Sterically hindered enols of carboxylic acids and esters. The ketonisation reactions of 2,2-bis(2,4,6-trimethylphenyl)ethene-1,1-diol and 2,2-bis(pentamethylphenyl)ethene-1,1-diol

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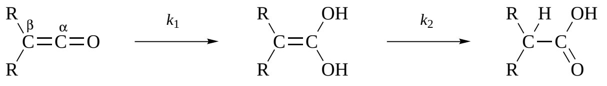
The ketonisation of two enols of carboxylic acids, 2,2-bis(2,4,6-trimethylphenyl)ethene-1,1-diol 2a and 2,2-bis(pentamethylphenyl)ethene-1,1-diol 2b have been studied at 25 °C in 1 : 1 acetonitrile–water. The stability of these compounds arises from the inhibition of the β-carbon site to protonation, and this effect is now quantified. A pK_a of 8.18 is reported for ionisation of the first hydroxyl group of $(Mes)_2C{=}C(OH)_2$ 2a and 8.63 for $(PMP)_2C{=}C(OH)_2$ 2b. A pH–rate profile has been determined over the full pH range for both species. General acid catalysis was detected, yielding Brønsted α values of 0.35 and 0.34 for 2a and 2b, respectively. Similarly, Brønsted α' values of 0.48 and 0.45 were calculated for general acid catalysis of both enolate mono-anions. Studies of the ketonisation of the enols of the corresponding methyl esters have permitted comparative studies on the reactivity of enols of carboxylic acids, esters and ketene acetals. The reactivity of $Mes_2C{=}C(OH)(OCH_3)$ lies closer to the enediol, $Mes_2C{=}C(OH)_2$ 2a than to the ketene acetal, suggesting that in this case, one hydroxy group is almost as efficient as two such groups in the stabilisation of the positive charge developing at C_β as protonation occurs.

Introduction

While the chemistry of enols of aldehydes and ketones has been well studied,[1] examples of observable 1,1-enediols (enols of carboxylic acids) are rare.[2–8] The problem lies in generating the enol tautomer at concentrations greater than the very low values pertaining at equilibrium. Recent work on the enolisation of ethyl acetate[9] yields a pK_E value of 18.6 which is very close to values obtained using theoretical calculations.[10] There is no general method for generating these elusive species; however, in some cases, 1,1-enediols may be generated as observable intermediates in the hydration of ketenes, as shown in Scheme 1.



1 2 3

a R = 2,4,6-$Me_3C_6H_2$- (Mes)
b R = 2,3,4,5,6-Me_5C_6- (PMP)

Scheme 1

1,1-Enediols are observed when $k_1 > k_2$, *i.e.*, when water attack is not rate determining. The enediol intermediate subsequently tautomerises to give the more stable carboxylic acid product. Electron-withdrawing substituents increase the rate of hydration but, conversely, decrease the relative rate of ketonisation, so that observation of the enediol intermediate is favoured.[11] Because the trajectory of approach of the nucleophilic water is in the plane of the ketene, some bulky substituents show a marked effect on the rate of hydration of ketenes.[12] However, in certain cases the enediol intermediate **2** may be observed, since the subsequent ketonisation to the acid **3** may be even more sensitive to steric substitution.[2,3,8]

Previously, we reported the observation of remarkably stable carboxylic acid enols, formed as observable intermediates in the hydration of the mesityl (Mes) and pentamethyl (PMP) ketenes, $(Mes)_2C{=}C{=}O$ **1a** and $(PMP)_2C{=}C{=}O$ **1b** in aqueous acetonitrile.[2,3] This has now permitted the direct measurement, using conventional techniques, of pH–rate profiles for ketonisation (formation of carboxylic acids) of these species; this not only confirms their identity but also provides basic data on the rates and equilibria for the ketonisation of these thermodynamically very unstable enols and of the enols of the corresponding methyl esters which are formed on the addition of methanol to the ketenes **1**.

