

Halogenation of enol tautomers of 2-cyanoacetamide and malonic acid

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Reactions of 2-cyanoacetamide (CA) with both bromine and iodine at low halogen concentration in aqueous acid solution were first order in halogen and CA, consistent with an interpretation involving rate-limiting halogenation of the enol tautomer. There was no acid dependence in the range 0.1–0.5 mol dm⁻³. The observed rate constants for bromination and iodination were very similar, indicating that both probably occurred at the encounter limit. This enabled a value for K_E , the equilibrium constant for enolisation, to be determined as 6×10^{-10} . There was strong evidence that at low acidities (pH ~ 4) enolisation is rate-limiting, but we were unable to achieve a fully zero-order kinetic dependence upon halogen. However we did obtain a value for the acid-catalysed enolisation rate constant k_e of 2.7×10^{-3} dm³ mol⁻¹ s⁻¹ from measurements of rates of deuterium exchange with the solvent. The bromination of malonic acid (ML) in dilute acid solution at low [Br₂] was zero-order in [Br₂] and we obtained a value of 1.3×10^{-2} dm³ mol⁻¹ s⁻¹ for the acid catalysed enolisation rate constant. There is some evidence which suggests that enolisation of ML takes place *via* the amide group rather than the carboxylic acid group. The results are compared with earlier studies.

In recent years there has been a growing interest in the characterisation of enol tautomers of carbonyl compounds other than those from ketones, in particular from carboxylic acids, esters and amides.¹ In general these compounds exist overwhelmingly in their keto forms and the enol tautomers are extremely difficult to observe directly. Theoretical calculations support this view,² which has been rationalised in terms of strong stabilisation of the keto forms by electron donation from the heteroatom (oxygen or nitrogen in the case of carboxylic acids, esters and amides) attached to the carbonyl group. However there is strong kinetic evidence that enols are reactive intermediates in, for example, halogenation (and other electrophilic) reactions of, for example, malonic acid and some of its derivatives.^{3,4} Under certain experimental conditions such reactions are kinetically zero-order in halogen, and the obvious conclusion is that rate determining enolisation is being observed. There is also compelling evidence that the enolisation in malonic acid derivatives involves intramolecular proton transfer. In some cases it has been possible to obtain some such enols in the pure state using the Fuson technique⁵ (employed originally for ketones), whereby there are present in the molecule large bulky groups which destabilise the keto form by inhibition of solvation. Hegarty and O'Neill⁶ obtained enols from carboxylic acids using bis(mesityl) and bis(pentamethylphenyl) groups, which were sufficiently stable in solution to allow successful structural determination. Similarly Frey and Rappoport⁷ obtained the enol of ditipylacetic acid (tipyl = 2,4,6-triisopropylphenyl), again in solution, but which had a greater kinetic stability. Kresge and co-workers⁸ generated enols of simpler ketones by flash photolysis methods to generate a ketene which underwent hydration to give the enol. In this way the enols of mandelic acid and other species were identified spectrally as short lived species, and the rate of their ketonisation measured. More recently poly(methoxycarbonyl)-cyclopentadiene structures have been synthesised⁹ which have been shown to be enolic in the solid state and in solution.

Much less is known regarding the enols of amides. Trofimenko¹⁰ claimed that the hydration of dicyanoketenimine

generated the enol form of dicyanoacetamide. More recently a systematic search¹¹ for the existence of enols derived from amides was conducted using powerful electron-withdrawing substituents in the amides in an attempt to stabilise the enol tautomer and a number were identified. Until recently the only kinetic investigation was that of the halogenation and nitrosation of malonamide.¹² Under appropriate conditions it was possible to obtain both limiting cases—where reactions were respectively (a) zero-order and (b) first-order in electrophile. Enolisation here is subject to acid-catalysis. The results enabled values of both K_E (the equilibrium constant for enolisation) and k_e (the rate constant for acid catalysed enolisation) to be obtained. In order to establish the generality of the enolisation of simple amides, we have now extended these kinetic studies to the reactions of 2-cyanoacetamide, CH₂(CN)CONH₂ (CA), and of malonic acid CH₂(CO₂H)CONH₂ (MA), and present the results in this paper. It is known¹³ that, as expected, bromination yields the 2-bromo product (and the dibromo at high bromine concentrations), and nitrosation the corresponding 2-oxime.¹⁴

In a recent publication, the Kresge group¹⁵ has measured the enolisation rate constant for 2-cyano-2-hydroxy-*N*-methylacetamide by hydrogen exchange and also the ketonisation of the enol (generated by flash photolysis of a diazo precursor). They find a value of 8.4×10^{-13} for K_E , and by use of known substituent effects upon K_E have obtained an estimate of 2×10^{-22} for the K_E of the parent *N*-methylacetamide for the first time.

