Reactions of β-Ketoamides. Part 1. Kinetics of Enolisation of Acetoacetamide in Water and of Acetoacetamide and Acetoacetanilide in Ethanol–Water

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Kinetic results are reported for the rates of enolisation (k_e) of acetoacetamide in water and for acetoacetamide and acetoacetanilide in ethanol–water (70:30 v/v) as measured by their rates of halogenation. The effects of nickel(II), zinc(II) and acetate on the rates of enolisation are also described. Unlike β-diketones, the enolisation of β-ketoamides is acid catalysed.

The rates of ketonisation (k_f) of the two β-ketoamides have also been investigated using stopped-flow spectrophotometry. The keto:enol ratios have been derived using the experimentally measured k_e and k_f values.

For some years now we have been investigating the kinetics and mechanisms of the reactions of metal ions with β-diketones in solution.[1] In order to study the mechanisms of these reactions it is necessary to have rate constants for the enolisation and ketonisation of the ligands. The reversible base-catalysed transformation of β-diketones into their enol forms is a reaction whose mechanism is now well established.[2,3] While the enolisation reaction is base-catalysed,[4–6] no acid catalysis has been observed in the case of β-diketones.[7,8]

Although β-ketoamides are closely related to β-diketones, both the ligands themselves and their metal complexes have not been investigated to the same extent as the latter. A number of studies have reported details of preparative methods for transition metal complexes, copper,[9–16] iron,[17–19] beryllium, aluminium and chromium.[19] Others have reported some stability constant data[21–23] while another study[24] reports details of the keto:enol ratios in a variety of organic solvents.

To date no studies of the rates of enolisation or ketonisation of β-ketoamides appear to have been carried out. We are now extending our investigations of the reactions of metal ions with 1,3-dicarbonyl compounds to include β-ketoamides. Part of this study involves an investigation of the kinetics and mechanisms of both the ketonisation and enolisation reactions of the ligands. Although NMR has been used to determine the keto : enol ratios of some β-diketones in solution,[25] this approach cannot be used when the enol content is low as is the case with β-ketoamides. Our initial investigations have been concentrated on the reactions of acetoacetamide and acetoacetanilide. We now report the results of our studies.

Experimental

Materials.—Acetoacetamide (Aldrich) and acetoacetanilide (Aldrich) were used as supplied. $ZnSO_4·7H_2O$ was used as the source of zinc(II). $Ni(ClO_4)_2·6H_2O$ was used as the source of nickel(II). Stock solutions of both nickel(II) and zinc(II) were standardised against standard solutions of ethylenediaminetetraacetate using Eriochrome Black-T and Murexide, respectively, as indicators.

Ethanol was distilled from magnesium and iodine. The ethanol–water solvent was prepared by adding 700 cm^3 of ethanol to a 1000 cm^3 volumetric flask and diluting to the mark with distilled water. Perchloric acid was used as the source of hydrogen ions and all solutions were adjusted to an ionic strength of 0.5 mol dm^{-3} with sodium perchlorate.

Stock solutions of bromine were prepared by adding the appropriate quantity of bromine to the solvent. Sodium bromide (0.1 mol dm^{-3}) was added in order to suppress hydrolysis of the bromine.

Kinetic Measurements.—UV–VIS spectra were recorded at 25 °C on either Cary 1 or Shimadzu UV260 spectrophotometers. Kinetic measurements were made using either the Cary 1 spectrophotometer or a HiTech SF20 stopped-flow apparatus which was interfaced to a BBC microcomputer. In the case of the latter, pseudo-first-order rate constants were calculated by fitting the absorbance data (70–100 data points) to eqn. (1)

$$A = A_\infty[1 - \exp(-kt)] + A_0 \exp(-kt) \qquad (1)$$

using a three-parameter curve-fitting routine in which the absorbance at time zero, A_0, the absorbance at infinity time, A_∞, and the rate constant k were treated as variables. Data for from three to four half-lives were used in these calculations. The reported rate constants are the average of at least three determinations.

pH Measurements were made with an AGB 3000 pH meter equipped with a Russell combination electrode. The filling solution in the reference compartment was 3 mol dm^{-3} NaCl. The electrode was calibrated to read hydrogen ion concentrations by titrating solutions of perchloric acid (0.001–0.002 mol dm^{-3}) with standard sodium hydroxide solutions.[26] Titrations were carried out in jacketed titration vessels through which water at 25 °C was circulating. End-points were determined using the method of Johansson.[27]

