shown in eqn. (5), where k^{dp} are the

$$k_{obs} = k^{dp}_{H_2O} + k^{p}_{H}[H_3O^+] + k^{dp}_{OH}[HO^-] + k^{p}_{H_2O} + k^{dp}_{B}[B] + k^{p}_{BH}[BH^+] \quad (5)$$

rate constants for deprotonation and k^p those for protonation by the various species. Substitution using equilibria (2)–(4) generates eqn. (6).

$$k_{obs} = [k^{dp}_{H_2O} + k^{dp}_{OH}(OH) + k^{dp}_{B}(B)]\left[1 + \frac{H_3O^+}{K_a^{CH}}\right] \quad (6)$$

At pH above pK_a^{CH}, k_{obs} measures the forward rate constants only and hence the observed rate constants, eqn. (1), give directly those for deprotonation only. Above pH 12, the formation of the carbanion is first order in hydroxide ion and the reaction is represented by equilibrium (3).

The second order rate constant for hydroxide ion promoted deprotonation, k^{dp}_{OH}, is 1.85×10^4 dm^3 mol^{-1} s^{-1}. The equilibrium constant, K_b, is given by K_a^{CH}/K_w and equals 1.42×10^7, from which the reverse protonation rate by water, $k^{p}_{H_2O}$, is calculated to be 1.30×10^{-3} s^{-1}. Clearly, the observed rate constant of 5.0×10^{-1} s^{-1} for the pH independent region of Fig. 3 does not correspond to the reverse protonation of the enolate carbanion (E$^-$) by water, $k^{p}_{H_2O}$, which is not expected in any case as the pH is above pK_a^{CH}.

Between pH 9 and 11.5, the observed pseudo first order rate constant for the appearance of E$^-$ is pH independent and corresponds to equilibrium (2). The observed rate constant of 5.00×10^{-1} s^{-1} is thus equal to $k^{dp}_{H_2O}$ and from the pK_a^{CH} of 8.86, the second order rate constant for protonation of the carbanion E$^-$ by the hydronium ion k^{p}_{H} is calculated to be 3.6×10^8 dm^3 mol^{-1} s^{-1}. These observed and calculated rate constants are summarised in Table 1.

The line in Fig. 3 is calculated using eqn. (6), with $k^{dp}_{B}(B) = 0$ as Fig. 3 represents the buffer independent reactions. The kinetic data for the appearance of the carbanion (E$^-$) based on the chromophore at 300 nm are not accurate enough to show the expected inflection [eqn. (6)] at the pH corresponding to the pK_a^{CH}, *i.e.* 8.86. This is because the observed rate is dominated by buffer concentration terms and the absorbance change becomes small when the equilibrium becomes unfavourable. Nonetheless, as reported later, the protonation rates were measured directly by looking at the disappearance of the chromophore by neutralisation of the carbanion at different pH. The observed rate constants corresponding to this reaction are shown in Fig. 3 and will be discussed later.

In contrast to the 3-phenylcoumaran-2-one (**1**), unsubstituted coumaran-2-one undergoes only base catalysed deprotonation and there is no pH independent ionisation. The higher pK_a^{CH} of this carbon acid (12.2 compared with 8.4, both in water) is also responsible for the smaller second order rate constant for hydroxide ion deprotonation, k^{dp}_{OH} of 1.34×10^3 dm^3 mol^{-1} s^{-1} in water, compared with 1.85×10^4 dm^3 mol^{-1} s^{-1} for 3-phenylcoumaran-2-one in 50% (v/v) dioxane–water.

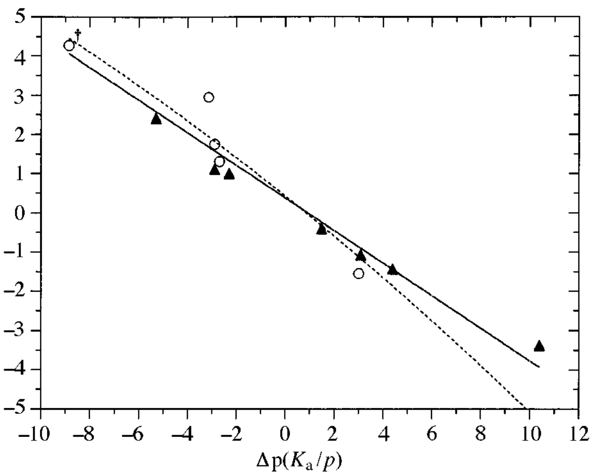
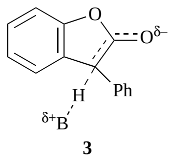


