Kinetics of the Enolisation Reaction of 2- and 3-Acetylthiophenes

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Measurements have been made on the rates of halogenation of 2- and 3-acetylthiophenes in dilute hydrochloric acid, in buffer solutions, in dilute hydroxide solutions and in the presence of several metal ion salts. The reactions are zero-order with respect to halogen concentration, with the rate-determining step being the formation of the enol or enolate ion. The enolisation reactions are general acid-base catalysed and catalytic constants for a number of acids and bases have been determined in water at 25 °C. The results have been compared with those of corresponding reactions of acetophenone. The close similarity between rate accelerations promoted by cadmium and zinc ions on the reactions of the acetylthiophenes and acetophenone suggests that the effect is due to coordination of the carbonyl oxygen in the transition states. For the sulphur atom of 2-acetylthiophene no evidence of participation in coordination was found. The results are discussed in relation to those of earlier studies on related systems.

Although the enolisation reaction of acetophenones has been extensively studied,[1,2] relatively little work[3–5] has been published on the heteroaromatic ketones.

It has recently been pointed out[4] that these studies would be interesting in order to ascertain the possibility of metal complexation with the heteroatom and/or the carbonyl oxygen atom, as well as the possibility of intramolecular catalysis by suitably placed acid or basic groups. Indeed, investigations of this kind have tended so far to concentrate on six-membered ring systems. As part of a wider study on proton transfer reactions in five-membered heterocyclic ketones we have determined in the present paper the rates of enolisation in water at 25 °C of 2-acetylthiophene (2AT) and 3-acetylthiophene (3AT) in the presence of hydronium ions, hydroxide ions, a number of general acids and bases and metal ions as catalysts. We have also carried out some of these measurements, not available from the literature, on acetophenone for comparison. From the results obtained it is hoped to gain useful information on the heteroatom effect on reactivity, as well as on the effect of metal complexation in metal-ion-catalysed reactions.

Experimental

Materials.—3AT was a commercial sample (Aldrich) recrystallized from light petroleum (fraction 40–60 °C) and had a melting point of 60–61 °C. 2AT and acetophenone were also commercial samples (Aldrich), purified by distillation under reduced pressure. All inorganic salts (KCl, KI, $ZnCl_2$, $CdCl_2$ and $NiCl_2$) were of AnalaR grade (Aldrich or Merck) and were used without further purification.

Kinetic Measurements.—The rate of halogenation of ketones bearing a C–H bond adjacent to the carbonyl group has been shown to be a measure of the rate of enolisation, or ionisation, except under conditions of very low halogen concentration, where the halogenation of the enol, or enolate ion, may become rate determining.[6] The enolisation reactions were followed by monitoring spectrophotometrically the rate of halogenation of the substrate using a Varian DMS 90 spectrophotometer or a Kontron Uvikon 860 equipped with a Hi-tech rapid-kinetic accessory in water at 25 ± 0.1 °C.

The rate of disappearance of iodine was followed by observing the decrease in absorbance due to triiodide at 353 nm. In all reactions $[I^-]$ was 0.01 mol dm^{-3} and the initial iodine concentrations were in the range 1–7 × 10^{-5} mol dm^{-3}. In each series of reactions the ionic strength was made up to 0.3 mol dm^{-3} by the addition of KCl.

Bromination rates were measured in dilute hydroxide solution (0.05–0.25 mol dm^{-3}) and an ionic strength of 0.3 mol dm^{-3} using an excess of bromine. In such solutions bromine is present entirely in the form of OBr^-, and its rate of disappearance was followed by observing the decrease in absorbance at 330 nm.

