Mechanism of hydrolysis of coumaran-2-ones

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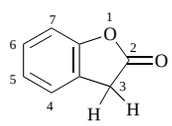
The hydrolysis of coumaran-2-one and 5-substituted 3-phenylcoumaran-2-ones is preceded by a pre-equilibrium involving the formation of an enolate anion at high pH. The pK_a of 3-phenylcoumaran-2-one is 8.39 in water at 25 °C and the 3-phenyl substituent increases the carbon acidity by 10^4. However, despite this ready carbanion formation, the conventional addition–elimination mechanism for hydrolysis of 3-phenylcoumaran-2-ones is confirmed by a solvent kinetic isotope effect of 0.63 and a Brønsted β_{lg} of −0.6. This is compatible with rate limiting formation of a tetrahedral intermediate.

Introduction

Coumaran-2-one† (**1**) and related analogues provide a complex



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and interesting array of possible reactions due to the different functionalities present in the molecule. The compounds are lactones and may undergo base hydrolysis either *via* an addition–elimination pathway or an E1cB mechanism.[1,2] Keto–enol tautomerisation is also possible, especially since the enol form is a benzofuran aromatic system. The acidity of the C3 hydrogen may be expected to influence the relative importance of the two mechanisms for hydrolysis. An outline of the possible reaction mechanisms for the hydrolysis of coumaran-2-one compounds is shown in Scheme 1.

It has been suggested[1,2] that such compounds may hydrolyse *via* an E1cB mechanism involving a ketene intermediate (K^-) formed from the enolate (E^-) rather than direct hydroxide addition to the carbonyl function to give the tetrahedral intermediate (T^-) followed by elimination of phenoxide to form the phenol-carboxylic acid product (A^{2-}). The related 5-nitrocoumaran-2-one is thought to hydrolyse *via* the addition–elimination pathway on the basis of the observed solvent kinetic isotope effects.[3]

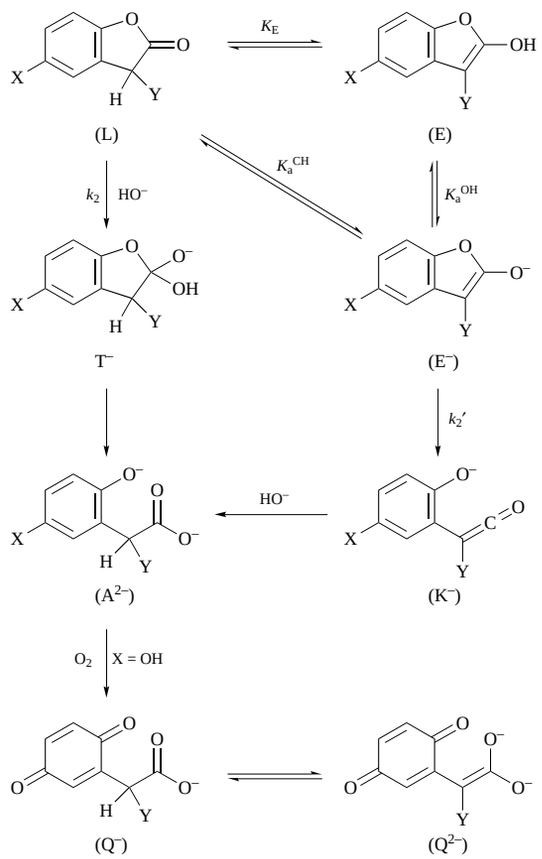
It is established[4] that small ring lactones necessarily have a *cis* (*E*) conformation rather than the more stable *trans* (*Z*) form which acyclic esters preferentially adopt. This difference is the basis of the explanation for the fact that cyclic esters generally hydrolyse faster than their acyclic analogues.[5–8] However, the cyclic nature of the lactones may also place some stereoelectronic constraints on the system, thus enhancing or prohibiting some pathways for reaction.

We now present results of our investigations into the mechanism of hydrolysis of coumaran-2-ones as part of a larger study including the investigation of these compounds as carbon acids, which is presented in the following paper.

Results and discussion

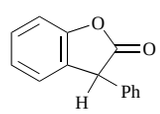
Keto–enol tautomerism

Scheme 1 shows the potential for coumaran-2-one compounds



Scheme 1

to undergo a tautomerisation reaction involving keto and enol forms in equilibrium. Despite the enol form being a relatively stable aromatic benzofuran system, there is no evidence to suggest that a significant proportion of the lactone exists as the enol. IR spectroscopy of 3-phenylcoumaran-2-one (**2**)



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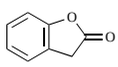
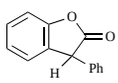
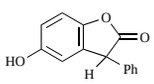
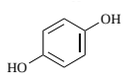
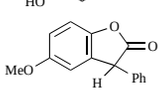
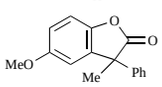
shows the ketone carbonyl vibration (1763 cm^{-1}, KBr disc) with no evidence of any enolic–OH.

