Halogenation and deuterium exchange in ethyl cyanoacetate. Enolisation mechanism and enol reactivity

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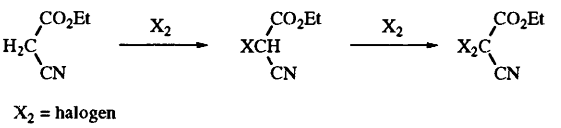
Reactions of ethyl cyanoacetate (ECA) in 30% dioxane–water with bromine, iodine and chlorine (with $[ECA]_0 \gg [Halogen]_0$) are all first-order processes and are not acid catalysed over the range studied (0.02–1.10 mol dm^{-3}). Values of the observed first-order rate constant divided by [ECA] are very similar for the three halogens, suggesting that all three react with the enol form of ECA at or near to the diffusion limit. This enables the determination of a pK_E value of 9.6 and a pK_a^E value for the acid dissociation of the enol of 2.1. The rate constant for enolisation is obtained by NMR measurements of the H–D exchange reaction and is shown to be independent of the acidity in the range 0.08–0.39 mol dm^{-3} D^+. The results are consistent with the enolisation mechanism involving rate-limiting water-catalysed proton removal from the methylene group, followed by rapid protonation of the enolate. The results are discussed in terms of the enolisation of other carboxylic esters and acids.

Currently there is a renewed interest[1] in keto–enol chemistry, particularly in carbonyl compounds other than simple ketones, in particular in carboxylic acids, esters and amides. A few enols derived from carboxylic acids (*i.e.* 1,1 diol enes) have been isolated, others have been generated by ketene hydration and characterised in solution.[2] This approach has used large substituent groups in the molecule which destabilise the keto form. The Kresge group has concentrated on obtaining quantitative information by generating unstable enols photochemically and measuring their ketonisation rate constants.[3] Since enolisation rate constants are easily obtained by halogen scavenging experiments, this allows the measurement of K_E without making any other assumptions. We have used the classical halogenation and deuterium exchange procedures to identify (kinetically) enol species and to establish some quantitative features. Data have been presented for the enols derived from malonamide (the first time an enol has been thus described for an amide),[4] malonic acid and ethyl hydrogen malonate.[5] Now we have extended our studies to include esters and the influence of electron-withdrawing groups, particularly the cyano group. This paper describes our results obtained for the reactions of ethyl cyanoacetate (ECA) $CNCH_2CO_2Et$. This compound is a well known carbon acid with a measured pK_a of 11.7[6,7] in water. It also readily undergoes halogenation to give the mono- and sometimes the di-halo compound, depending upon the reaction conditions [reaction (1)].[8–10]



$$H_2C(CO_2Et)(CN) \xrightarrow{X_2} XCH(CO_2Et)(CN) \xrightarrow{X_2} X_2C(CO_2Et)(CN) \quad (1)$$

X_2 = halogen

Table 1 Values of k_0 at different [ECA] for bromination, iodination and chlorination

[Halogen]/mol dm^{-3}	[ECA]/mol dm^{-3}	$k_0/10^{-2}$ s^{-1}
Br_2 5 × 10^{-4} [a]	0.050	9.3
	0.075	14.6
	0.010	18.4
	0.015	28.8
	0.020	37.4
I_2 6 × 10^{-4} [a]	0.050	5.6
	0.075	7.6
	0.010	9.2
	0.015	11.5
	0.020	13.4
Cl_2 1 × 10^{-3} [b]	0.025	4.6
	0.050	7.4
	0.100	11.5
	0.150	18.0
	0.200	24.2

[a] At 0.10 mol dm^{-3} $[H^+]$. [b] At 0.53 mol dm^{-3} $[H^+]$.