For the iodination reactions a zero-order loss of iodine was observed (over at least 95% of the reaction) and there was no evidence of reversibility. The rate law had the form shown in eqn. (1), where S refers to the substrate (2AT, 3AT or acetophenone) and $[I_2]_{tot}$ refers to the total concentration of iodine ($[I_2] + [I_3^-]$).

$$-d[I_2]_{tot}/dt = k_e\,[S] \qquad (1)$$

Bromination reactions were irreversible and zero-order in OBr^-. The rate law for bromination was similarly given by eqn. (2).

$$-d[OBr^-]/dt = k_e\,[S] \qquad (2)$$

This kinetic behaviour is expected when the ionisation (or enolisation) of the ketone is rate-determining. Further details on the kinetic procedure adopted have been reported elsewhere.[7]

Results

Iodination of 2AT *and* 3AT *in Dilute Hydrochloric Acid.*—Reaction rates were measured with concentrations of the substrate in the range 1–3 × 10^{-2} mol dm^{-3} and HCl concentrations in the range 0.002–0.06 mol dm^{-3}. The observed rate law was given by eqn. (3) with k_e being of the form shown in

$$k_e = k_o + k_H\,[H^+] \qquad (3)$$

eqn. (1). The following results were obtained: $k_o = -1.64\ (\pm 2.92) \times 10^{-9}\ s^{-1}$; $k_H = 3.95\ (\pm 0.10) \times 10^{-6}\ dm^3\ mol^{-1}\ s^{-1}$ for 2AT and $k_o = 1.49\ (\pm 0.71) \times 10^{-8}\ s^{-1}$; $k_H = 1.18\ (\pm 0.02) \times 10^{-5}\ dm^3\ mol^{-1}\ s^{-1}$ for 3AT. As the intercepts, k_o, of eqn. (3) in both cases are subject to a very large uncertainty the 'spontaneous' (water-catalysed) rate constants, k_{H_2O}, were

Table 1 Catalytic constants (k/dm^3 mol^{-1} s^{-1}) for the enolisation of 2-acetylthiophene (2AT), 3-acetylthiophene (3AT) and acetophenone at 25 °C and ionic strength 0.3 mol dm^{-3} (KCl)

Acid or Base	2AT	3AT	Acetophenone
H_2O[a]	2.00 (±0.16) × 10^{-9}	2.22 (±0.30) × 10^{-9}	4.11 (±0.20) × 10^{-9}
Hydronium ion	3.95 (±0.10) × 10^{-6}	11.8 (±0.2) × 10^{-6}	10.0 × 10^{-6} [7a]
Chloroacetic acid[b]	2.77 (±0.02) × 10^{-7}	6.63 (±0.20) × 10^{-7}	
Chloroacetate[b]	1.76 (±0.22) × 10^{-8}	4.45 (±0.77) × 10^{-8}	
Mandelic acid[b]	3.59 (±0.99) × 10^{-8}	4.64 (±1.67) × 10^{-8}	
Mandelate[b]	2.52 (±0.09) × 10^{-7}	6.27 (±0.19) × 10^{-7}	
Acetate[c]	5.80 (±0.44) × 10^{-7}	6.58 (±0.45) × 10^{-7}	8.4 (±0.3) × 10^{-7} [7a]
Hydrogenphosphate[d]	3.21 (±0.05) × 10^{-5}	3.07 (±0.07) × 10^{-5}	
Borate[e]	1.81 (±0.25) × 10^{-4}	1.50 (±0.21) × 10^{-4}	1.71 × 10^{-4} [14]
Hydroxide ion	0.275 (±0.015)	0.246 (±0.012)	0.24 [9a]

[a] Units are s^{-1}. [b] From k_e measured at r = 0.5; 1; 3; 5. [c] From k_e measured at r = 1; 3. [d] From k_e measured at r = 1; 3; 5. [e] From k_e measured at r = 3; 5.

Table 2 Rates of bromination of 2AT and 3AT in NaOH solutions at 25 °C and ionic strength 0.3 mol dm^{-3} (KCl)

	2AT[a]		3AT[b]	
[NaOH]/ mol dm^{-3}	$k_e/10^{-2}$ s^{-1}	k_c(calc)/ 10^{-2} s^{-1} [c]	$k_c/10^{-2}$ s^{-1}	k_e(calc)/ 10^{-2} s^{-1} [d]
0.048	2.04	1.80	—	—
0.05	—	—	0.79	0.55
0.075	2.23	2.54	0.96	1.16
0.1	3.47	3.23	1.49	1.78
0.15	4.57	4.61	3.20	3.01
0.175	5.04	5.29	3.75	3.62
0.2	5.87	5.98	4.20	4.24
0.25	7.61	7.36	5.38	5.47

[a] k_o = 4.81 (±2.37) × 10^{-3} s^{-1}; k_{OH} = 0.275 (±0.015) dm^3 mol^{-1} s^{-1}. [b] k_o = −6.84 (±1.98) × 10^{-3} s^{-1}; k_{OH} = 0.246 (±0.012) dm^3 mol^{-1} s^{-1}. [c] Calculated values from eqn. (5). [d] Calculated values from eqn. (6).

measured directly in water. The value of k_{H_2O} for acetophenone was also measured directly for the same reason.[7a] The results obtained are shown in Table 1.