Results

(a) Reactions of 2-cyanoacetamide CA

Reactions of both bromine (2.5×10^{-4} mol dm⁻³) and iodine (7×10^{-5} mol dm⁻³) with CA in at least a 20-fold excess in 0.1 mol dm⁻³ aqueous acid solution were quite rapid and gave excellent first-order kinetic behaviour. In all cases reactions were followed in a stopped-flow spectrophotometer, by noting

Table 1 Values of k_1 for the bromination of CA with $[\text{Br}_2] 2.5 \times 10^{-4} \text{ mol dm}^{-3}$

[CA]/mol dm ⁻³	[H ⁺]/mol dm ⁻³	k_1/s^{-1}
0.025	0.500	0.066
0.050	0.500	0.103
0.100	0.500	0.173
0.125	0.500	0.196
0.150	0.500	0.220
0.050	0.500	0.074
0.050	0.625	0.077
0.050	0.750	0.075
0.050	0.875	0.082
0.050	1.000	0.093

Table 2 Values of k_1 for the iodination of CA with $[\text{I}_2] 7.0 \times 10^{-5} \text{ mol dm}^{-3}$

[CA]/mol dm ⁻³	[H ⁺]/mol dm ⁻³	k_1/s^{-1}
0.025	0.250	0.083
0.050	0.250	0.143
0.124	0.250	0.308
0.149	0.250	0.389
0.198	0.250	0.522
0.150	0.063	0.264
0.150	0.125	0.325
0.150	0.375	0.379
0.150	0.500	0.378

the disappearance of the halogen absorbance at the appropriate wavelength. Reactions were also found to be first order in CA and independent of $[\text{H}^+]$ above about 0.1 mol dm^{-3} . The experimental values of k_1 , the measured first-order rate constants, are given in Tables 1 and 2 for bromination and iodination respectively.

The results indicate that we are looking at rate-limiting reaction of the halogen with the enol tautomer of CA [eqn. (1)],



i.e. when the rate of ketonisation is much greater than the rate of enol halogenation ($k_k[\text{H}^+] \gg k_2[\text{halogen}]$, where k_k is the rate constant for ketonisation of the enol and k_2 the rate constant for halogenation of the enol, assuming for the moment that ketonisation and enolisation are acid-catalysed processes). We obtain values for k_2K_E (K_E is the enolisation equilibrium constant) for both halogenation reactions, (a) from the [CA] dependence and (b) from the experiments at different acidities, which are given in Table 3.

A product analysis was carried for the bromination of CA, adding bromine slowly to a ten-fold excess of CA in dilute acid solution. The product was analysed by proton NMR and showed clearly that under these conditions a mixture of the mono- and di-brominated product was formed. The singlet at 3.6 ppm due to the methylene protons in CA disappeared as expected in the dibromo product and was shifted to 5.6 ppm in the monobromo product. The protons of the amide group were split into a doublet (probably due to restricted rotation around the C–N bond) and were shifted from 7.6 and 7.4 in CA to 8.0 and 7.8 in the monobromo product and 8.5 and 8.3 in the dibromo product. The integration gave ratios of 1 : 1 for the amide protons : methylene protons in CA and 2 : 1 for the same ratio in the monobromo product. When the experiment was repeated at equal concentrations of CA and bromine, only the dibromo compound was formed. A similar experiment using iodine gave evidence of the monoiodo product by a (smaller) shift of the methylene proton signal to 3.8 ppm.