Fig. 4 Brønsted correlation for the second order rate constants (k_{OH}) for the deprotonation of α-carbonyl carbon acids by hydroxide ion in water at 25 °C.[11,13] The change in equilibrium constant, ΔpK_a, is given by pK_a^{CH} − pK_w + log p, where pK_a^{CH} is the pK_a of the carbon acid. pK_w is the dissociation constant of water, taken as 15.7 for those reactions in water and 17.4 for 3-phenylcoumaran-2-one (**1**) in 50% (v/v) dioxane–water (†), and p is the statistical correction for the number of acidic protons. Brønsted line is defined by a series of acyclic carbon acids (shown as triangles) and cyclic compounds as open circles. The dashed line shows the predicted curvature using the Marcus equation (8), which results from using a log k_o value of 0.42.

In this study, a series of aminosulfonic acids were used as buffers and their corresponding pK_a values in 50:50 (v/v) dioxane–water systems are shown in Table 2. The observed pseudo first order rate constants for the formation of the carbanion (E$^-$) were determined as a function of buffer concentration as illustrated in Fig. 1 and the second order rate constants from the fraction of free base present as shown in Fig. 2. The reaction corresponds to that represented by equilibrium (4). For buffers with pK_a^{BH} greater than pK_a^{CH}, the derived k_B values, eqn. (1), correspond to k^{dp}_{B}, the rate constants for deprotonation by the conjugate base of the buffer and are shown in Table 2.

A plot of the logarithm of these second order rate constants as a function of pK_a^{BH} is linear with a slope representing the Brønsted value β_B of 0.52 for the general base catalysed deprotonation of the lactone. The value of β_B indicates that proton transfer is approximately half complete in the transition state[13] **3**, and is in the range expected[3,4] for deprotonation of carbon acids of similar pK_a by amine bases, *i.e.* 0.5 ± 0.1.



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Brønsted relationships for carbon acids and intrinsic barriers for deprotonation

The lactone L is a relatively strong carbon acid with a pK_a of 8.86 in 50:50 (v/v) water–dioxane. This low pK_a is due to the aromatic benzofuran type system formed upon ionisation and to the stabilising effect of the 3-phenyl substituent.[2] The rates of deprotonation of a series of carbon acids by hydroxide ion are often related to the pK_a of the acid and Fig. 4 shows a plot of log k^{dp}_{OH} against the pK_a of the carbon acid taken from the

Table 2 Catalytic constants for the general base catalysed deprotonation (k_B) of 3-phenylcoumaran-2-one (**1**) and the protonation of its anion by the conjugate acid form of the base (k_{BH}) using aminosulfonic acid buffers in 50:50 (v/v) aqueous dioxane at 25 °C and ionic strength of 0.05 mol dm^{-3} (NaCl)

Buffer	pK_a^{BH}[a]	k_B/ mol dm^{-3}	k_{BH}/mol dm^{-3}
2-(*N*-Morpholino)ethanesulfonic acid (MES)	6.46	(19.6)[b]	4.92×10^3
3-(*N*-Morpholino)propanesulfonic acid (MOPS)	7.26	(74.7)	2.98×10^3
N-Tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid (TAPS)	8.24	1.10×10^2	(4.60×10^2)
2-(*N*-Cyclohexylamino)ethanesulfonic acid (CHES)	8.99	9.12×10^2	(6.76×10^2)
3-(Cyclohexylamino)-2-hydroxy-1-propanesulfonic acid (CAPSO)	9.50	9.25×10^2	(2.12×10^2)
3-(Cyclohexylamino)-1-propanesulfonic acid (CAPS)	10.26	1.60×10^3	(63.9)

[a] The pK_a^{BH} values were determined from pH measurements in 50:50 (v/v) dioxane–water, $I = 0.05$ mol dm^{-3}. [b] Values in parentheses are calculated from eqn. (12).

literature[11,14] for a series of α-carbonyl substituted derivatives. Although a stronger acid than those previously measured, 3-phenylcoumaran-2-one has a small positive deviation from this Brønsted plot, the slope of which is 0.43. The linearity of this Brønsted relationship now spans 19 pK_a units and covers proton transfers in both the thermodynamically favourable and unfavourable directions. There appears to be some ambiguity about the effects of substituents on the linearity of Brønsted plots. Changing the basicity of the base removing the proton from carbon acids often generates non-linear plots or changes in Brønsted exponents.[15]