Iodination of 2AT *and* 3AT *in Buffer Solutions.*—The rates of iodination of 2AT and 3AT were also studied in a number of buffer systems. Acetylthiophene concentrations ([S]) were varied over a wide range (1–4 × 10^{-2} mol dm^{-3}), but kinetic measurements were normally carried out with [S] *ca.* 2 × 10^{-2} mol dm^{-3}. The observed rate constant, k_e [eqn. (1)], was of the form shown in eqn. (4), in which B represents the basic

$$k_e = k_o + k_B\,[\mathrm{B}] \qquad (4)$$

component of the buffer. In each case k_e values were measured at six or more different concentrations of B in a range of *ca.* a factor of 10.

The value of k_B depends on the buffer ratio, r, for both substrates, 2AT and 3AT, in chloroacetate and mandelate buffers, showing that the acid components of these buffers, A, are catalytically active. Individual rate constants for the separate contributions of basic and acid components of the buffers were calculated graphically in a straightforward manner,[6] or by means of a multiple regression analysis (see below), from the experimental data and are reported in Table 1. In contrast k_B of acetate is independent of the buffer ratio, r, and represents the second-order rate constant of the acetate-anion-catalysed reaction (Table 1). In the case of hydrogenphosphate and borate buffers k_B also depends on r. This dependence can be accounted for by the relatively high pH values of the buffers and the very high catalytic activity of the hydroxide ion in the present enolisation reactions (see below). Indeed, pH measurements (Radiometer PHM 84) of reaction solutions at constant r but variable concentrations of A and B show that hydroxide-ion activity changes considerably throughout the solutions investigated, probably as a consequence of an incomplete compensation by the external electrolyte (KCl) of the ionic strength effect on the activity coefficient of OH^-. Therefore, for hydrogenphosphate and borate buffers, a previously described[8] multiple linear regression treatment of experimental data was performed in terms of known k_e, a_{OH}, [B] and [A], and corrected second-order rate constants accordingly derived (see Table 1).

Values of k_o [eqn. (4)] determined in carboxylate buffers with pH < *ca.* 6 are subject to large uncertainties as small changes in the slope of k_e *versus* [B] plots lead to large variations in k_o. However, intercept values determined in hydrogenphosphate and borate buffers are more reliable as k_o makes a much larger contribution to the observed k_e values. Consequently an estimate of the hydroxide-ion-catalysed rate constants, k_{OH}, of 2AT and 3AT was attempted in terms of the above multiple linear regression analysis[8] and the following results were obtained: k_{OH} = 0.37 ± 0.04 dm^3 mol^{-1} s^{-1} for 2AT and k_{OH} = 0.27 ± 0.10 dm^3 mol^{-1} s^{-1} for 3AT. Each is an average of individual values determined in the two buffer systems. These values are in reasonable agreement with experimental values measured directly from bromination reactions (see below).

In each case k_e values calculated from eqn. (4), using experimental k_o and k_B values agreed with experimental values to within 4%. Individual rate constants obtained in the various buffers are available upon request.