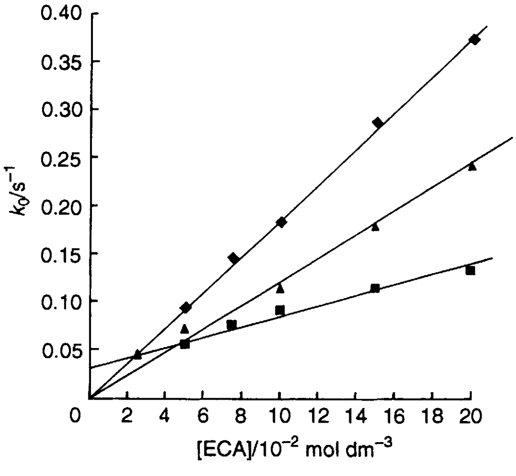


Fig. 1 First-order rate constants (k_0) for the reaction of ECA with chlorine (▲), bromine (◆) and iodine (■)

Results and discussion

Halogenation

The kinetics of the reactions of bromine, iodine and chlorine with ECA were carried out in 30% dioxane–water solvent (for solubility reasons) in a conventional UV–VIS spectrophotometer or a stopped-flow spectrophotometer. In all cases we used $[ECA]_0 \gg [Halogen]_0$ and monitored the reaction by disappearence of the halogen absorbance. We worked in acid solution, and at all acidities reactions were perfectly first-order in [Halogen]. Table 1 shows the variation of the first-order rate constant k_0 with [ECA]. In each case the plots of k_0 *vs.* [ECA] are linear (see Fig. 1). For bromination and chlorination, the plots pass very close to the origin, but for iodination there is a small but significant intercept, which can be interpreted in terms of the well known reversibility of iodination reactions generally.[10] Table 2 shows the results of the investigation of the acidity dependence of the reactions. It is clear for all three

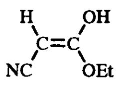
Table 2 Values of k_0 over a range of acidity for the bromination, iodination and chlorination of ECA (0.05 mol dm^{-3})

[Halogen]/mol dm^{-3}	$[H^+]$/mol dm^{-3}	$k_0/10^{-2}$ s^{-1}
Br_2 5×10^{-4}	0.10	7.1
	0.20	6.8
	0.30	6.6
	0.40	6.9
	0.50	7.0
	0.70	6.9
	1.00	6.8
I_2 6×10^{-4}	0.02	6.4
	0.03	7.3
	0.10	5.0
	0.15	5.6
	0.20	6.6
	0.30	7.3
	0.40	7.9
Cl_2 1.5×10^{-3}	0.30	6.7
	0.50	6.5
	0.70	6.9
	0.90	7.4
	1.10	9.1

halogenation reactions that there is no dependence of k_0 upon $[H^+]$ over the acid ranges used, within the experimental error of measurement, although the scatter of values particularly for the iodination reactions is perhaps a little greater than expected.

The results are consistent with a rate limiting reaction between the halogens and a reactive intermediate derived from ECA. The likely candidates are the enol and enolate (carbanion) derivatives. The enolate can be ruled out, given the lack of the acidity dependence, unless the enol is fully converted to the enolate at these acidities which is unlikely. A probable value for the ionisation of the enol pK_a^E will be discussed later.

The striking feature of the results is the remarkable similarity between the reactivities of all three halogens as measured by the slopes of the plots in Fig. 1, *i.e.* 1.9, 0.52 and 1.1 dm^3 mol^{-1} s^{-1} for bromination, iodination and chlorination, respectively. Normally there is a very large reactivity difference between the halogens in the order $Cl_2 > Br_2 > I_2$ for electrophilic halogenation. Typically, approximate relative reactivities are[11] in the ratios $10^3 : 10 : 10^{-5}$. The only sensible explanation of our results is that all of the reactions are at, or are very close to, the diffusion controlled limit. For many enols such rate constants have been measured, mostly for bromination reactions and the results do show only a very small substrate dependence,[12] with many of the values in the range 2–5 × 10^9 dm^3 mol^{-1} s^{-1}, in water at 25 °C. The enols derived from carboxylic acids and esters would be expected to be at least as reactive and the deactivating effect of a cyano group in our case could well be offset by the presence of the OEt group (**1**). The nearest comparison we can make with literature values is the corresponding situation with the enol derived from malonamide (**2**),[4] where bromine, iodine, nitrosyl bromide and nitrosyl thiocyanate all appear to react at or near the diffusion limit.