We also attempted to identify the other limiting condition when enolisation is rate limiting *i.e.* when $k_k[\text{H}^+] \ll k_2[\text{halogen}]$

Table 3 Values of k_2K_E for iodination and bromination of CA

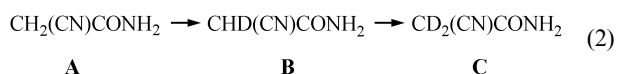
Reaction	Method	$k_2K_E/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
Iodination	Constant [CA], varying $[\text{H}^+]$	2.54 ± 0.01
Iodination	Constant $[\text{H}^+]$, varying [CA]	2.50 ± 0.08
Bromination	Constant [CA], varying $[\text{H}^+]$	1.61 ± 0.07
Bromination	Constant $[\text{H}^+]$, varying [CA]	1.24 ± 0.06

Table 4 Approximate values of the zero-order rate constants k_0 in the bromination ($[\text{Br}_2] \sim 2 \times 10^{-3} \text{ mol dm}^{-3}$) of CA at low acidity using acetic acid–acetate buffers

pH	[CA]/mol dm ⁻³	$k_0/10^{-4} \text{ mol dm}^{-3} \text{ s}^{-1}$
4.12	0.050	3.34
4.12	0.075	4.31
4.12	0.100	5.49
4.12	0.125	6.71
4.46	0.050	5.05
4.46	0.075	7.86
4.46	0.100	9.32
4.46	0.125	12.6
5.27	0.050	11.9
5.27	0.075	14.5
5.27	0.100	19.2
5.27	0.125	22.9

by working at low acidities, since we were limited in our ability to increase [halogen] significantly. We found that at around pH 4 in acetic acid–acetate buffers, reactions initially were zero-order in [halogen], but this was only maintained for 20–30% reaction when linearity of the absorbance–time plot gave way to a degree of curvature. It was clear that under these conditions enolisation was partly rate-limiting, but that we had not fully achieved the appropriate limiting condition. Nevertheless we measured zero-order rate constants k_0 from the first part of the reaction, which we recognise are subject to possible significant error. These results (shown in Table 4) however are sufficiently clear to demonstrate that reactions are under these conditions, first-order in CA and also show strong base-catalysis by acetate ion. Because of the inability to achieve fully zero-order kinetics and the complication due to base catalysis, we sought to obtain the enolisation rate constant by way of deuterium exchange experiments using D_2SO_4 . This procedure was used successfully by Hansen and Ruoff¹⁶ for the enolisation of malonic acid, where the results were in reasonable agreement with those derived from halogenation experiments. We have also used the same procedure successfully earlier in the case of enolisation of ethyl cyanoacetate.¹⁷

During exchange with D_2SO_4 – D_2O the singlet peak in the proton NMR spectrum from the methylene protons (at 3.6 ppm) was replaced by a triplet arising from the mono-deuterated species **B** (due to coupling with the deuterium atom). Over a longer time period there was evidence of conversion to the di-deuterated species **C**. Reaction was monitored by the decreasing singlet peak integral due to **A**.



Unfortunately it was not possible (as was the case with ethyl cyanoacetate) to obtain reliable values for the concentration of **B** because of the broad peaks encountered. We could only then get the rate constant for the conversion of **A** into **B**. Three runs were carried out in the acid range 0.1 – 0.3 mol dm^{-3} . Good first-order plots were obtained in each case, following the disappearance of **A**. The first-order rate constants k_1 are given in Table 5. Clearly the reaction is acid-catalysed and there is an excellent straight line plot between k_1 and $[\text{D}_2\text{SO}_4]$, which passes through the origin and the slope gives the acid-catalysed

Table 5 The first-order rate constants k_1 for proton exchange in CA with D_2SO_4

$[D_2SO_4]/\text{mol dm}^{-3}$	$k_1/10^{-4} \text{ s}^{-1}$
0.05	1.76 ± 0.34
0.10	3.53 ± 0.15
0.20	5.87 ± 0.43

Table 6 Zero-order rate constants k_0 for the bromination ($[Br_2] = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$) of ML

$[ML]/\text{mol dm}^{-3}$	$[H^+]/\text{mol dm}^{-3}$	$k_0/10^{-4} \text{ mol dm}^{-3} \text{ s}^{-1}$
0.037	0.80	3.38
0.048	0.80	4.30
0.100	0.80	9.10
0.147	0.80	14.2
0.196	0.80	18.5
0.032	0.05	0.30
0.032	0.10	0.41
0.032	0.20	0.78
0.032	0.30	1.39
0.032	0.40	1.86
0.032	0.50	2.10
0.032	0.60	2.66
0.032	0.80	3.58

enolisation rate constant as $2.7 \pm 0.3 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. At these acidities we have taken D_2SO_4 to be a monobasic acid.