Bromination of 2AT *and* 3AT *in Dilute Sodium Hydroxide Solutions.*—Ionisation rates in dilute hydroxide solutions were too rapid to measure using zero-order conditions as described above. The rates were measured instead under pseudo-first-order conditions as rates of bromination in solutions containing a slight excess of bromine.[9,7a–c] The values of k_e obtained [eqn. (2)] are reported in Table 2 where k_e (calc) are calculated values from eqns. (5) and (6) for 2AT and 3AT, respectively.

$$\text{2AT: } k_e/\mathrm{s}^{-1} = 4.81\ (\pm 2.37) \times 10^{-3} + 0.275\ (\pm 0.015)\,[\mathrm{OH}^-] \qquad (5)$$

$$\text{3AT: } k_e/\mathrm{s}^{-1} = -6.84\ (\pm 1.98) \times 10^{-3} + 0.246\ (\pm 0.012)\,[\mathrm{OH}^-] \qquad (6)$$

The very small negative value of the intercept in eqn. (6) must surely be a reflection of experimental error as, of course, it has no physical meaning. In other words, under the adopted experimental conditions (Table 2) the only detectable processes are the hydroxide-ion-catalysed ionisations of 2AT and 3AT.

Table 3 Metal-ion-catalysed iodination of 2AT, 3AT and acetophenone at 25 °C

Substrate	Catalyst	$k_o/10^{-9}$ s^{-1}	$k_M/10^{-8}$ dm^3 mol^{-1} s^{-1}	$10^3k_M/k_{H^+}$
2AT	Cd^{2+}	1.77 (±0.07)	3.22 (±0.18)	8.15
	Zn^{2+}	1.89 (±0.68)	20.9 (±1.7)	52.9
3AT	Cd^{2+}	1.47 (±0.11)	2.73 (±0.28)	2.31
	Zn^{2+}	0.47 (±1.00)	19.0 (±2.5)	16.1
Acetophenone	Cd^{2+}	2.21 (±0.13)	4.56 (±0.34)	4.56
	Zn^{2+}	0.56 (±1.37)	31.8 (±3.4)	31.8

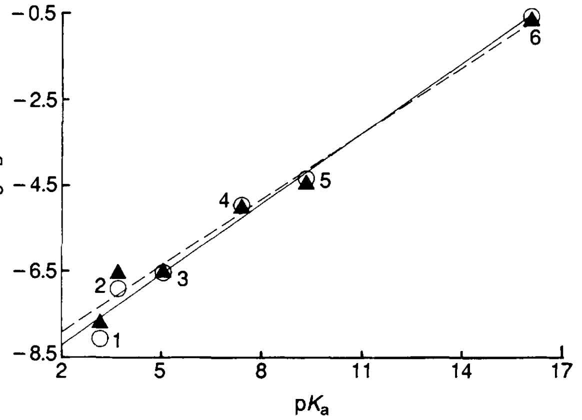


Fig. 1 Brønsted plots for the base-catalysed enolisation of 2AT (○, solid line) and 3AT (▲, dotted line). (1) Chloroacetate; (2) mandelate; (3) acetate; (4) hydrogenphosphate; (5) borate; (6) hydroxide.

Metal-ion-catalysed Iodination of 2AT, 3AT *and Acetophenone*.—The effect of Zn^{2+}, Cd^{2+} and Ni^{2+} on the rates of iodination of the three ketones under investigation was studied in unbuffered solutions (pH *ca.* 5.5). Substrate concentrations were *ca.* 2 × 10^{-2} mol dm^{-3} and the concentrations of I_2 and I^- were the same as those for reactions in the absence of metal ions. Ionic strength was 0.3 mol dm^{-3} for all reactions. Rates were measured at a number of metal-ion concentrations in the range 0.0025–0.075 mol dm^{-3}. For Ni^{2+} the observed rate constants, k_e, of the form shown in eqn. (1), were $k_e = 2.34\ (\pm 0.36) \times 10^{-9}$ s^{-1} for 2AT, $k_e = 2.94\ (\pm 0.35) \times 10^{-9}$ s^{-1} for 3AT and $k_e = 5.11\ (\pm 0.64) \times 10^{-9}$ s^{-1} for acetophenone in the range of concentrations investigated. These are essentially coincident, within experimental error, with the corresponding 'spontaneous' rate constants, k_{H_2O} (see Table 1), showing that k_e values are independent of Ni^{2+} concentration. For the remaining metal ions, Cd^{2+} and Zn^{2+}, k_e showed a linear increase with increasing metal-ion concentration.