The pK_a of acetic acid in ethanol–water (70:30 v/v) was determined by titrating 50 cm^3 of a 0.005 mol dm^3 solution with 0.1 mol dm^3 NaOH using a Metrohm 716 Titrino. Refinement of the potentiometric data was carried out using SUPERQUAD.[28]

The equilibrium between the keto and enol tautomers of β-diketones is frequently represented as in eqn. (2) where HE and

$$HK \underset{k_f}{\overset{k_e}{\rightleftharpoons}} HE \qquad (2)$$

HK represent the keto and enol tautomers respectively and k_e and k_f represent the rates of enolisation and ketonisation. The rate constant k_e can be determined using a bromination procedure. Since the reaction of any enol present with bromine is very rapid, a limiting rate of bromination is reached which is given by eqn. (3). In the situation, the concentration of HK is

$$-\frac{d[Br_2]}{dt} = -\frac{d[HK]}{dt} = k_e[HK] \qquad (3)$$

Table 1 Rate constants for enolisation of acetoacetamide in water at 25 °C and ionic strength 0.5 mol dm^{-3}

pH	$k_e/10^{-3}$ s^{-1}
1.05	11.6
1.35	6.48
1.67	3.51
1.94	2.98
2.09	2.82
2.60	2.36
3.095	2.30
3.67	2.18

Table 2 Rate constants for enolisation of acetoacetamide in ethanol–water (70:30 v/v) at 25 °C and ionic strength 0.5 mol dm^{-3}

pH	$k_e/10^{-2}$ s^{-1}
1.50	1.33
2.00	0.806
3.00	0.590
4.20	0.425
5.20	0.311
6.37	0.265
8.20	0.261
8.90	0.273
9.88	0.399
11.10	0.640

Table 3 Rate constants for enolisation of acetoacetanilide in ethanol–water (70:30 v/v) at 25 °C and ionic strength 0.5 mol dm^{-3}

pH	$k_e/10^{-2}$ s^{-1}
1.21	0.654
1.67	0.602
2.41	0.500
3.21	0.426
4.08	0.360
4.81	0.328
5.60	0.315
6.49[a]	0.342
7.69[a]	0.413

[a] Two data points in basic region not used in derivation of eqn. (8).

given by eqn. (4) where A is the absorbance due to bromine at

$$[\mathrm{HK}] = \frac{A}{\varepsilon l} + (a - b) \qquad (4)$$

452 nm, ε is the extinction coefficient of bromine, a is the initial concentration of β-ketoamide and b is the initial concentration of bromine. Substituting for HK in eqn. (2) from eqn. (4) and integrating gives eqn. (5), where C is a constant. Thus, a plot of

$$-\ln\left[\frac{A}{\varepsilon l} + (a - b)\right] = k_e t + C \qquad (5)$$

the left hand side of eqn. (4) against time should give a straight line plot of slope k_e.

The rate of ketonisation (k_f) was measured by adjusting solutions of the ketoamide to pH values between 11 and 12 where appreciable quantities of the enolate ion were present and then reacting the resultant solution with acid in the stopped-flow apparatus. The substrate concentration was 1.0 × 10^{-4} mol dm^{-3}. Protonation of the enolate ion to give the enol tautomer is rapid and the return to the equilibrium concentrations of keto and enol tautomers can be measured by monitoring the resultant absorbance changes. The first-order rate constant obtained is equal to ($k_e + k_f$).