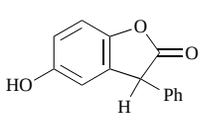
† IUPAC name for coumaran is 2,3-dihydrobenzofuran.

Table 1 Extinction coefficients for initial enolate anion formation, ε^o, and for the final products of hydrolysis (or ionisation in the case of phenols), ε^∞, at λ_{max} in 1% dioxane for reactions of various lactones, esters and phenols in NaOH solutions (0.1 mol dm^{-3}). I = 0.1 mol dm^{-3} (KCl), at 25 °C.

Starting material	λ_{max}/nm	$\varepsilon^o/10^4$ dm^3 mol^{-1} cm^{-1}	$\varepsilon^\infty/10^3$ dm^3 mol^{-1} cm^{-1}
	286	—	2.41
	291	—	4.33
	304	1.72	3.43
Ph_2CHCO_2Ph	286[a]	—	7.44
	323	1.06	3.45
	324	—	3.56
	290	2.00	7.10
	304	—	3.75

[a] 11% (v/v) dioxane–water.

The ^{13}C and ^{1}H NMR spectra of the coumaran-2-ones **2**, **3** and **4** in [$^2H_6$]DMSO showed signals relating only to those



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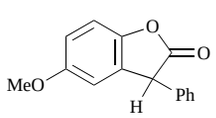

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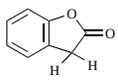
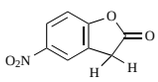
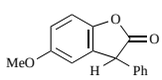
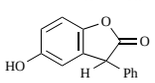
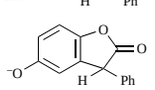
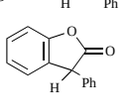
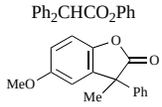
expected for the keto-tautomer. The ^{13}C NMR spectrum for **2** shows four quaternary carbons and not five as would be observed if the enol tautomer was present in any spectroscopically significant amount. Similarly, only five quaternary carbons were observed for **3** and **4** rather than six as would be expected for the enol. The ^{1}H NMR spectrum for **3** shows a strong distinctive signal at 5.32 ppm assigned to the 3-H. However, upon addition of D_2O the signal corresponding to this 3-H disappeared within the time period taken to repeat the NMR scan. This rapid exchange presumably occurs through the enol–enolate system and is indicative of an acidic 3-H (Scheme 1).

Similar experiments with **1** showed that the protons in the unsubstituted coumaran-2-one were not exchangeable over a similar timescale.

UV–VIS spectroscopy

3-Phenylcoumaran-2-ones **2**, **3** and **4** show no observable absorbance changes at neutral or acidic pH, however at high pH, a large increase in absorbance is observed at around 300 nm. The chromophore was seen to be reversible upon acidification of the solution, producing a sigmoidal dependence of absolute absorbance on pH, therefore facilitating the measurement of the apparent pK_a values reported in Table 2. The values of the extinction coefficients are shown as ε^o in Table 1 and are significantly greater than that for phenoxide ion. These chromophores for the 3-phenyl derivatives were subsequently observed to decay ($t_{\frac{1}{2}} \approx 10$ min in 0.1 mol dm^{-3} NaOH) to give absorbances with extinction coefficients similar to those observed for the hydrolysis products of **1**, shown as ε^∞ in Table 1. When the acidic 3-H is replaced by an alkyl group, as in

Table 2 Second order rate constants for the hydroxide ion catalysed hydrolysis, k_{OH}, of some lactones and esters with the corresponding ionisation constants, pK_a, for the phenolic leaving group (1g) and for the ester or lactone acting as a carbon acid (ca) in water (1% dioxane). I = 0.1 mol dm^{-3} (KCl), at 25 °C.

Compound	k_{OH}/dm^3 mol^{-1} s^{-1}	pK_a (1g)	pK_a (ca)
	72.4	9.95[a]	12.29
$PhCH_2CO_2Ph$	1.10[c]	9.95	18.7[b]
	1.29×10^3[d,e]	7.15[f]	9.74[d]
$NO_2C_6H_4OAc$	14[d]	7.15[f]	—
	1.62×10^2	10.2[a]	8.4
	1.82×10^2	9.96[a]	8.39
	56.3	11.39[a]	11.0
	5.01×10^2	9.95[a]	8.39
Ph_2CHCO_2Ph	1.24	9.95[a]	—
	8.13	10.2[a]	—

[a] Ref. 25. [b] In DMSO, ref. 5. [c] Ref. 10. [d] Ref. 3. [e] Ref. 17. [f] Ref. 11.