The rate law for Zn^{2+}- and Cd^{2+}-catalysed iodination of 2AT, 3AT and acetophenone was given by eqn. (7) where $[M^{2+}]$

$$k_e = k_o + k_M\,[M^{2+}] \qquad (7)$$

represents the molar concentration of either Zn^{2+} or Cd^{2+}, with no evidence of 'levelling off' at higher concentrations. The results obtained are reported in Table 3. Values of k_e, calculated from eqn. (7), using k_o and k_M values from Table 3 agreed, to within 8%, with experimental values. Individual rate constants obtained in the various metal-ion solutions are available upon request.

UV Spectra of 2AT *and* 3AT *in the Presence of Metal Ions*.—Addition of Zn^{2+} or Cd^{2+} ions in the concentration range 0.075–1.5 mol dm^{-3} in no way affected the UV spectra of 2AT and 3AT in water.

Discussion

Inspection of the results collected in Table 1 shows that 2AT, 3AT and acetophenone generally display similar reactivity (within a factor of 3) over a very large range of rate constants, under different experimental conditions.

The 'spontaneous' and acetate-catalysed reactions show a tendency for acetophenone to be more reactive than either 2AT and 3AT, while for very fast (hydroxide-ion-catalysed) reactions a 'levelling off' effect makes the three ketones nearly equally reactive. It is known[10] that the 2-thienyl and 3-thienyl groups may behave as either electron-withdrawing or electron-donating groups, as compared to the phenyl group, depending upon the side-chain and reaction-type. Apparently these three aromatic groups exhibit rather similar electronic effects in the enolisation reactions of the corresponding methyl ketones. This is probably coincidental for unsubstituted derivatives. In fact it has been shown[4] that the effect of substitution at both the 4- and 5-position in 2-acetylthiophene is a good deal more marked than *meta-* and *para-*substitution of acetophenones in the hydroxide-catalysed detritiation reaction. Calculated Hammett ρ values[4] are 1.61 and 1.03 for substituted 2-acetylthiophenes and acetophenones, respectively. A closer inspection of the results presented in Table 1 allows some interesting conclusions to be made regarding 2AT and 3AT.

In acid-catalysed reactions 3AT is more reactive than 2AT by factors of 3, 2.4 and 1.3 in the presence of hydronium ions, chloroacetic acid and mandelic acid, respectively. This might be due to the electron-withdrawing effect of the sulphur atom which makes 3AT relatively more basic than 2AT. Indeed the accepted mechanism for the acid-catalysed process[6,7d] involves a pre-equilibrium proton transfer to the carbonyl group, with subsequent C–H ionisation being assisted by the conjugate base of the acid catalyst.

In base-catalysed reactions 3AT is still more reactive than 2AT in the presence of weak bases, but the reverse is true for stronger bases where 2AT becomes (slightly) more reactive. Relative rates (3AT/2AT) are 2.5, 2.5, 1.1, 0.96, 0.83 and 0.89 for chloroacetate, mandelate, acetate, hydrogenphosphate, borate and hydroxide, respectively. This can be seen in Fig. 1 where Brønsted correlations of log k *vs.* pK_a (corrected for statistical factors[11]) are reported for 2AT and 3AT. The two straight lines intersect at pK_a = 10.9. It should be noted that both Brønsted relationships hold over a very large ΔpK_a range (*ca.* 12 pK_a units) for bases of different structure and charge type. Even hydroxide ion, a catalyst whose negative deviations from Brønsted plots are quite common,[1,12] fits remarkably well in the present cases. The commonly observed deviation of the hydroxide ion is most likely the result of desolvation which precedes proton transfer in the transition states of many proton transfer reactions.[13] Calculated β values are 0.51 ± 0.03 (*n* 6, *i* −8.94 ± 0.29, *n* 6, *r* 0.991) and 0.55 ± 0.03 (*n* 6, *i* −9.31 ± 0.28, *n* 6, *r* 0.993) for 3AT and 2AT, respectively.

However looking at Fig. 1 and the correlation parameters (slopes and intercepts) it could be concluded that the two Brønsted correlations are statistically indistinguishable. As a matter of fact points for both 2AT and 3AT give one excellent Brønsted correlation (β 0.53 ± 0.02, *n* 12, *i* −9.13 ± 0.19, *r* 0.991). The occurrence of a unique correlation stresses the similarity in the behaviour of 2AT and 3AT, and of the corresponding transition states.