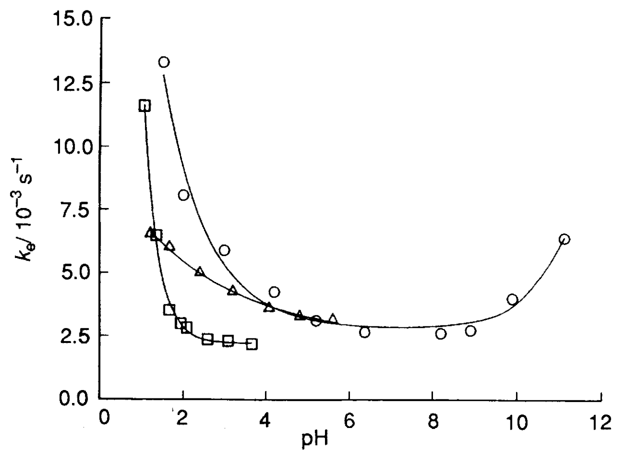

Fig. 1 Plot of rates of enolisation of β-ketoamides □, acetoacetamide in water; ○, acetoacetamide in ethanol–water (70:30 v/v); Δ, acetoacetanilide in ethanol–water (70:30 v/v) at 25 °C and ionic strength 0.5 mol dm^{-3} NaClO$_4$

Results

Other workers have used an iodination procedure to determine the rate of ketonisation of acetylthiophenes.[29] However, iodination of the β-ketoamides proved to be reversible in dilute and concentrated acid and consequently the iodination reaction could not be used to determine the rate of ketonisation. The alternative bromination technique was used.

Bromination of Acetoacetamide in Aqueous Acid Solution.—Table 1 shows the kinetic data obtained for bromination of acetoacetamide in aqueous solution. The kinetic data are described by eqn. (6). Fig. 1 shows a plot of the experimental

$$k_e = 2.21 \times 10^{-3} + 0.181[\mathrm{H}^+]^{1.23} \qquad (6)$$

data and the values calculated using eqn. (6) (solid line) and it is clear that it gives an excellent representation of the kinetic data. The data may also be fitted to eqn. (7) although the fit is less

$$k_e = 2.14 \times 10^{-3} + 0.074[\mathrm{H}^+] + 0.35[\mathrm{H}^+]^2 \qquad (7)$$

good than for eqn. (6) with R = 3.4% compared to 2.9% in the former where R is given by eqn. (8).

$$R = 100\left[\frac{\Sigma(k_{\mathrm{obs}} - k_{\mathrm{calc}})^2}{\Sigma k_{\mathrm{obs}}^2}\right]^{\frac{1}{2}} \qquad (8)$$

Bromination of Acetoacetamide and Acetoacetanilide in Ethanol–Water (70:30 v/v).—Due to insolubility of acetoacetanilide in water, the kinetics of the enolisation were studied in ethanol–water (70:30 v/v). Reaction rates were measured with concentrations of the substrate of *ca.* 3.1 × 10^{-3} mol dm^{-3} and hydrogen ion concentrations in the range 0.03–7.9 × 10^{-12} mol dm^{-3}. The experimental results are shown in Tables 2 and 3.

It is apparent from the data in Tables 2 and 3 that the enolisation of acetoacetamide and acetoacetanilide is both acid and base catalysed. In order to determine the extent of the acid

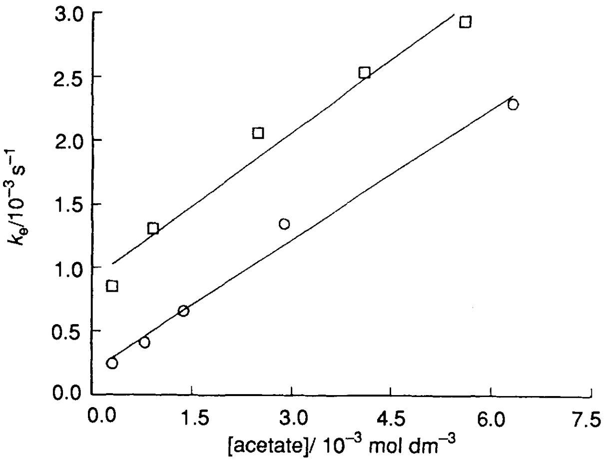

Fig. 2 Plot of acetate catalysed contribution to the enolisation of acetoacetamide [○] and acetoacetanilide [□] in ethanol—water (70:30 v/v) at 25 °C and ionic strength 0.5 mol dm^{-3} $NaClO_4$

Table 4 Rate data for acetate and metal catalysed enolisation of ketoamides in ethanol–water (70:30 v/v) at 25 °C and ionic strength 0.5 mol dm^{-3} $NaClO_4$