5-methoxy-3-methyl-3-phenylcoumaran-2-one, only a relatively slow formation of a chromophore was observed at 304 nm corresponding to the phenoxide ion of the hydrolysis product (Table 1).

Solution phase spectrometry of 4 at high pH

Characterisation of the starting material and hydrolysis products of **3** was carried out *in situ* using the soft ionisation electrospray mass spectrometry technique. The coumaranone **3** was dissolved in aqueous NaOH (2 mol dm^{-3}) and a negative ion electrospray mass spectrum recorded immediately, with a second spectrum recorded after 180 min. The mass of the product formed immediately in aqueous solution at high pH corresponds to loss of a proton from the lactone (m/z = 225). After 180 min, a mass to charge ratio of 243 was observed, corresponding to the addition of a water molecule.

The substituted coumaranone **3** was also reacted in basic solution (2 mol dm^{-3} NaOH) but one portion was neutralised and extracted immediately, a second after 180 min. The positive ion electrospray mass spectrum of the products revealed that after immediate neutralisation of the product in basic solution, an ion with m/z ratio of 225 was observed, corresponding to the m/z ratio for the starting material lactone. After 180 min of reaction in base, the neutralised and extracted product gave an ion with m/z ratio of 244, the expected mass from the product of base hydrolysis of **3**.

The ^{13}C NMR spectrum of 5-hydroxy-3-phenylcoumaran-2-one (**3**) in 25% D_2O–75% [$^2H_6$]DMSO containing NaOD was recorded and compared with that in neutral [$^2H_6$]DMSO. In the solution at high pH, the signal due to the methine carbon observed at 49.6 ppm in neutral DMSO disappeared and a quaternary signal at 82.4 ppm was introduced. Most other signals were shifted upfield. The signal corresponding to the 3-H in the ^{1}H NMR spectrum also disappeared under these conditions. Upon acidification, the ^{13}C NMR spectrum returned to that of the lactone starting material, *i.e.* the resultant loss of the observed quaternary signal at 82.4 ppm coincided with the

regeneration of a methine signal at 50.4 ppm. Similarly, when **3** was reacted in basic solution (2 mol dm^{-3} NaOH) with neutralisation and extraction both immediately and after 180 min of reaction time, the results of NMR spectroscopy were comparable with those observed *in situ*. Upon immediate neutralisation of the product formed at high pH, the ^1H NMR spectrum was similar to that of the starting material lactone with the characteristic D-exchangeable 3-H proton observed at 5.32 ppm. After 180 min of reaction time prior to neutralisation, the ^1H NMR spectrum had characteristics of a carboxylic acid product, with a broad signal based around 12 ppm, corresponding to CO_2H, and the 3-H signal did not exchange with D_2O, as expected.

An obvious conclusion which may be drawn from all of these results is that there is a reversible equilibrium formation of the enolate anion (E^-). Formation of a highly delocalised benzofuran type system would satisfactorily account for the observed increase in UV absorbtivity, compared with the ring opened product observed spectroscopically for the hydrolysis products or ionisation of phenol (Table 1). In basic solution, this enolate anion then undergoes time dependent hydrolysis to the hydroxy acid (A^{2-}) (Scheme 1).

The *m*/*z* ratio of 243 observed in the mass spectrum after 180 min of reaction of **3** in basic solution corresponding to the product of decay observed in the UV experiment is attributed to the formation of the ring opened carboxylic acid product (Scheme 1) which is also supported by NMR evidence.

Equilibrium constants

The pK_a^{CH} values of the 3-phenylcoumaran-2-one carbon acids measured in aqueous solution in this study are reported in Table 2 and are based on the sigmoidal dependence of the absorbance of the enolate chromophore on pH. The acidity of the parent coumaran-2-one could not be determined by titration because the rates of ionisation were not much higher than those for hydrolysis. However, the pK_a could be determined kinetically as described in the following section and was found to be 12.25, which can be compared with a reported value of 13.5 in DMSO.[5] An equilibrium cycle involving the lactone (L), enol (E) and enoloate (E^-) with their related equilibrium constants can be seen in Scheme 1 and eqn. (1) can therefore be derived.

$$pK_a^{CH} = pK_E + pK_a^{OH} \quad (1)$$

The 'thermodynamic' pK_a^{CH} of **2** in aqueous 1% dioxane at 25 °C is 8.39 and it is estimated that less than 1% of the coumaran-2-one exists as the enol, *i.e.* $pK_E > 2$ and therefore $pK_a^{OH} < 6.4$. It is therefore apparent that the stabilising effects of the aromaticity in the benzofuran system and the 3-phenyl substituent are more effective in the negatively charged enolate anion than in the neutral enol. The pK_a of 8.4 for **2** is low when compared with the value of 12.3 for the unsubstituted compound **1**. Delocalisation of the negative charge by the phenyl substituent is obviously very effective. The change of 10^4 in acidity brought about by the α-phenyl substituent may be compared with the difference in pK_a in water for $PhCH_2CHO$ of 13.1 and CH_3CHO of 16.7, whereas the effect of a second phenyl substituent on the more acidic $PhCH_2CHO$ to give Ph_2CHCHO (pK_a 10.4) is only 2.7 pK_a units.[9]