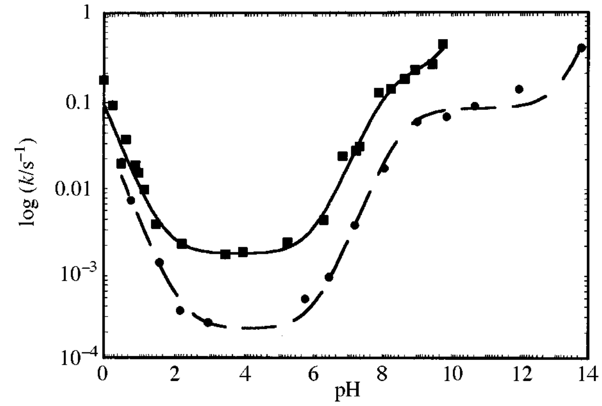


Fig. 1 pH–log rate profiles for the ketonisation of enediols **2a** (■) and **2b** (●) in 50% aqueous acetonitrile at 25 °C

Results and discussion

Rate profiles

The pH–log rate profiles shown in Fig. 1 were obtained in 1 : 1 water–acetonitrile and were constructed using experimental pH values (see Experimental). The ene-1,1-diols were preformed at low buffer concentration at pH *ca.* 4 (where the subsequent ketonisation is slowest) and the solution were 'aged' until the hydration was essentially complete. The pH was then changed by the addition of a more concentrated buffer solution which also defined the final solvent composition. A mixed organic solvent with water was used rather than water alone for solubility reasons.

The profiles show a well defined acid catalysed region, a pH independent region, a base catalysed region which levels off, and finally at higher base concentrations a second base catalysed region is evident but without rate saturation. The terms

Table 1 Summary of rate and equilibrium constants for reactions associated with the ketonisation of enediols **2a** and **2b** in 50% aqueous acetonitrile at 25 °C

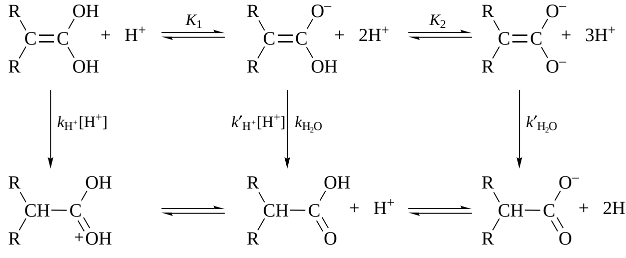
	Rate constant[a]	
Species	R = Mes	R = PMP
$(R)_2C{=}C(OH)_2$	$k_{H^+} = 0.15$ $pK_1 = 8.18$	$k_{H^+} = 4.0 \times 10^{-2}$ $pK_1 = 8.63$
$(R)_2C{=}C(OH)O^-$	$k'_{H^+} = 2.38 \times 10^5$ $k_{H_2O} = 7.84 \times 10^{-2}$	$k'_{H^+} = 9.18 \times 10^4$ $k_{H_2O} = 0.21$
$(R)_2C{=}C(O^-)_2$	—	$k'_{H_2O}K_2/K_w = 0.50$

[a] $dm^3 mol^{-1} s^{-1}$.

representing the rate constants for protonation of the neutral enol by hydronium ion, the mono-enolate by hydronium, and the mono-enolate and di-enolate by water are each denoted by k_{H^+}, k'_{H^+}, k_{H_2O} and k'_{H_2O}, respectively. The equilibrium constants for successive ionisations of the enediol are denoted K_1 and K_2. The experimental data fits well to eqn. (1) yielding values for each of the terms which are listed in Table 1.

$$k_{obs} = k_{H^+}[H^+] + \{(k_{H_2O} + k'_{H^+}[H^+])/(1 + [H^+]/K_1)\} + k'_{H_2O}/(1 + [H^+]/K_2) \quad (1)$$

Acid catalysis is interpreted in terms of protonation of the neutral enediol by hydronium ion. The pH independent region may be interpreted in terms of pre-equilibrium formation of the enolate monoanion followed by rate-determining protonation by hydronium ion. The alternative mechanism, whereby the neutral enol undergoes protonation by solvent water, would be expected to yield a much lower rate constant when compared with the rate of reaction of H_3O^+ with the neutral enediol. The well defined base-catalysed region of the pH profile is explained using a similar argument, but where solvent water is the dominant protonating species. At high pH values rate saturation is observed at pH = pK_1, where ionisation of the first hydroxyl group is complete. At more basic pH values, where ionisation of the second hydroxyl group is important, base catalysis is again observed. However, the pK_a for formation of the dianion (pK_2) could not be determined satisfactorily. These processes are summarised in Scheme 2.