Substrate	Catalyst	$k_{cat}/10^{-1}$ dm^3 mol^{-1} s^{-1}
Acetoacetamide	Acetate	3.47 (±0.23)
Acetoacetanilide	Acetate	3.45 (±0.34)
Acetoacetamide	Ni^{2+}	6.94 (±0.27)
Acetoacetamide	Zn^{2+}	2.16 (±0.15)
Acetoacetanilide	Ni^{2+}	2.71 (±0.15)
Acetoacetanilide	Zn^{2+}	1.90 (±0.18)

and base catalysis the kinetic data for acetoacetamide and acetoacetanilide were fitted to eqns. (9) and (10) respectively. In

$$k_{e0} = 2.75 \times 10^{-3} + 0.039[H^+]^{0.39} + 0.39[OH^-]^{0.49} \quad (9)$$

$$k_e = 2.31 \times 10^{-3} + 6.98 \times 10^{-3}[H^+]^{0.17} \quad (10)$$

the case of acetoacetanilide, the rate of enolisation increased rapidly as the pH was increased above 7 and hence could not be determined by conventional spectrophotometry.

Acetate Catalysed Bromination of Acetoacetamide and Acetoacetanilide.—The rates of bromination of acetoacetamide and acetoacetanilide in ethanol–water (70:30 v/v) were also studied in the presence of various concentrations of acetate buffer. Six different buffer concentrations in the range 3.3–10.0 × 10^{-3} were used. The pH varied between 4.45 and 6.13. Plots of the corrected rate constants (k_{corr}) against total buffer concentration showed upward curvature and it became apparent that the buffer anion was the active catalyst. In order to determine the value of k_{cat} it was necessary to determine the value of the pK_a of acetic acid in ethanol–water (70:30 v/v). This was found to be 5.85 (±0.01). Plots of k_{corr} against acetate ion concentration were linear (Fig. 2) and yielded the k_{cat} values shown in Table 4.

Metal Ion and Acetate Catalysed Bromination of Acetoacetamide.—The effects of Ni^{2+} and Zn^{2+} on the rates of bromination of acetoacetamide and acetoacetanilide were investigated in unbuffered ethanol–water (70:30 v/v) solutions in the pH range 5–6. Substrate concentration was *ca.* 3 × 10^{-3} mol dm^{-3}. Rates were measured at a number of metal ion concentrations in the range 0.001–0.02 mol dm^{-3}. k_e increased linearly with increase in metal ion concentration, eqn. (11), where k_0 is the uncatalysed rate constant and k_{cat} is the metal catalysed reaction. The results are shown in Table 4. The values calculated for k_0 are in good agreement with those determined during the bromination experiments carried out in the absence of metal ion catalysis.

$$k_e = k_0 + k_{cat}[M] \quad (11)$$

Ketonisation of Acetoacetamide and Acetoacetanilide.—The rate of ketonisation, k_f, of acetoacetamide in aqueous solution was investigated as described in the Experimental section. The rate constants were found to have the form of eqn. (12). Similar

$$k_f = k_f^0 + k_f^H[H^+] \quad (12)$$

results were found for the ketonisation of both acetoacetamide and acetoacetanilide in ethanol–water (70:30 v/v). The results are shown in Table 5.

Discussion

The enolisation of keto compounds is frequently studied using halogenation techniques. Although two procedures, iodination and bromination are possible, the former is the most widely used. However, in the present studies, the iodination procedure did not prove satisfactory in that the reactions were reversible and zero-order kinetics were not observed. This behaviour is not unprecedented as other workers have observed similar behaviour, particularly in acid solution.[30,31] Consequently, the enolisation of both acetoacetamide and acetoacetanilide was studied using the bromination procedure described in the Experimental section. Solubility considerations precluded studies of the enolisation of acetoacetanilide in aqueous solution.

The results presented here demonstrate that both the enolisation and ketonisation of β-ketoamides are acid catalysed while the enolisation is subject to base catalysis. This is in contrast to β-diketones where although the enolisation is base catalysed, neither the enolisation nor ketonisation is subject to acid catalysis. Unlike previous investigations,[29] plots of k_e against hydrogen ion concentration were not linear and the data are best described by eqns. (6) (7) and (9) (10). Fig. 1 shows that eqn. (9) is a good description of the variation of k_e with acid concentration for the enolisation of acetoacetamide in ethanol–water (70:30 v/v). It is apparent from Tables 1 and 2 that the enolisation proceeds more rapidly in ethanol–water than in water. The rates of enolisation of both ketoamides are comparable in ethanol–water. Apart from the enolisation of acetoacetamide in water, attempts to fit the data using integer values for the exponent of the hydrogen ion dependence were unsuccessful.