Although the unsubstituted coumaran-2-one (**1**) in DMSO solution has a pK_a of 13.5,[5] the acyclic analogue, phenyl α-phenylacetate has a much higher pK_a in DMSO of 18.7.[5] The cyclic nature of compounds such as **1** serves to reduce the pK_a significantly which is probably simply the result of some aromatic character in the carbanion formed upon ionisation.

pH–rate profiles for hydrolysis of 3-phenylcoumaran-2-ones

The pseudo first order rate constants observed for the decay of the initial absorbance at around 300 nm for **2**, **3** and **4** were determined as a function of pH. These constants represent the formation of the hydrolysis product (A^{2-}) and the non-linear

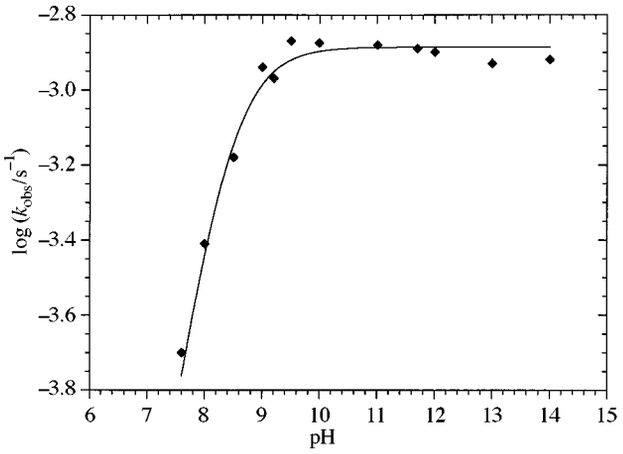


Fig. 1 pH–rate profile for the observed pseudo first order rate constants for the hydrolysis of **2** in aqueous solution (1% dioxane), at 25 °C, I = 0.1 mol dm^{-3} (KCl)

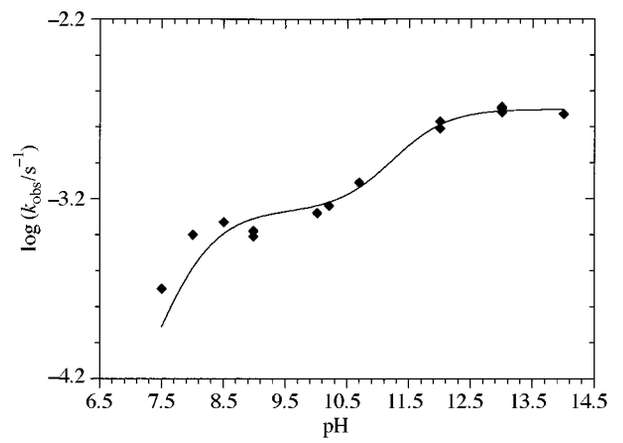


Fig. 2 pH–rate profile for the observed pseudo first order rate constants for the hydrolysis of **3** in aqueous solution (1% dioxane), at 25 °C, I = 0.1 mol dm^{-3} (KCl)

pH–rate profile for **2** is shown in Fig. 1. Below the point of inflection, the observed rate constants are first order in hydroxide ion concentration, whereas above this pH, the rate becomes pH independent. The point of inflection corresponds to the measured pK_a for **2** of 8.4, and so the apparently unusual pH–rate profile simply reflects the ionisation of the carbon acid. At pH values below the pK_a, the reactant is effectively the lactone, whereas above the pK_a, it is the enolate anion (E^-) which either undergoes a pH independent collapse to the ketene which is subsequently hydrated or it is hydrolysed by returning to the lactone *via* the equilibrium process.

A similar change in the kinetic dependence of the rate of hydrolysis upon pH is observed for coumaran-2-one (**1**). However, for this unsubstituted derivative, the rate is first order in hydroxide ion concentration up to pH 12 and only becomes pH independent at NaOH concentrations above 0.1 mol dm^{-3}. The kinetics are slightly more complicated than those for the 3-phenyl derivatives because the rate of base catalysed enolisation is only about 10-fold higher than that for hydrolysis. Nonetheless, the kinetic pK_a determined from the point of inflection is 12.25.