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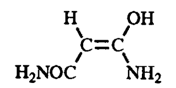
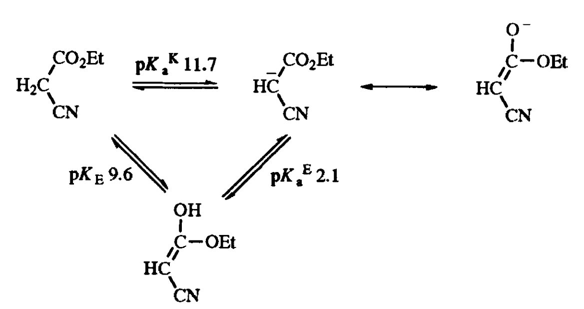


2

If we assume that halogenation of ECA occurs by rate-limiting diffusion controlled halogenation of the enol [reaction (2)], then the rate of reaction is given by eqn. (3) if K_E is small as is likely to be the case. We can now estimate a value for K_E assuming[13] a value of 5 × 10^9 dm^3 mol^{-1} s^{-1} for the encounter process. This procedure has been widely adopted by Toullec *et al.*[13] to obtain K_E values for some ketones, using a particularly low [Halogen] to ensure that reaction of the enol is rate limiting, rather than the enolisation process itself. We have used an average value for kK_E from Fig. 1 and also from the data in Table 2 and arrive at a value of (2.6 ± 0.4) × 10^{-10} for K_E or a pK_E value of 9.6. We previously[14] suggested a maximum value of *ca.* 11 from nitrosation experiments using NOSCN which probably does not react at the diffusion limit. This enables us to propose (using Scheme 1) a value of 2.1 for the acid dissociation of the enol. Kresge *et al.*[15] have discussed the acidity of a number of enols derived from carboxylic acids, and have commented on the extra acid-strengthening effect of a second OH group (or OEt group in our case), which makes these enols surprisingly strong acids. They obtained a value for pK_a^E of 0.99 for 2-cyano-2-phenylethene-1,1-diol (the enol derived from 2-cyano-2-phenylacetic acid). Our value for the enol from ECA fits in well with this value if we assume that the effects of OEt and OH are comparable and that the additional 2-phenyl substituent is worth *ca.* 1 pK_a unit in the acid strengthening sense. It is therefore not likely that we have a significant pathway for halogenation *via* the enolate if our pK_a^E value is reasonable, given the acidity range used in our experiments. It is difficult, particularly with Cl_2 and Br, to work at higher pH values because the halogen is converted to other species (such as BrO^-, *etc.*).

$$\mathrm{ECA} \underset{}{\overset{K_E}{\rightleftharpoons}} \mathrm{ENOL} \xrightarrow[k]{\text{Halogen}} \mathrm{PRODUCT} \qquad (2)$$

$$\text{Rate} = kK_E[\text{Halogen}][\text{ECA}] \qquad (3)$$



Scheme 1

The pK_E value of 9.6 is compatible with the published value of 7.22 determined by Kresge *et al.*[15] for the enolisation of 2-cyano-2-phenylacetic acid, given that the additional phenyl group would be expected to increase the enol content because of its ability to stabilise the carbon–carbon double bond in the enol.[16] In simple carbonyl compounds this effect is equivalent to *ca.* 3 pK_E units, *e.g.* as found for the enols of acetaldehyde and phenylacetaldehyde.[17] So our value is reasonably in line with literature values.

In our nitrosation experiments with ECA[14] we were able to identify clearly the reaction *via* the enol and enolate (carbanion) species, principally because we were able to work at pH values as high as 3.2 where (if our pK_a^E value is correct) a substantial amount of the enol is deprotonated. We reported a value for the bimolecular rate constant for the reaction of ONSCN with the enolate as 6.1 × 10^8 dm^3 mol^{-1} s^{-1} and a value of 2.5 × 10^{-2} dm^3 mol^{-1} s^{-1} for the product of the rate constant for reaction of the enol and K_E. Using our present value of K_E we can obtain a value of 1.0 × 10^8 dm^3 mol^{-1} s^{-1} for the bimolecular rate constant for reaction of ONSCN with the enol form. As expected this is somewhat less than the value for the enolate reaction but the ratio is not large given that we are now almost within a power of 10 of the diffusion limit.