Scheme 2

Brønsted exponents

Ketonisation rate constants were measured in several buffer solutions. The extrapolated buffer-independent rate constants were, however, unsuitable for use in the pH–log rate profile due to the large uncertainties in their values. For this reason, rate constants at various pH values were measured using a potentiostat. Other buffers were found to be unsuitable due to low solubility in the chosen solvent medium. The oxidative formation of a stable free radical was promoted by phosphate buffers, and borax buffers were found to complex with the substrate making them unsuitable for this study.

Rate constants for the ketonisation of 1,1-enediols were measured in dichloroacetic, chloroacetic, glycolic and acetic acid buffer solutions. Buffer catalysis was observed in all cases yielding straight line plots. A typical example of such a plot is given for the reaction of **2a** in acetic acid buffers in Fig. 2. From the dependences, the buffer acid and base component k_{AH} and k_{A^-} have been deduced using eqn. (2), where K_{AH} is the dissociation constant of the buffering species. In most cases both buffer acid and buffer base catalysis were observed. Where the contribution for general acid catalysis was small, eqn. (3) was used. Finally, the general acid catalysis of the enolate anion $R_2C{=}C(OH)O^-$ can be determined from the overall general base catalysis, using the function of the substrate present in the enolate form, $K_1/([H^+] + K_1)$, where under the experimental conditions, $[H^+] \gg K_1$ so that eqn. (4) may be used to calculate k'_{AH}.

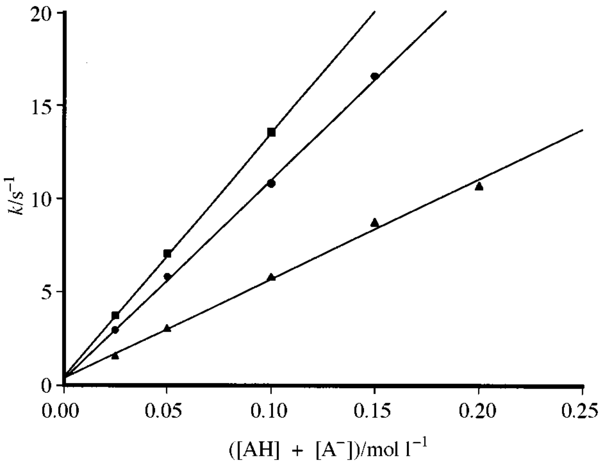


Fig. 2 First-order rate constants for the ketonisation reactions of **2a** catalysed by acetic acid at 25 °C *versus* total buffer concentration at different buffer ratios (AcOH/AcO⁻); 1.78 (■), 1.00 (●), 0.33 (▲)

$$k_{obs} = k_0 + \{(k_{HA}[H^+]/K_{AH}) + k_{A^-}\}[A^-] \quad (2)$$

$$k_{obs} = k_0 + \{k_{HA} + (k_A K_{AH})/[H^+]\}[AH] \quad (3)$$

$$k'_{AH} = (k_A - K_{AH})/K_1 \quad (4)$$

These values in turn may be used to construct Brønsted plots, yielding α values of 0.35 and 0.34 for **2a** and **2b**, respectively. A further Brønsted exponent, corresponding to general acid catalysis of the enolate mono-anion, α', was obtained from plots of k'_{HA} *versus* pK_a, yielding Brønsted values of 0.48 and 0.45 for both species. The low α values obtained for the ketonisation of both enediols reflects their reactivity, indicating an early transition state. The ketonisation reactions of $(Mes)_2C{=}C(OH)_2$ **2a** and $(PMP)_2C{=}C(OH)_2$ **2b** showed both general acid and general base catalysis. This is the expected behaviour, in as much as ketonisation can occur either through direct rate-determining proton transfer from an acid to the β-carbon of the enediol, producing general acid catalysis, or by prior ionisation of the enediol to the monoenolate followed by proton transfer from the acid to that species, which is equivalent to general base catalysis.