The pH–rate profile for **3** is shown in Fig. 2 where a second inflection is observed at higher pH. The two apparent pK_a values obtained from this kinetic plot are 8.4 and 11.0. The lower pK_a value represents ionisation to the enolate anion, whereas the value of 11.0 corresponds to ionisation of the phenolic hydroxy group (Scheme 2).

The theoretical lines in Figs. 1 and 2 are based on eqn. (2) for hydrolysis of **2** and eqn. (3) for that of **3**. Kinetic pK_a values

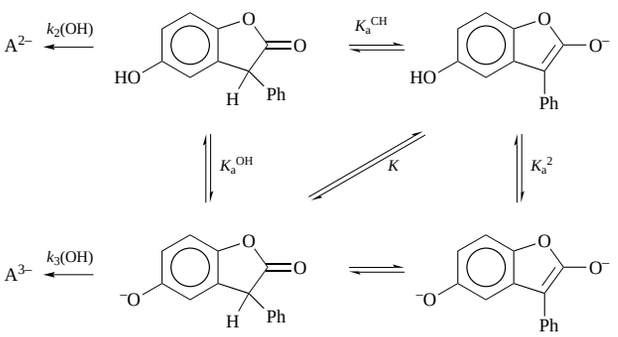
$$k_{obs} = \frac{k_2[^-OH][H^+]}{K_a^{CH} + [H^+]} = \frac{k_2 K_w}{K_a^{CH} + [H^+]} \quad (2)$$

$$k_{obs} = \frac{k_2[HO^-][H^+]}{K_a^{CH} + [H^+]} + \frac{k_3[HO^-][H^+]K}{K_a^2 + [H^+] + K[H^+]} = \frac{k_2 K_w}{K_a^{CH} + [H^+]} + \frac{k_3 K_w K}{K_a^2 + [H^+] + K[H^+]} \quad (3)$$

were calculated from the lines generated in Figs. 1 and 2, and were in close agreement with the measured thermodynamic pK_a values. The pH–rate profile for **3** is not so well defined for the region at low pH mainly due to problems of solubility.

At pH values greater than pK_a^{CH}, eqn. (2) reduces to $k_{obs} = k_2K_w/k_a^{CH}$, and the observed pseudo first order rate constant is pH independent. Whereas at pH values less than pK_a^{CH}, $k_{obs} = k_2[HO^-]$ and the rate constant is first order in hydroxide ion concentration. Only the lactone is susceptible to attack by hydroxide ion and $[H^+]/(K_a^{CH} + [H^+])$ represents the fraction of the lactone present as a function of pH. The kinetically equivalent mechanisms involving the ketene intermediate (K^-) (Scheme 1) are discussed later.

Eqn. (3) may be interpreted similarly as shown in Fig. 3 where it is seen that at pH values below pK_a^{CH}, the models for **2** and **3** are similar. The additional terms included for ionisation of the 5-hydroxy function of **3** in eqn. (3) are shown in Scheme 2.



Scheme 2

Rates of hydrolysis of coumaran-2-ones and related esters

Table 2 shows a series of second order rate constants for the alkaline hydrolysis of coumaran-2-ones and related esters, along with the corresponding pK_a values for the leaving groups (1g) and for the derivatives acting as carbon acids (ca).

The rate of hydrolysis of cyclic esters is known[5–8] to be generally greater than that of their corresponding acyclic analogues and this is supported by the examples cited here. The second order rate constant for the hydrolysis of **1** is 72.44 dm^3 mol^{-1} s^{-1} compared with 1.10 dm^3 mol^{-1} s^{-1} for the acyclic analogue phenyl α-phenylacetate,[10] *i.e.* a 66-fold rate difference. A 92-fold increase in the second order rate constant was observed for 5-nitrocoumaran-2-one compared with *p*-nitrophenyl acetate.[3] An even greater increase of 404-fold is observed here for the hydrolysis of the 3-phenyl derivative (**2**) compared with phenyl α,α-diphenylacetate (Table 2). This appears to be due to an enhanced reactivity of the lactone rather than a decrease in that of acyclic ester although the similarity in reactivity between the mono- and di-phenylacetates could arise from opposing electronic and steric effects. Blocking the ionisation of 3-H by methylation also has the effect of decreasing the rate of hydrolysis 20-fold, which is probably attributable to the introduction of an unfavourable steric effect upon formation of the tetrahedral intermediate.