Deuterium exchange experiments

We found it difficult experimentally to achieve the change in the rate-limiting step from the reaction of the enol to the enolisation stage by increasing the [Halogen]. In principle this can be

Table 3 Values of k_1 and k_2 [reaction (5)] for deuterium exchange in ECA at three acid concentrations

$[D^+]$/mol dm^{-3}	$k_1/10^{-4}$ s^{-1}	$k_2/10^{-4}$ s^{-1}
0.08	5.6 ± 0.5	1.4 ± 0.4
0.20	5.4 ± 0.3	2.3 ± 0.4
0.39	5.8 ± 0.8	2.5 ± 0.8

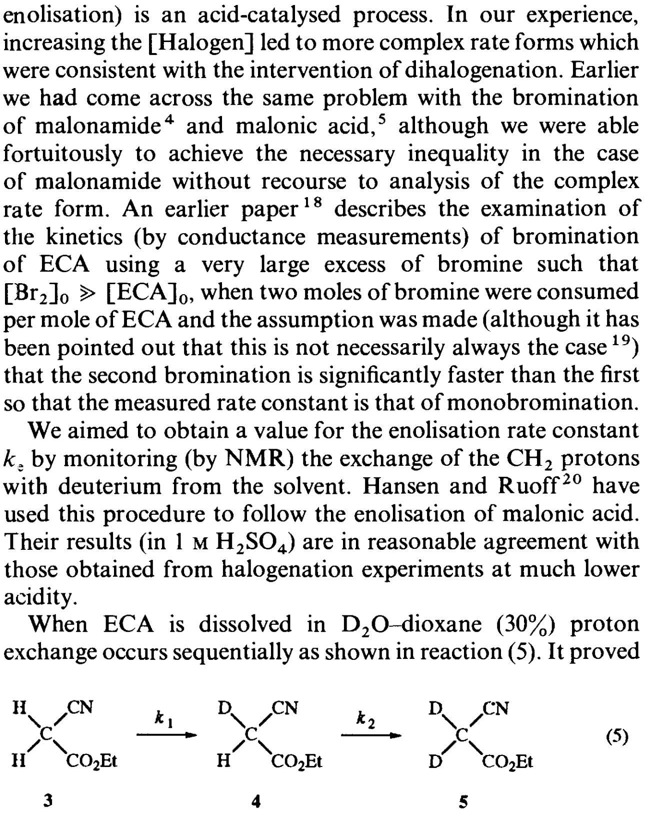
achieved when k[Halogen] $\gg k_k$ [reaction (4)]. The k_k term

$$\text{ECA} \underset{k_k}{\overset{k_e}{\rightleftharpoons}} \text{ENOL} \xrightarrow[k]{\text{Halogen}} \text{PRODUCT} \qquad (4)$$

might include a term in $[H^+]$ if ketonisation (and therefore enolisation) is an acid-catalysed process. In our experience, increasing the [Halogen] led to more complex rate forms which were consistent with the intervention of dihalogenation. Earlier we had come across the same problem with the bromination of malonamide[4] and malonic acid,[5] although we were able fortuitously to achieve the necessary inequality in the case of malonamide without recourse to analysis of the complex rate form. An earlier paper[18] describes the examination of the kinetics (by conductance measurements) of bromination of ECA using a very large excess of bromine such that $[Br_2]_0 \gg [ECA]_0$, when two moles of bromine were consumed per mole of ECA and the assumption was made (although it has been pointed out that this is not necessarily always the case[19]) that the second bromination is significantly faster than the first so that the measured rate constant is that of monobromination.

We aimed to obtain a value for the enolisation rate constant k_e by monitoring (by NMR) the exchange of the CH_2 protons with deuterium from the solvent. Hansen and Ruoff[20] have used this procedure to follow the enolisation of malonic acid. Their results (in 1 M H_2SO_4) are in reasonable agreement with those obtained from halogenation experiments at much lower acidity.