These enols were the first reported examples of observable 1,1-enediols.[2] Their unusual kinetic stability is attributed entirely due to steric effects in the proton transfer to the β carbon. A recent paper by Rappoport and co-workers reports the observation of similarly stable enols.[9] Ditipyl ketene (tipyl = 2,4,6-triisopropylphenyl) undergoes hydration to yield, to date, the longest lived 1,1-enediol **2** generated in solution. It showed remarkable kinetic stability, undergoing ketonisation in 42 : 5 : 3 [$^2H_7$]DMF–[$^2H_8$]THF–H_2O with a half life of *ca.* 95 min at 30 °C, which allowed for complete spectral characterisation. This compares with the half lives for ketonisation of *ca.* 8 and 90 min for **2a** and **2b**, respectively, in 1 : 1 acetonitrile–water at 25 °C.

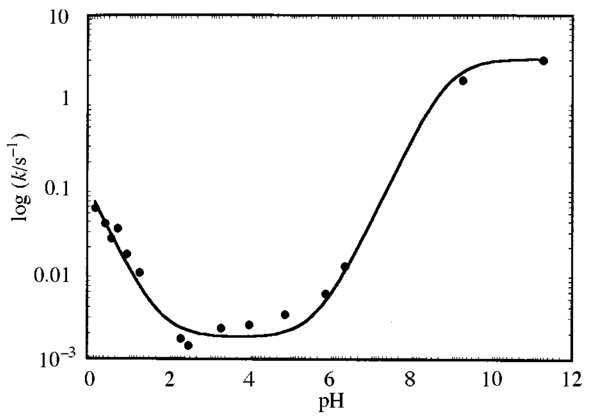


Fig. 3 pH–log rate profile for the ketonisation of the enol of the ester **4** in 50% aqueous acetonitrile at 25 °C

Reactivity of enols of esters

The corresponding enol of the methyl ester, $(Mes)_2C{=}C(OH)(OCH_3)$, shows very similar reactivity when compared with **2**. This enol undergoes ketonisation to yield the more stable tautomer, *i.e.* the ester $(Mes)_2CHCO_2CH_3$. The pH–log rate profile (Fig. 3) shows the characteristic behaviour of an enol reaction. Fitting the experimental data to a modified form of eqn. (1), where the term for reaction of the dianion is omitted, yields values $k_{H^+} = 0.11$ dm^3 mol^{-1} s^{-1}, $k'_{H^+} = 1.53 \times 10^6$ dm^3 mol^{-1} s^{-1}, $k_{H_2O} = 3.09$ dm^3 mol^{-1} s^{-1} and $pK_a = 8.92$ which are quite close to the values obtained for the enediol **2a**.

The rate-limiting step in both reactions is proton transfer to the double bond. It has been demonstrated that the acid catalysed enol ether hydrolysis[13] is significantly slower when compared to the analogous enol ketonisation[14] reactions in acid. This is thought to be due to stabilisation of the developing positive charge through solvation of the hydroxyl group which undergoes hydrogen bonding. Surprisingly, our results seem to indicate that the presence of the second hydroxy group in the enediol **2** is not important until relatively high pH values. This contrasts with the results obtained for the acid catalysed hydrolysis of the corresponding dimethyl acetal,[15] $(Mes)_2C{=}C(OCH_3)_2$, $k_{H^+} = 2.215 \times 10^{-4}$ dm^3 mol^{-1} s^{-1}, which shows a marked decrease in reactivity on replacement of the second hydroxy group by a methoxy group.

Experimental

pH was measured using a Radiometer pH meter 26 and a Metrohm combined pH glass electrode. The pH control of unbuffered solutions was achieved using an autoburette, Radiometer ABU12 and a Radiometer Titrator 11 where necessary. However, during our kinetic experiments the pH did not vary significantly and the addition of acid/base was often minimal. A thermostatted glass cell was fitted with quartz windows, the longer path length (5 cm) permitting the use of more dilute solutions. UV spectra were obtained from a Cary 210 equipped with a thermostatted cell compartment. Temperature control was achieved using a Techne TE8D Tempette water bath and pump and a Techne RB12 Refrigerated Bath and are within ±0.5 °C. Stopped-flow experiments were carried out using a Hitech support unit SF-3L connected to a Hitech Timer-Delay Unit TDU-43. A Thorn EMI power supply unit type PM28B was used with the photomultiplier. Kinetic analysis was carried out by direct link through an ADC to a BBC microcomputer.