Linear free energy relationships are often used as diagnostic tools for the elucidation of transition state structures. For proton transfer from carbon acids to bases, the free energy change of the process may be modified by changing substituents in either the acid (*e.g.* to give a Brønsted α_{CH}) or the base (*e.g.* to give a Brønsted β_B).[13] The deprotonation of carbon acids which lead to resonance stabilised carbanions are sometimes characterised by asynchronous or ‘imbalanced’ transition state structures as indicated by α_{CH} and β_B not being equal.[4,16,17] It is usually assumed that β_B can be viewed, at least, as an approximate measure of proton or charge transfer at the transition state.[18,19] However, the numerical value of α_{CH} is often determined by the amount of resonance stabilisation/delocalisation and solvational changes which is not strongly coupled to the degree of proton transfer, *i.e.*, there is a lag or imbalance between the various processes.[4,16,17]

Marcus theory[20,21] basically predicts non-linear free energy relationships because of its quadratic form, eqns. (7) and (8),

$$\Delta G^\ddagger = \Delta G_o{}^\ddagger + \frac{\Delta G_o}{2} + \frac{\Delta G_o{}^2}{16\Delta G_o{}^\ddagger} \qquad (7)$$

$$\log k = \log k_o - \frac{\Delta pK_a}{2} - \frac{\Delta pK_a^2}{205 - 16 \times \log k_o} \qquad (8)$$

where $\Delta G^\ddagger$ is the free energy of activation for reaction of a given ΔG_o, the free energy change for the process, and $\Delta G_o{}^\ddagger$ is the ‘intrinsic barrier’ corresponding to the free energy of activation when ΔG_o is zero. The associated rate constants are k and k_o, the intrinsic rate constant. In the case of proton transfer ΔG_o is given by the difference in pK_a between the proton donor and acceptor. The smaller the intrinsic barrier the larger is k_o, then the greater is the curvature in the LFER predicted by Marcus theory. A linear relationship over an extensive range of ΔG_o (ΔpK_a) implies a small k_o, *i.e.* a large intrinsic barrier.

When a linear free energy relationship gives a constant Brønsted exponent, *i.e.* it is not curved over a range of free energies for the reaction, then the simplest interpretation is that the transition state structure is ‘constant’. Non-linear relationships occur due to:[22] (*i*) a change in rate limiting step; (*ii*) reactivity–selectivity relationships as predicted by Hammond or Thornton effects; (*iii*) a quadratic or polynomial dependence on ΔG_o as predicted by Marcus theory. For the Brønsted relationship given in Fig. 4, log k_o is 0.47 and the dotted line is the curvature predicted from this value using eqn. (8). The observed correlation does not appear to fit well with the suggested non-linearity. It is intriguing that there now appears to be an obligation to explain why linear free energy relationships are so linear over an extended range!

Within the context of Marcus theory, linearity is attributable to either a large intrinsic barrier (which is not the case as indicated by log k_o) or to a variable intrinsic barrier which changes with ΔG_o. If the barrier to enolisation decreases as the carbonyl compound becomes more reactive, then curvature becomes less and the correlation could appear linear.

Protonation of the enolate carbanion and the pK_a of the enol

The reverse reaction, protonation of the carbanion (E^-) to regenerate 3-phenylcoumaran-2-one (L) was also studied directly (Scheme 1). This involved generating the carbanion by dissolving the lactone **1** (1×10^{-4} mol dm^{-3}) in 50:50 (v/v) dioxane–water containing NaOH (1×10^{-4} mol dm^{-3}). This solution was contained in one syringe of the stopped flow spectrometer whilst the solution with which it was neutralised was contained in the other, the two being mixed in equal volume. The reaction was then followed by monitoring the decrease in absorbance at 300 nm, which again could be used to generate pseudo first order rate constants.