When ECA is dissolved in D_2O–dioxane (30%) proton exchange occurs sequentially as shown in reaction (5). It proved



(5)

possible to monitor the disappearance of **3** by the decrease in the intensity of the singlet at $\delta = 3.35$, and also the appearance of **4** by the formation of a triplet centred at $\delta = 3.34$. Values of [**5**] cannot be obtained directly but can be computed from the mass balance. The system can be treated in terms of the conventional A ⟶ B ⟶ C sequential steps using eqns. (6) and (7).

$$[3] = [3]_0 e^{-k_1 t} \qquad (6)$$

$$[4] = k_1[3]_0(e^{-k_1 t} - e^{-k_2 t})/(k_2 - k_1) \qquad (7)$$

Plots of [**3**] and [**4**] as a function of time are shown in Figs. 2 and 3 respectively for a typical experiment. Values of k_1 and k_2 were obtained by curve fitting procedures. The solid lines in the figures are the calculated values. We obtained k_1 and k_2 values at three different acidities and the results are shown in Table 3. Values of k_2 are not as precise as those of k_1 because of the experimental problems encountered in the integral measurement of quite small and overlapping NMR signals.

It is reasonable to assume that deuterium exchange occurs *via* proton loss and reprotonation of the enol form. We obtain an average value for k_1 from Table 3 of 5×10^{-4} s^{-1}. The corresponding value obtained by Pearson and Dillon[18] using

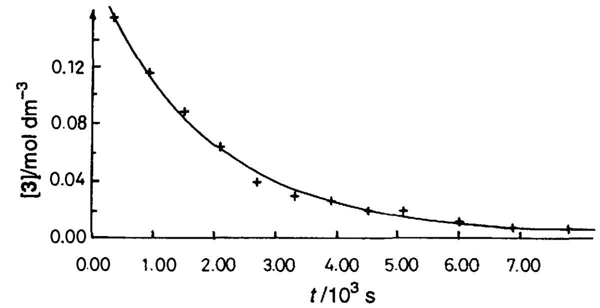


Fig. 2 The disappearance of ECA (**3**) with time in the exchange reaction with deuterium from the solvent. Initial [**3**] 0.209 mol dm^{-3}, $[D^+]$ 0.20 mol dm^{-3}.

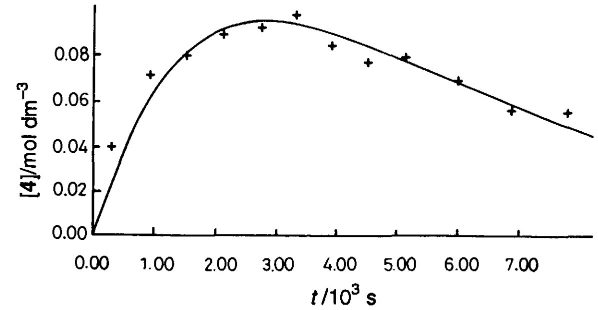
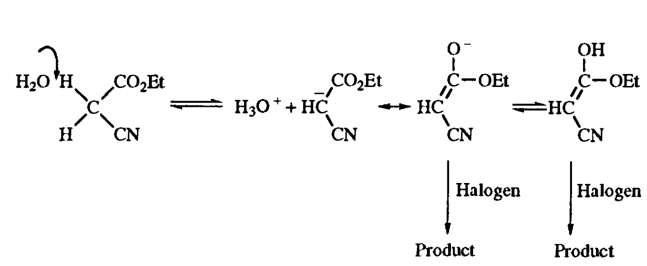


Fig. 3 The concentration of the monodeuteriated species (**4**) as a function of time in the exchange reaction of ECA (**3**) with deuterium from the solvent. Initial [**3**] 0.209 mol dm^{-3}, $[D^+]$ 0.20 mol dm^{-3}.

bromination kinetics at very high $[Br_2]$ is 1.2×10^{-3} s^{-1}. This would lead to a value for the solvent isotope effect $(k_e)_{H_2O}/(k_e)_{D_2O}$ of 2.2. This is within the range expected from the theory of solvent isotope effects[21] using the fractionation factor $l = 0.69$ for each OD^+ site involved in a proton transfer equilibrium. Our value is close to the maximum possible ($1/l^2 = 2.1$) which suggests that the transition state is very product-like.