As with acyclic esters, electron withdrawing substituents increase the rate of alkaline hydrolysis of the lactones which is reflected in a Brønsted β_{1g} of −0.6 (not shown). The magnitude and sign of β_{1g} is similar to the recently reported value of −0.4

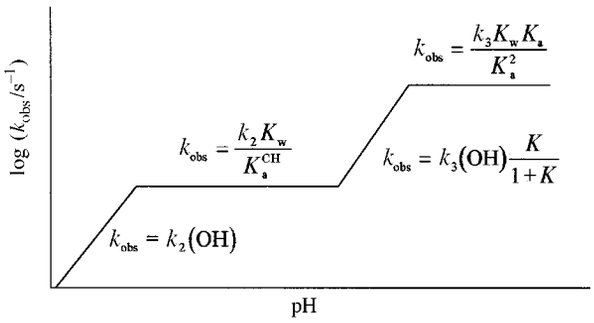


Fig. 3 Model pH–rate profile for the hydrolysis of 5-hydroxy-3-phenylcoumaran-2-one (**3**); see text for the definition of the constants

for the hydrolysis of a series of alkyl α-phenylacetate esters, covering a pK_a range of 6 units.[10] Both values are consistent with rate limiting formation of a tetrahedral intermediate with little or no fission of the carbonyl carbon–phenoxy oxygen bond in the transition state.

Solvent kinetic isotope effects

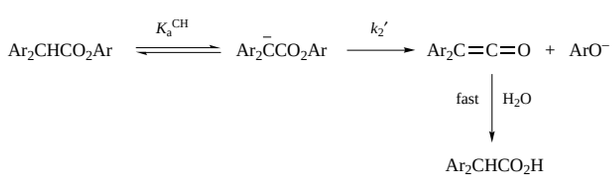
Solvent kinetic isotope effects (SKIE) on the observed rate constants for hydrolysis for 3-phenylcoumaran-2-one (**2**) were measured in the pH independent region, *i.e.* at pH above the pK_a, in both NaOH and NaOD solutions. The observed pseudo first order rate constant for the reaction in D_2O was 8.13×10^{-4} compared with 1.15×10^{-3} s^{-1} in H_2O. The observed rate constants for hydrolysis are lower in D_2O than in H_2O resulting in an observed solvent kinetic isotope effect of $k_{obs}^{H_2O}/k_{obs}^{D_2O} = 1.41$.

The observed isotope effect of 1.41 is complex in that the mathematical expression for k_{obs} incorporates the effect of isotopic solvents on the dissociation constant for the carbon acid and the dissociation constants K_w for H_2O and D_2O. The corresponding K_w values[11] are $10^{-14.00}$ and $10^{-14.78}$ at 25 °C for H_2O and D_2O, respectively, and the experimentally determined values of the 'thermodynamic' pK_a values are 8.39 and 8.90, respectively, in H_2O and D_2O, so it is possible to calculate the solvent isotope effect on the second order rate constants for hydrolysis, k_2, from eqn. (2), with $K_a^{CH} > [H^+]$, giving eqn. (4).

$$\frac{k_2^{H_2O}}{k_{obs}^{D_2O}} = \frac{k_{obs}^{H_2O}}{k_{obs}^{D_2O}} \frac{K_a^{H_2O}}{K_a^{D_2O}} \frac{K_w^{D_2O}}{K_w^{H_2O}} \quad (4)$$

The kinetic solvent isotope effect on k_2 is thus calculated to be 0.63.

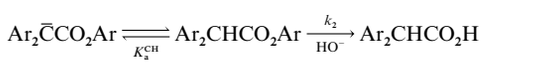
Scheme 3 gives a general model for the hydrolysis of the ester



Scheme 3

occurring by an E1cB mechanism involving the enolate anion (E^-). A pre-equilibrium exists between the lactone form (L) and its enolate anion (E^-) (Scheme 1), which could subsequently react to form the acid product (A^{2-}) *via* a ketene intermediate (K^-).

Scheme 4 shows a general model for ester hydrolysis *via* the



Scheme 4

addition–elimination pathway by hydroxide ion attack on the neutral ester. Although a sigmoidal dependence upon pH is

predicted for both the E1cB mechanism and the addition–elimination pathway, the rate expression for the former is given by eqn. (5). At high pH, $H^+ \ll K_a^{CH}$ and thus eqn. (5) reduces to eqn. (6), whereas for the addition–elimination pathway, eqn. (2) reduces to eqn. (7).

$$k_{obs} = \frac{k'_2 K_a^{CH}}{K_a^{CH} + [H^+]} \quad (5)$$

$$k_{obs} = k'_2 \quad (6)$$

$$k_{obs} = \frac{k_2 K_w}{K_a^{CH}} \quad (7)$$

The elimination step to form ketene (k'_2) in Scheme 3 is likely to be the rate determining step at high pH above pK_a^{CH} unless ketene formation was reversible. That k'_2 should be rate limiting, rather than hydration of the ketene is to be expected considering the rapid rate of hydration known in many cases.[12–16] The SKIE on k'_2 would thus be the directly observed value of 1.41, although it would be expected to approximate to unity as this step does not involve significant interaction with solvent apart from solvation changes. If ketene formation was reversible and its hydration rate limiting, then intramolecular trapping of the ketene by phenoxide would be faster than that by water. If the ketene was trapped with hydroxide ion then above the pK_a the rate would be pH dependent and would show an inverse solvent isotope effect.