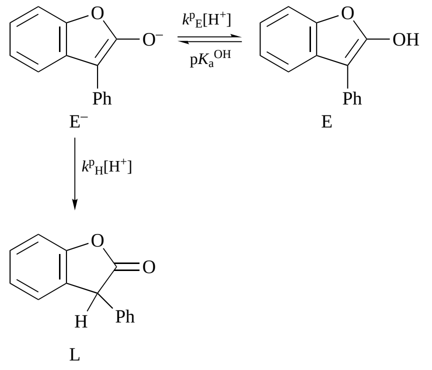
Protonation of the enolate anion (E^-) could occur at one of two sites: O-protonation would generate the neutral enol (E), whereas C3-protonation gives the lactone (L) (Scheme 1). As described in the Introduction, the enol could not be detected by simple spectroscopic techniques. O-protonation is therefore thermodynamically less favourable than C-protonation, and the lactone (L) is the final product resulting from neutralisation of the carbanion (E^-). However, the rate of O-protonation is generally higher than that for C-protonation of resonance stabilised carbanions.

Rates of protonation of oxygen bases by H_3O^+ usually proceed at diffusion controlled limits.[23] The rate of C-protonation of E^- by H_3O^+, k_H^p, calculated from equilibrium (2) and the measured value of $k_{H_2O}^{dp}$, is 3.6×10^8 dm^3 mol^{-1} s^{-1}, and is thus 10–100-fold lower.

At pH values below the pK_a of the enol (pK_a^{OH} of Scheme 1), the initial kinetically controlled product should be the enol (E) which is subsequently converted to the lactone (L) (Scheme 2). Hence, under these conditions, initial quenching of the carbanion should generate the enol (E). The ‘reactant’ for lactone formation is thus effectively the neutral enol and the rate of protonation at a pH below the pK_a of the enol, should follow eqn. (9) as a function of pH.

$$k_{obs} = k_H^p[H_3O^+]\frac{K_a^{OH}}{K_a^{OH} + [H_3O^+]} \qquad (9)$$

The observed pseudo first order rate constant for the formation of the lactone (L) from the enolate carbanion (E^-) does indeed show a sigmoidal dependence upon pH as shown in Fig. 3. From this, the second order rate constant for the protonation of the enolate carbanion by hydronium ion is determined to be 1.27×10^8 dm^3 mol^{-1} s^{-1}, which can be compared with the



Scheme 2

earlier calculated value of 3.6 × 10^8 dm^3 mol^{-1} s^{-1}. The value of K_a^{OH} is $10^{-6.0}$, corresponding to a pK_a^{OH} of 6.0. Assuming that this equals the 'thermodynamic' value and knowing the value of pK_a^{CH} gives a novel kinetic method of evaluating pK_E [Scheme 1, eqn. (10)]. 3-Phenylcoumaran-2-one thus shows a pK_E of 2.9

$$pK_E = pK_a^{CH} - pK_a^{OH} \qquad (10)$$

which is in agreement with our failure to obtain any spectroscopic evidence for the enol. The value obtained here can be compared with the reported equilibrium constant, pK_E, for indan-2-one of 3.84[9] or 4.09[24] which is, as expected, greater than that for **1**.

It is conceivable that the observed rate constants at pH values below the point of inflection at pH 6, reflect a change in mechanism rather than rate limiting protonation of the enolate by H_3O^+. Logically, this would be the kinetically equivalent process of pH independent protonation of the enolate anion (E^-) by H_2O. The plateau in the observed rate constants seen in this study (Fig. 3) shows that this process would proceed with the observed pseudo first order rate constant of 1.6 × 10^2 s^{-1}, which is over 10^5-fold greater than the rate constant for protonation of the enolate anion by water (1.30 × 10^{-3} s^{-1}) calculated from the observed deprotonation of the lactone by hydroxide ion using equilibrium (3). The first order rate constant for ketonisation of the enolate anion of indan-2-one by H_2O is 6.95 s^{-1}, which is around 30-fold higher than the rate constant for ketonisation of the corresponding enol of indan-2-one of 0.21 s^{-1} in water.[9]

In buffer solutions at pH below the pK_a^{CH} the pseudo first order rate constant for protonation of the carbanion (E^-) by the conjugate acid of the buffer is given by eqn. (11) where $[B]_{tot}$

$$k_{obs} = k^p_{BH}[BH^+]\frac{K_a^{OH}}{K_a^{OH} + [H_3O^+]} = k^p_{BH}\frac{[H_3O^+]}{K_a^{BH} + [H_3O^+]}[B]_{tot}\frac{K_a^{OH}}{K_a^{OH} + [H_3O^+]} \qquad (11)$$

is the total buffer concentration. At pH values above pK_a^{OH}, the pK_a of the enol form, the slopes, k_{cat}, obtained from plots of k_{obs} against total buffer concentration, behave as expected from eqn. (11). At pH values below and around pK_a^{OH}, the values of k_{obs} were corrected by the term $K_a^{OH}/(K_a^{OH} + [H_3O^+])$ before the rate constants k^p_{BH} were calculated.