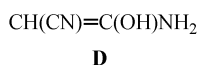
(b) Reactions of malonamic acid ML

Malonamic acid proved rather difficult to synthesise in a pure state and so we were rather limited in our ability to carry out rate measurements. Spontaneous loss of carbon dioxide occurs, generating acetamide. It was possible to obtain reasonably good kinetic data for bromination of ML when $[Br_2]$ was $\sim 1 \times 10^{-3} \text{ mol dm}^{-3}$ in the acid range $0.05\text{--}0.8 \text{ mol dm}^{-3}$ always with $[ML]$ in at least a 20-fold excess. Most runs showed good zero-order behaviour, but there was a tendency for there to be a small rapid decrease of absorbance preceding the linear drop, particularly at the higher $[ML]$. This suggests that there is some impurity present, which reacts more rapidly with bromine. We have ignored these small discrepancies and report zero-order rate constants in Table 6. It is quite clear that reaction is fully first-order in ML and also in H^+ , since both appropriate plots gave excellent straight lines which passed through the origin. This enabled us to generate from the two sets of experiments two values of k_e , the rate constant for acid-catalysed enolisation, as 1.20 ± 0.10 and $1.37 \pm 0.03 \times 10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ respectively, which represents an excellent level of agreement. We take the average value for k_e to be $1.3 \pm 0.1 \times 10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. We were unable experimentally to achieve the other possible limiting case when reaction of the enol is rate-limiting.

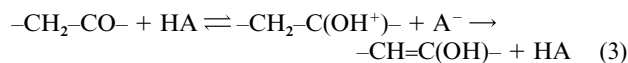
Discussion

(a) Reactions of CA

At halogen concentrations convenient for spectrophotometric analysis ($Br_2 \sim 2 \times 10^{-4} \text{ mol dm}^{-3}$ and $I_2 \sim 7 \times 10^{-4} \text{ mol dm}^{-3}$) and at acidities $> \sim 0.1 \text{ mol dm}^{-3}$, reaction with CA (always in large excess) is first-order in halogen and CA and independent of acidity. There is thus no kinetic evidence for involvement of the enolate (carbanion) as is expected from the published pK_a value for CA of 13.45. Our results are consistent with rate limiting halogenation, of the enol form of CA. There was strong evidence that the enol (**D**) is involved, from the change towards a zero-order dependence on halogen at very low acidities.



There was a small positive intercept for the plots of the measured first-order rate constants vs. $[CA]$, which is readily explicable for iodination by the likelihood of a small degree of reversibility, which is well-known in iodination. Generally this is not a problem with bromination in water, so the result is a little puzzling. However, from the slopes of these plots, and the results from the acidity variation, we obtain consistent results for the product k_2K_E (see Table 3). In addition there is a reasonably close correspondence between the bromination and iodination results, when normally bromination in water is orders of magnitude more rapid than is iodination. The only sensible rationalisation is that both reactions are taking place at, or close to, the encounter-controlled limit. This has previously been noted on many previous occasions, e.g. in the halogenation of ketones at low $[\text{halogen}]$.¹⁹ Workers have usually used a value of $5 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for the encounter-controlled process. This is slightly lower than the value predicted by the theory.²⁰ However, it has been argued (on the basis of an extended study of the bromination of enols derived from ketones)²¹ that these reactions are not fully diffusion-controlled, and that a more appropriate average value to take for the second-order rate constant is $3.4 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. Using this value and an average value of $2 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for the product k_2K_E from Table 3, we obtain a value of 6×10^{-10} for K_E for CA. This compares with a similar value of 8×10^{-10} for the enolisation of malonamide (using the more recent appropriate value for k_2). These numbers are the same within the experimental error in their determination. Similarly the deuterium isotope exchange measurements gave a value of k_e , the acid-catalysed enolisation rate constant, of $2.7 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, which compares favourably with the literature value¹² of 3.3×10^{-3} for the corresponding reaction of malonamide. It appears that substitution of $-\text{CONH}_2$ by the more electron-withdrawing $-\text{CN}$ group makes little difference. This finding is consistent with the accepted mechanism for acid-catalysed enolisation²² [eqn. (3)]



which involves rapid proton transfer from a general acid to the carbonyl oxygen atom, followed by rate limiting proton abstraction by A^- (water in our case). Substituent effects on the rate of such enolisations (of ketones) are small and follow no pattern, since the effect on the oxygen basicity (first step) is offset by the effect on the α -hydrogen atom acidity. Much the same occurs in the acid-catalysed hydrolysis of esters.