Conversely, the SKIE calculated for k_2 of 0.63 is typical for rate limiting attack of HO^-/DO^- on a carbonyl ester function. This suggests that despite the hydrolysis occurring under conditions where the carbanion conjugate base of the lactone is more stable than the neutral precursor, *i.e.* at pH values above the pK_a, the mechanism for the base hydrolysis for 3-phenylcoumaran-2-ones follows the traditional addition–elimination pathway[3] rather than the E1cB mechanism.[1,2] The energy barrier to the unimolecular elimination of phenoxide ion from the carbanion must be greater than that for the bimolecular direct nucleophilic attack of hydroxide ion on the carbonyl carbon of the low concentration of lactone present to generate the relatively unstable tetrahedral intermediate. Of course, the unimolecular ring opening of the E1cB mechanism destroys the benzofuran aromaticity of the enolate anion and generates a relatively unstable ketene. Those factors which make the carbanion more stable than the lactone are lost by following the E1cB pathway.

There are also stereoelectronic reasons why the E1cB mechanism does not occur: fission of the C–O bond is facilitated by the incipient carbonyl oxygen lone pair in an sp^2 orbital, which is less than optimal compared with donation from a p-orbital.[17]

Oxidation products of 3 in water at high pH

A substituted quinone derivative (Q) is thought to be the ultimate product of hydrolysis of **3** at pH > pK_a^{OH} (Scheme 1) as a result of oxidation of the dianionic dihydroquinone species. The ^1H and ^{13}C NMR spectra of **3** in basic solution shows the formation of two species as the concentration of the lactone starting material is diminished which indicates initial formation of the enolate species and the oxidised product of hydrolysis.

An observed colour change, from colourless to pink in a solution of **3** at high pH accompanied an increase in absorbance at 470 nm in the visible region of the spectrum, with an extinction coefficient of 4×10^3 dm^3 mol^{-1} cm^{-1}. The unsubstituted quinone has a maximum absorption at 434 nm,[18] with an extinction coefficient which is approximately 2000-fold less than the substituted quinone derivative thought to exist here. It is not expected that the carboxylic acid derivative would significantly increase the absorbtivity of the molecule, however, it may be that the ene-1,1-diol species (Q^{2-}, Scheme 1) is the predominant form thus accounting for the large increase observed.

The existence of enols of carboxylic acids, or ene-1,1-diols, has now been widely observed[15,19–21] and in one case, a stable free radical of the diol resulted in the formation of a pink solution[15] which was later avoided by degassing the solutions prior to use. In this study, the reactions of **3** were found to be particularly sensitive to dissolved oxygen, and so the reducing agent dithiothreitol was incorporated into the reaction solutions (10^{-2} mol dm^{-3}) which removed the oxidation problems. The addition of this reagent was shown to have no effect upon the kinetics of the hydrolysis of **3**.

Experimental

Kinetics

UV–VIS wavelength scans and absorbance–time measurements were recorded on either a Gilford 2600 or a Cary13 spectrophotometer. Temperature was maintained at 25 °C by a water bath and peltier system, respectively. Generally, a 10^{-2} mol dm^{-3} stock solution of the ester in 1,4-dioxane (25 μl) was injected into an aqueous solution of buffer (2.5 cm^3) and a wavelength scan recorded between 220 and 800 nm to determine the maximum change in absorbance. Absorbance–time measurements were recorded at λ_{max} in order to obtain pseudo first order rate constants k_{obs}/s^{-1}. These rate constants followed exponential form according to the law $A = A_o e^{-kt} + C$, where A is absorbance, k and t are the rate constant and time values and C is the absorbance offset. These values were modelled to this equation using the 'Enzfitter' data processing package[22a] and the corresponding values entered into the pH–rate profiles in Figs. 1 and 2 using the 'Scientist' data fitting software package.[22b] Other graphs were plotted using Microsoft Excel.

When observing the increase in absorbance for 5-methoxy-3-methyl-3-phenylcoumaran-2-one in NaOH, the solvent contained 4% (v/v) 1,4-dioxane–water prior to injection of the stock solution in order to assist solubility.

pK_a determinations

The pK_a values for the carbon acids **2** and **3** were determined by titration. The coumaran-2-one (25 μl of 1×10^{-4} mol dm^{-3} in dioxane) was injected into various concentrations of dilute HCl and NaOH solutions at the extreme pH, and a series of pH buffers at intermediate pH values. The UV absorbance values at the corresponding λ_{max} (Table 1) were monitored as a function of pH, resulting in a sigmoidal relationship, from which pK_a was determined according to eqn. (8), where A_{A^-} and A_{HA} are

$$A_{\lambda_{max}} = \frac{K_a}{[H^+] + K_a}(A_{A^-} - A_{HA}) + A_{HA} \quad (8)$$

the absorbances corresponding to the completely undissociated acid at low pH and the corresponding anion at high pH.