Table 4 shows that enolisation of the ketoamides studied here is catalysed by Ni^{2+}, Zn^{2+} and acetate. The catalytic effect of acetate is the same for both ligands. However, the catalytic effect of Ni^{2+} is greater by a factor of three than that of Zn^{2+} for acetoacetamide while the difference is considerably less in the case of acetoacetanilide. The catalysis of the enolisation of β-ketoesters by metal ions has long been recognised[32,33] and has been ascribed to a small degree of complex formation between the metal ion and the keto form of the ester. In the case of the β-ketoamides investigated here, the degree of complex formation with either Ni^{2+} or Zn^{2+} would be very small indeed in the pH range 5–6. However, it would be greater for Ni^{2+} than Zn^{2+} and this coupled with the higher pK_a of acetoacetanilide could account for the different metal activation factors observed in this investigation and this suggests that the observed acceleration is due to complex formation with the keto form of the ligand. Such complexes have of course been previously

Table 5 Acid catalysed rate constants for ketonisation of acetoacetamide and acetoacetanilide in water and ethanol–water (70:30 v/v)

Solvent	Substrate	k_f^O/s^{-1} [a]	$k_f^H/dm^3\ mol^{-1}\ s^{-1}$
Water	Acetoacetamide	0.494 (±0.150)	45.1 (±2.4)
Ethanol–Water (70:30 v/v)	Acetoacetamide	0.0819 (±0.0241)	30.1 (±0.45)
Ethanol–Water (70:30 v/v)	Acetoacetanilide	0.101 (±0.007)	3.03 (±0.14)

[a] k_f^O is acid independent term.

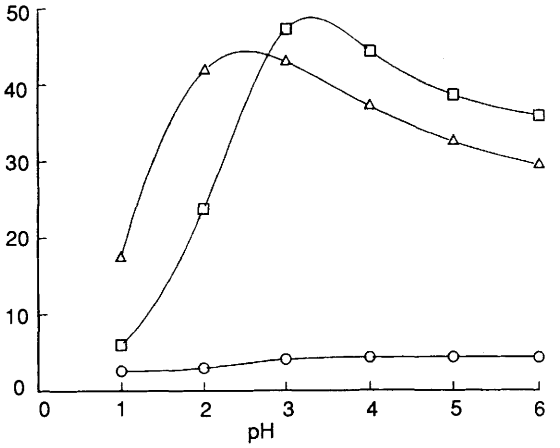

Fig. 3 Plot of enol:keto ratio (k_e/k_f) against pH for β-ketoamides; ○, acetoacetamide in water; □, acetoacetamide in ethanol–water; △, acetoacetanilide in ethanol–water (70:30 v/v) at 25 °C and ionic strength 0.5 mol dm^{-3} NaClO$_4$

observed,[34–36] and recent work has highlighted the significant catalytic effect of metal ions on the enolisation of 2-acetylcyclohexanone.[37]

The enol:keto ratio of β-carbonyl compounds is given by k_e/k_f. Using the values of k_e and k_f determined, the enol:keto ratios were calculated at a number of different hydrogen ion concentrations. The results are shown in Fig. 3. Consistent with expectations is the fact that the enol:keto ratio of acetoacetamide is significantly greater in the less polar ethanol:water solvent mixture. In aqueous solution, acetoacetamide exists more than 99.5% in the keto form and the enol:keto ratio varies little with hydrogen ion concentration. However, in ethanol–water, the enol:keto ratios of both ketoamides exhibit maxima. This is quite different to the situation pertaining for β-diketones where at pHs less than 7 due to the absence of acid catalysis, the enol:keto ratio is virtually independent of hydrogen ion concentration. This has important consequences for kinetic studies of the metal complexation reactions, most of which are carried out at pHs less than 7, because the enol:keto ratio as represented by k_e/k_f is an important parameter in the rate law.[1]

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