HPLC analysis was performed by injection onto either a C_{18} bondapak column or a Waters Associates reverse phase Radial-PAK cartridge, which was pressurised inside a Waters Radial Compression Module. Mobile phase was pumped through the system using a Waters 501 LC pump. Detection was achieved by a Waters LC spectrophotometer model 455. Peak areas were obtained by electronic integration with a Waters 745 Data Module.

Table 2 Summary of the second-order rate constants for general acid catalysed ketonisation of enediols **2a** and **2b** in 50% aqueous acetonitrile at 25 °C

	k_{AH}/dm^3 mol^{-1} s^{-1}			
Species	$(Mes)_2C{=}C(OH)_2$	$(Mes)_2C{=}C(OH)O^-$	$(PMP)_2C{=}C(OH)_2$	$(PMP)_2C{=}C(OH)O^-$
Cl_2CHCO_2H	0.550	—	0.112	—
$ClCH_2CO_2H$	0.155	5.75×10^3	0.041	5.30×10^2
$HOCH_2CO_2H$	0.074	1.70×10^3	7.9×10^{-3}	78.1
CH_3CO_2H	—	5.03×10^2	0.011	3.44

Materials

Inorganic materials used for kinetic measurements were AnalaR™ grade, where possible. The salts employed, *e.g.* sodium acetate and sodium chloride, were finely ground and dried at 120 °C for 2 h before use. Water was doubly distilled using an Exelo Water Still. Dissolved carbon dioxide was removed by vigorous boiling, followed by cooling while attached to a soda lime trap.

Solution of sodium hydroxide and hydrochloric acid were prepared by dilution of Rhône Poulenc Volucon ampoules. The sodium hydroxide solution was standardised by titration with potassium hydrogen phthalate, with Bromophenol Blue as indicator. HPLC grade organic solvents were used where possible for kinetic solutions. Both ketenes were synthesised as described in earlier papers.[2,3]

Kinetics

Due to interference from free radical formation, solutions were deoxygenated before use. Dissolved CO_2 was removed from water by boiling. Solvents and solutions were deoxygenated by bubbling oxygen free nitrogen through them. Nitrogen was passed through a chain of reagents, including Fiesers solution to remove oxygen, saturated lead(IV) tetraacetate to remove sulfur dioxide, soda lime to remove CO_2 and calcium chloride and silica gel to remove moisture. A system with two reservoirs in series was used—bubbling a gas through a solution may cause changes in concentration due to loss of the volatile solvent, thus the loss of solvent from the second reservoir was compensated for by the gain from the first.

Kinetics were monitored spectrophotometrically using a Cary 210 at appropriate wavelengths in the ultraviolet region, or using a Hitech Stopped Flow. In all cases the rates were studied under pseudo-first order conditions for a final substrate concentration of *ca.* 10^{-4} mol dm^{-3}.

Pseudo-first order rate constants were calculated from data covering several half lives and using experimental infinity values. Plots of log $(A_t - A_{infin})$ *versus* t, where A_t is the absorbance of the solution at any time t, and A_{infin} is the experimental absorbance of the solution under kinetic conditions of t = infin, gave straight lines of slope equal to $k_{obs}/2.303$. In certain cases, where the infinity value was not well defined, *e.g.* due to a consecutive slower reaction, the Guggenheim or Swinbourne methods of calculation were used. Rates were reproducible to within 4% of the mean value.

The Hitech Stopped Flow was equipped with a premix chamber, so that aged solutions of the enediol could be generated from the ketene. A third syringe was used to generate solutions of the enediol in the required buffer solution. The rates were determined at each concentration at least eight times and a mean value calculated. The reproducibility under these conditions was reasonable, *ca.* ±8%.

For kinetic experiments involving the enol of the ester, the ketene, $(Mes)_2C{=}C{=}O$, was incubated with HPLC grade methanol for 120 s, and the preformed enolester was studied in the same manner as the enediols.

In all cases, the identity of the final product was confirmed using HPLC analysis and UV spectrophotometry, by comparison with an authentic sample of the product.

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