On statistical grounds k_1 should equal $2k_2$ whereas we find it equals $2.3k_2$ if we use only the last two values for k_2 in Table 3. This difference gives the secondary isotope effect, *ca.* 1.15, which is a reasonable value resulting from the changing hybridisation ($sp^3 \longrightarrow sp^2$) in the transition state. A similar value of 1.3 was estimated for the secondary isotope effect for the enolisation of malonic acid.[20]

Our results in Table 3 show that enolisation is not an acid-catalysed process even in acid solutions up to 0.39 mol dm^{-3}. Simple ketones undergo enolisation in acid solution primarily *via* the well known acid-catalysed mechanism which involves rapid reversible protonation of the carbonyl oxygen atom as the first stage. The more acidic are the protons in the ketone, the greater is the contribution of an 'uncatalysed' pathway, which is better described as the base (water in this case) catalysed reaction or as the base (water) catalysed ionisation, shown in Scheme 2. In principle both the enolate (carbanion) and enol can react with the halogen. The absence of an acid-catalysed pathway here is perhaps not surprising given that the more acidic β diketones only undergo that pathway[22] at acidities



Scheme 2

greater than 0.1 mol dm^{-3} and there is no acid catalysis of enolisation of 1,3-dichloroacetone even at 1 mol dm^{-3} acid concentration.[23] The very powerfully electron-attracting cyano group promotes the proton transfer to the solvent (Scheme 2) whilst inhibiting protonation of the carbonyl oxygen atom.

Comparison with the enolisation of other carboxylic esters, acids and amides is limited by the paucity of literature data, but it appears that the enolisation of diethyl malonate[18,24] proceeds by the same pathway as ECA. Reactions of malonic acid and substituted malonic acids are complicated by the incursion of another mechanism involving intramolecular proton transfer from one CO_2H group to the carbonyl group of the other.[5] The enolisation of malonamide however proceeds by the acid-catalysed pathway in dilute acid solution.[4] More recent work[25] with cyanoacetamide [$CH_2(CN)CONH_2$] and malonamic acid [$CH_2(CO_2H)CONH_2$] shows that this is also the case with these amides. This may well be due to the greater basicity of the carbonyl oxygen atom in amides generally (pK_a *ca.* 0)[26] compared with that in carboxylic acids and esters (pK_a *ca.* -6 to -8).[27]

Experimental

Materials used were all commercial samples of the highest purity grade available. Purity of the organic compounds was confirmed by NMR analysis. ECA solutions were prepared in 30% (by volume) dioxane–water solvent and used in the kinetics experiments the same day. The halogens were dissolved in the solvent and the solutions standardised by iodide–thiosulfate titrations and also from extinction coefficients obtained from standardised solutions. Halogen kinetics were carried out at 25 °C in a conventional UV–VIS spectrophotometer or, for the faster reactions, in a stopped-flow spectrophotometer, both interfaced with a PC. Reactions were followed by noting the disappearence of the halogen absorbances at 390 nm (Br_2), 460 nm (I_2) and 323 nm (Cl_2). The initial [ECA] was always in a greater than twenty fold excess over the [halogen]. First-order behaviour was found throughout. The quoted k_0 values are the means of at least three (and sometimes many more) determinations and were generally reproducible within ± 5%. The deuterium exchange experiments were carried out in a 400 MHz NMR spectrometer. The system was not thermostatted but the reaction mixture stayed very close to 25 °C throughout. We measured the decreasing peak area of the singlet at δ 3.35 due to the CH_2 protons and also the increasing peak area of the triplet due to the monodeuteriated compound. The triplet arises from coupling of the proton with deuterium. The protons of the C_2H_5 group (CH_3 triplet at δ 0.80 and CH_2 quartet at δ 3.80) were not exchanged during the reaction, and were used as a reference signal to calibrate the spectra. There was evidence of some hydrolysis of ECA towards the end of the reaction, as noted by the appearance of the spectrum of ethanol. The overlap between the CH_2 and CHD signals made it necessary to use an extrapolation procedure to determine the part of the CHD peak hidden by the CH_2 peak.

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