The calculated β values (0.51 and 0.55 as well as 0.53) can be compared with the reported β value of 0.71 for acetophenone.[14] As the Brønsted β value represents a measure[6,12,15] of the degree of proton transfer in the transition state, it appears that the transition states for the ionisation reaction of 2AT and 3AT are significantly more 'symmetrical' than that of acetophenone in spite of their very similar reactivities (Table 1).

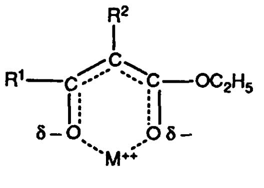
Catalysis and inhibition by metal ions in proton transfer reactions of several biologically important five-membered heterocyclic molecules have been extensively investigated, particularly by Jones and coworkers.[16] The results show that metal-coordinated species are more reactive than the neutral substrates by several orders of magnitude. However, the only kinetic work, at least to our knowledge, on metal-ion-catalysed enolisation of heterocyclic ketones is by Cox[3] on 2-acetylpyridine. Complex formation between 2-acetylpyridine and Zn^{2+}, Ni^{2+} and Cu^{2+} leads to rates up to 2×10^5 times larger than that of the uncomplexed substrate. It was also found[3] that, under the same reaction conditions, no significant rate acceleration was observable for the enolisation of 4-acetylpyridine and concluded that both nitrogen and oxygen atoms of 2-acetylpyridine are involved in coordination in the transition state of the reaction.

Metal activating factors (*maf*)[16] for 2AT, 3AT and acetophenone can probably be best seen with reference to the proton in order to get adimensional figures (last column of Table 3). The proton is in fact the most effective cationic catalyst being 20–400 times more effective than both Cd^{2+} and Zn^{2+}. As mentioned above no catalysis by Ni^{2+} was observed. The following order of decreasing activity was found: $H^+ \gg Zn^{2+} > Cd^{2+}$.

The very similar *maf* values observed (Table 3) for 2AT and 3AT by either Cd^{2+} or Zn^{2+} prove that the sulphur atom of 2AT is not involved in chelation to these two metal ions. Monodentate coordination of the sulphur atom of 2AT and 3AT can also be excluded in view of the very similar *maf* found for acetophenone. This is of course understandable in view of the fact that, while the nitrogen atom of pyridine[3] contributes one electron to the aromatic π system, the sulphur atom of thiophene contributes a pair of electrons to the aromatic system. As a consequence of this difference in electron demand from nitrogen and sulphur it is well known that pyridine and thiophene display dramatically different physicochemical properties, including Brønsted and Lewis basicities. The catalysis by certain metal ions in the enolisation reactions of β-ketoesters has long been known[17] and attributed to a small amount of complex formation between the metal ion and the keto-form of the ester. 'In such a complex, the proton is bound much more loosely than in the free ester and the rate with which it is transferred to a base is therefore much greater'.[17a] As the quantitative relationship between rate constant, k_e, and molar concentration of the metal ion, $[M^{2+}]$, [eqn. (7)] and the relative kinetic accelerations are generally the same for ketoesters[17] and the present aromatic ketones, an analogous interpretation might well be suggested. However, as complex formation could be detected for neither the keto forms of the ketoesters[17] nor the present ketones, it seems preferable (and is kinetically equivalent) to attribute the observed rate accelerations to the participation of the metal cations in stabilizing the corresponding reaction transition states.

Some particular inversions of relative catalytic efficiency among the different metal ions found for the aromatic ketones under investigation with respect to the orders found[17] for ketoesters might be revealing. For example, while Ni^{2+} is very effective in catalysing the enolisation of ethyl 2-oxocyclopentanecarboxylate,[17b] this cation is unable to promote the enolisation reactions of 2AT, 3AT and acetophenone.

On the other hand Zn^{2+} and, particularly, Cd^{2+} are much more effective as catalysts towards the three aromatic ketones than towards β-ketoesters. These differences may be due to the fact that Ni^{2+} and, probably, Cu^{2+} can be involved in chelation with two oxygen atoms of the ketoesters in a transition state with the structure shown (**1**). An analogous chelation effect is of course impossible for acetophenone and 3AT and has also been disproved for 2AT.



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