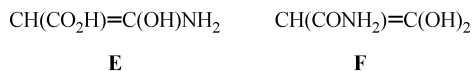
We can, using the Kresge approach,¹⁵ use our pK_E value of 9.2 for CA to estimate the pK_E of the parent amide acetamide, making use of the approximate substituent effects upon pK_E values, notably the ΔpK_E for the CN group of 9.4. This yields a pK_E for acetamide of ~ 18.6 , which unfortunately is not in particularly good agreement with a similar estimate of 21.7 for *N*-methylacetamide.¹⁵

The product analysis with the bromine reaction confirmed that the monobromo and possibly some dibromo products were formed. Our product work was necessarily carried out at somewhat higher concentration than were the kinetic experiments, which may exaggerate the % dibromo product. In any case the kinetic curves were all smooth and consistent with rate limiting monobromination of the enol. Any subsequent reaction is likely to be fast (and post-rate limiting), given the expected much higher K_E for the monobromo compound. This is a familiar situation in the halogenation of enols from simple ketones.

(b) Reactions of ML

We were limited by purification difficulties in our attempt to get kinetic data for the halogenation of ML. However it was

possible to carry out some bromination experiments over a wide acidity range. Reactions were zero-order throughout (with $[ML] \gg [Br_2]$), apart from a small initial deviation which we attribute to the presence of an impurity. Reactions were first order in ML and H^+ indicating rate-limiting acid-catalysed enolisation. We find no evidence of intramolecular proton transfer as is the case with malonic acid and its derivatives, at least over the acid range covered, 0.05–0.80 mol dm⁻³. There are of course two possible modes of enolisation in ML, involving the amide function (E) or the carboxylic function (F), and it is not easy to distinguish between these possibilities.



Acid-catalysis of enolisation generally disappears when the carbon acidity of the α -proton is increased (when there are powerful electron-attracting 2-substituents e.g. as in 1,3-dichloroacetone²³ and other examples). This does not seem to be the case with malonamide, cyanoacetamide and malonamic acid. This probably arises because of the increased basicity (for oxygen protonation) of amides (typical pK_a -0.7) compared with carboxylic acids and esters (typical pK_a -6 to -8). This can be taken to be an argument in favour of the suggestion that enolisation of malonamic acid occurs in the amide group following oxygen protonation. The enolisation of 2-hydroxy-2-cyano-*N*-methylacetamide is also an acid-catalysed process in this acid region.¹⁵

Experimental

Malonamic acid was prepared by the method of Jeffery and Vogel²⁴ from ethyl hydrogen malonate and aqueous ammonia. Repeated recrystallisation from pentan-3-one gave significant amounts of acetamide impurity (as detected by ¹H NMR measurements). This was reduced by washing with pentan-3-one and allowing the product to dry slowly on the top of an oven. This gave a sample with mp 116 °C (lit. 121 °C). Repeated purification attempts did not yield a product with a higher melting point. All other materials were commercial samples of the highest purity grade available. Kinetic halogenation measurements were carried out in a stopped-flow UV-visible spectrophotometer interfaced with the appropriate software. All reactions were carried out in water at 25 °C, with the reactants CA or ML in at least a 25-fold excess over the halogen. Reactions were followed by noting the disappearance of the halogen absorbance (at 390 nm for bromine and 460 nm for iodine). First-order and zero-order plots were analysed in the conventional manner. The deuterium exchange experiments for CA were carried out using D₂SO₄-D₂O measuring the decreasing methylene proton signals with time using methanol as an internal standard. All the D-exchange experiments gave good first-order plots for the disappearance of CA.

Bromine (1 g) in water was added slowly to a solution of CA (5 g) in water (300 cm³). The product was extracted with ether, dried, the solvent removed and the proton NMR spectrum run on a 200 MHz spectrometer.

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