Fig. 5 shows Brønsted plots of variation in observed rate constants with pK_a^{BH} for deprotonation and protonation of the carbon acid by the amine buffers, in which calculated reverse rate constants were obtained from the experimentally determined values using eqn. (12). The intersection of the two lines

$$k_{BH} = \frac{K_a^{BH}}{K_a^{CH}}k_B \qquad (12)$$

enables direct determination of the intrinsic rate constant, k_o, of Marcus theory,[20,21] where $k_o = k_{BH} = k_B$ and $K_a^{CH} = K_a^{BH}$. The value of log k_o for 3-phenylcoumaran-2-one, determined from the intersection of the lines in Fig. 5, is 2.60, and is in the mid-range of known values,[25] indicating a relatively small requirement for structural and solvational reorganisation for charge stabilisation. The logarithm of the intrinsic rate constant for proton abstraction from 1,2,3,4-tetrachloropentadiene (pK_a 8.32) is 3.59 dm^3 mol^{-1} s^{-1} which is similarly thought to be mid-range compared with other values.[5,25,26] The value of k_o is generally related to the pK_a of the carbon acid but some recent reports have demonstrated lower k_o values for the ionisation of systems which have low pK_a values due to significant resonance stabilisation by π acceptors compared with inductive effects resulting in transition state imbalances.[25–32] Amongst the lowest known log k_o value reported for such systems is 0.90 dm^3 mol^{-1} s^{-1} for bis(2,4-dinitrophenyl)methane, pK_a 10.9, reflecting the large amount of reorganisation of solvent and molecular structure required to delocalise the generated charge into the remote nitro substituents.[25] By contrast, log k_o for malononitrile is much higher with a value of around 7, suggesting, for this system, little requirement for significant solvational and geometrical changes in the transition state.

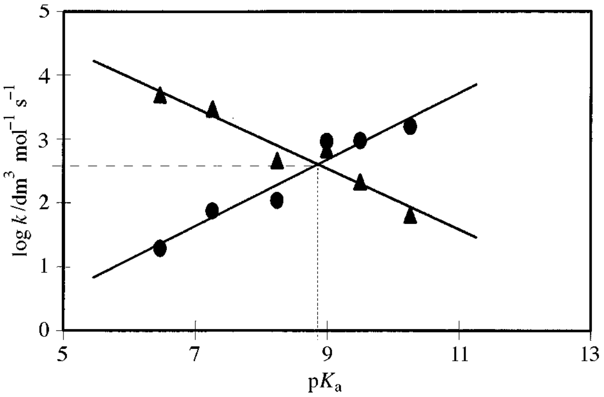


Fig. 5 Brønsted plots for the ionisation of 3-phenylcoumaran-2-one by aminosulfonic acid buffers in 50:50 (v/v) H_2O–dioxane; $T = 25$ °C; $I = 0.05$ mol dm^{-3}

Kinetic isotope effects on the rate of deprotonation of 3-phenylcoumaran-2-one (1)

The pseudo first order rate constants for the appearance of the UV chromophore generated by **1**, which are first order in hydroxide ion concentration, were measured at high pH using stopped flow spectrometry both in D_2O and H_2O solutions [50% (v/v) dioxane]. The calculated second order rate constant, k^{dp}_{OD}, for the appearance of the chromophore at 300 nm in NaOD is 6.74 × 10^3 dm^3 mol^{-1} s^{-1}, and in NaOH the corresponding rate constant, k^{dp}_{OH}, is 1.85 × 10^4 dm^3 mol^{-1} s^{-1} which results in an observed isotope effect, k^{H_2O}/k^{D_2O}, of 2.74.