Materials

Solvents. Commercially available 1,4-dioxane (98+%) was used throughout and was distilled (from sodium/benzophenone prior to use if dry dioxane was required). Glass distilled water was used for preparation of buffers and other aqueous systems.

Commercially available deuterium oxide (99.9+% purity) or NaOD was obtained from Goss Scientific Ltd., or other similar suppliers.

Buffers. Buffers used in this study were generally aminosulfonic acids supplied to 99% purity by Sigma, or AnalaR carbonate buffers. Higher pH (>11) was effected by aqueous NaOH solutions, titrated with 1.000 mol dm^{-3} HCl for accurate concentrations.

Coumaran-2-ones and esters. 5-Hydroxy-3-phenylcoumaran-2-one (**3**) was prepared under nitrogen by condensation of mandelic acid (10.4 g, 0.07 mol) with hydroquinone (5.6 g, 0.05 mol) in sodium dried toluene (55 ml) with 98% sulfuric acid

(4.5 ml). Upon mixing, the solution was allowed to reflux at 90–95 °C for 3 h, after which, the mixture was cooled to 85 °C and water added (50 cm^3) and the solution stirred for a further hour. The mixture was then washed with saturated sodium hydrogen carbonate and cold water. The solid was isolated by filtration. The product was passed through a silica column (flash chromatography) using a gradient system of (0–100%) hexane–ethyl acetate as solvent. Pale pink needle-like crystals mp 152–153 °C. ν_{max}/cm^{-1} 3383.8 (5-OH), 1763.1 (C=O); δ_H 5.4 (3-H), rapidly disappears on addition of D_2O.

3-Phenylcoumaran-2-one (**2**) was prepared following a reported method.[23] Recrystallised from 95% ethanol, mp 109–112 °C (lit.[23] 113–114 °C). ν_{max}/cm^{-1} 1804 (C=O); δ_H 5.37 (3-H), rapidly disappears on addition of D_2O.

5-Methoxy-3-phenylcoumaran-2-one (**4**) was recrystallised from 95% ethanol. TLC: (Chloroform) one product, $R_f = 0.4$; (90% chloroform–hexane) $R_f = 0.4$.

Coumaran-2-one (**1**) is commercially available (Aldrich).

5-Methoxy-3-methyl-3-phenylcoumaran-2-one was prepared by methylation of **3** according to a literature method.[24] Sodium hydride (2.26 g 60% in mineral oil) was washed with hexane (3×2 cm^3) and slowly added whilst stirring in an ice–water bath to dry dimethylformamide (DMF) (20 cm^3; 99+%) under an inert atmosphere. A solution of **3** in DMF (6 cm^3) was added dropwise with cooling to the NaH in DMF. This brown solution was then stirred for 1.5 h at room temperature.

Methyl iodide (3.4 g) in DMF (4 cm^3) was added dropwise over 15 min to the resulting suspension and allowed to stir at room temperature overnight. The mixture was then added to an excess of 0.1 mol dm^3 HCl (150 cm^3), extracted with diethyl ether and purified by column chromatography to reveal a golden oil which could not be crystallised. ν_{max}/cm^{-1} 1798.1 (C=O); δ_H 1.90 (CH_3, 3H, s), 3.73 (–OMe, 3H, s).

Phenyl α,α-diphenylacetate. Phenol (1.25 g, 0.01 mol) was dissolved in 10% NaOH (20 cm^3), to which diphenylacetyl chloride (2.3 g, 0.02 mol) was added. The mixture was shaken vigorously for 10 min. The resulting solid was filtered and washed with water, followed by recrystallisation from hot methylated spirits (twice minimum amount of solvent was used to dissolve the solid, so that solvation was maintained before the temperature fell below the melting point of the ester). Yield of pure material = 0.06 g, Mp = 66–67 °C (*cf.* acid chloride 49–53 °C). ν_{max}(KBr disc)/cm^{-1} 1744 (C=O), (*cf.* acid chloride 1700 cm^{-1}). TLC (dichloromethane) single spot, R_f 0.7. δ_H([$^2H_6$]DMSO) 5.55 (2-H, s, 1H), 7 (Ar-*H*, m, 15H).

Acknowledgements

We thank the EPSRC and Zeneca, UK for financial support (CASE award) of this project (D. M. H.).

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Paper 7/07946J
Received 4*th November* 1997
Accepted 24*th December* 1997