The stock solutions of **1** for these reactions contained 50% (v/v) dioxane–H_2O(D_2O) which results in deuterated **1** in the solutions containing D_2O, as a result of the exchange.[2] Consequently, the observed isotope effect is a combination of both the primary and the secondary solvent kinetic isotope effects. In general, replacing HO^-/H_2O by DO^-/D_2O results in a kinetic solvent isotope effect of $k_{HO}/k_{DO} = 0.72 \pm 0.05$.[33] This can be combined with the experimentally determined value of 2.74 to yield an estimated primary kinetic isotope effect of $k_H/k_D = 3.81$ which confirms rate limiting carbon–hydrogen bond fission. This is, however, on the low side given the indication of a fairly symmetrical transition state from the Brønsted parameters.[15]

Conclusions

This study has found that 3-phenylcoumaran-2-one is a carbon acid with a low pK_a of 8.4 in water, which is 3.8 units less than that compared with the parent coumaran-2-one, and is attributed to the relatively large carbanion stabilising effect of the 3-phenyl substituent.[2] Upon enolisation, a stable aromatic benzofuran system is formed, which requires relatively little molecular reorganisation for charge stabilisation, reflected in the measured intrinsic rate constant, k_o of 398 dm^3 mol^{-1} s^{-1} ($\log k_o = 2.60$). This value is in the mid-range of reported values calculated with other carbon acids with similar pK_a values.

The Brønsted coefficient for deprotonation of the carbon acid **1** by a series of bases (β_B) is 0.52 and that for reprotonation by the conjugate acid of the buffer (α_{BH}) is 0.48. Variation of the pK_a of the carbon acid gives a Brønsted coefficient α_{CH} of 0.43, which indicates that the progress of proton transfer is about half complete in the transition state and there is little evidence of imbalance.

The pK_a for the enol has been determined kinetically from the rates of protonation of the enolate carbanion as 6.0, from which the pK_E for enol formation from 3-phenylcoumaran-2-one is calculated to be 2.9.

Experimental

Synthesis of 3-phenylcoumaran-2-one is described in our previous paper.[2]

Buffers and other reagents

High purity aminosulfonic acid buffers were purchased from Sigma and were used as supplied. Glass distilled water and distilled dioxane were used for all buffer preparations.

pK_a measurements in 50% dioxane

The pK_a of the sodium salt of the aminosulfonic acids was determined by titration with 1.000 mol dm^{-3} HCl (volusol reagent) in 50% dioxane. The pH electrode response was slow due to the large organic content of the system.

Kinetic measurements

Kinetic measurements were made using either a HI-Tech SF-61 or an Applied Photophysics SX.18MV stopped flow instrument, with an ultraviolet detector at the appropriate wavelength. For measurements in the forward direction, pH > pK_a^{CH}, substrate (10^{-4} mol dm^3) was dissolved in 50% dioxane and the rate of formation of the enolate monitored in buffers under basic conditions. In the reverse direction, the enolate ion (10^{-4} mol dm^3) was generated in 10^{-4} mol dm^{-3} NaOH (50% dioxane) and the stock solution cooled so as to slow down the resultant hydrolysis reaction. The rate of disappearance of the enolate was then followed in acidic buffers.

The substrate was contained in one syringe of the apparatus with the buffer reagent in the other, resulting in a two-fold dilution on mixing. Absorbance changes were observed to follow an exponential form, *i.e.* $Y = Ae^{-kt} + C$, where A is the change in absorbance, k and t are the pseudo first order rate constant and time respectively, and C is the absorbance offset.

Curve fitting for Figs. 3, 4 and 5 was achieved using the 'Scientist' data fitting software package,[34] and other graphs were plotted using Microsoft Excel.

pK_a determinations

Coumaran-2-ones. The measurement of the ionisation constants for the coumaran-2-ones was made in H_2O, D_2O and 50:50 (v/v) dioxane–water using the general method described in the previous paper.[2]

Buffers. The pK_a values of the buffers in Table 2 were determined as follows. Either a 50:50 (v/v) dioxane–water solution of the sodium salt of the buffer (commercially available) was titrated with 0.05 mol dm^{-3} HCl (Volusol reagent) in 50:50 (v/v) dioxane–water, or the buffer base [in 50:50 (v/v) dioxane–water] was titrated directly with a 50:50 (v/v) dioxane–water solution of NaOH. The pH was measured upon the addition of each aliquot of acid or base. A sigmoidal relationship was observed and the K_a was calculated using the 'Enzfitter' program according to the equations $\alpha = \frac{[H^+]}{[H^+] + K_a}$ for the neutral buffer species and $\alpha = \frac{K_a}{[H^+] + K_a}$ for neutralisation of the salt, where α is the fraction of free acid in either case.

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