Enol and Enolate (Carbanion) Intermediates in Nitrosation. Reactions of Ethyl Cyanoacetate, Diethyl Malonate and Malononitrile

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Rate constants have been obtained for the reactions of ethyl cyanoacetate (ECA) and diethyl malonate (DEM) with nitrous acid in acid solution, over a range of acid concentrations and also in the presence of chloride, bromide, thiocyanate ions or thiourea. The reaction products are the corresponding oximes, and all of the results are consistent with a reaction mechanism involving rate-limiting attack by the nitrosating species XNO at both the enol and enolate (or carbanion) forms of the substrate. At low acidities reactions *via* the enolate are dominant. Many of these reactions, particularly those of DEM, occur at or near the diffusion-controlled limit. The findings are compared with those obtained earlier for the nitrosation reactions of malononitrile (MN) and with the kinetic results of the halogenation of DEM, and are discussed in terms of the involvement of enol and enolate intermediates and their relative reactivities towards electrophilic species. Under our experimental conditions there was no evidence of rate-limiting enol formation.

It has now been firmly established[1] that simple ketones react with nitrous acid (or with any carrier of NO^+) to give generally oxime products, *via* the enol tautomers of the ketone. Either the enolisation step or the reaction of the enol can be made rate-limiting by a suitable adjustment of the reaction conditions or the choice of substrate. The situation is thus very similar to that which pertains for halogenation of ketones, and indeed for a number of other reactions. In some cases, when there are other suitable electron-withdrawing groups present, part, or all, of the reaction can take place *via* the enolate (or carbanion) form.[2] The distinction between reaction *via* the enol and the enolate can readily be made from a study of the variation of the measured rate constant with the acidity of the medium. Recently,[3] it was established that even in dilute acid solution malononitrile undergoes nitrosation *via* its carbanion form; not unexpectedly such reactions take place at the encounter rate for a range of XNO species, making this carbanion the most reactive substrate studied in nitrosation chemistry. At the present time, there is a renewed interest in the generation and reactions of enols.[4] One particular area of interest is the recognition of enols derived from carbonyl-containing compounds other than simple ketones. Enols derived from a carboxylic acid and an ester have recently been synthesised[5] by Fuson's approach using large substituent groups which destabilise the keto form. Enols from simple carboxylic acids and esters have also been suggested as short-lived intermediates in halogenation reactions based on kinetic studies,[6] and have also been identified by flash photolysis methods.[7] Equilibrium constants for enolisation of simple carboxylic acids have been predicted by calculation to be very small.[8] None have been measured directly, although a few have been estimated by indirect routes, the most recent[7] and probably the most reliable being that for mandelic acid as 4×10^{-16}.

We wished to extend our earlier work on malononitrile (MN) to cyano esters and diesters to establish the pattern of reactivity in nitrosation *via* enol and/or enolate (carbanion) intermediates, and chose to work with ethyl cyanoacetate (ECA), diethyl malonate (DEM) as well as with MN to determine the effect of progressive replacement of cyano groups by ester groups.

Experimental

All of the materials were of the highest purity grade available and were purified further by distillation where necessary. Fresh sodium nitrite solutions were made up on the day of use. The product oximes were all synthesised by literature methods,[9] eqns. (1)–(3), and used to identify the products in the kinetic

$$\underset{\text{MN}}{CH_2(CN)_2} \xrightarrow{HNO_2/H^+} HON{=}C(CN)_2 \qquad (1)$$

$$\underset{\text{ECA}}{NCCH_2CO_2Et} \xrightarrow{HNO_2/H^+} HON{=}C(CN)CO_2Et \qquad (2)$$

$$\underset{\text{DEM}}{CH_2(CO_2Et)_2} \xrightarrow{HNO_2/H^+} HON{=}C(CO_2Et)_2 \qquad (3)$$

reaction product mixtures, which were formed quantitatively. Rate measurements were carried out at 25 °C in 30% dioxane–water solvent, usually by conventional UV spectrophotometry or, in some cases of fast reactions, by stopped-flow spectrophotometry. For MN, reactions were followed at 310 nm noting the oxime formation, whereas for ECA and DEM it was more convenient to measure the disappearance of the absorbance due to nitrous acid at 370 or 386 nm. In all cases the substrate was in at least a twenty-fold excess over the nitrous acid. Throughout, good first-order behaviour was found. The quoted values of the observed first-order rate constants k_0 are the mean values of at least four separate determinations and the reproducibility was better than ±2%.

Results

Because of solubility problems it was not possible to carry out our kinetic experiments with both ECA and DEM in water and so we chose to work with 30% dioxane–water (by volume). Thus it was necessary, if valid comparisons were to be made, to repeat some of the experiments with MN (previously carried out in water) in 30% dioxane–water. The earlier results[3] were all consistent with reaction *via* the carbanion (as outlined in Scheme 1) and the expression for the first-order rate constant k_0 (defined by rate = $k_0[HNO_2]_T$) expected from Scheme 1 is given by eqn. (4). The ionisation of nitrous acid to *nitrite ion*

$$\begin{array}{lr} HNO_2 \rightleftharpoons H^+ + NO_2^- & K_N \\ CH_2(CN)_2 \rightleftharpoons {}^-CH(CN)_2 + H^+ & K_a \\ HNO_2 + X^- + H^+ \rightleftharpoons XNO + H_2O & K_{XNO} \\ {}^-CH(CN)_2 + XNO \longrightarrow ONCH(CN)_2 + X^- & k_2 \\ ONCH(CN)_2 \longrightarrow HON{=}C(CN)_2 & \text{fast} \end{array}$$

Scheme 1

must be taken into account if the pH of the medium is greater

$$k_0 = k_2K_aK_{XNO}[MN][X^-][H^+]/(K_N + [H^+]) \quad (4)$$

than *ca.* 2. The form of eqn. (4) has previously been demonstrated[3] for reactions in water and values of k_2 obtained. In the present study, values of k_2 were obtained for reaction in 15% and 30% dioxane–water solvents at constant pH 3.1, (*a*) from experiments at constant [MN] whilst varying $[X^-]$ and (*b*) at constant $[X^-]$ with varying [MN]. The results are collected in Table 1, together with the earlier results obtained in water.[3] It is clear that there is a reasonably good agreement between the procedures (*a*) and (*b*) and also that there is only a small difference in k_2 values over the range of solvents used. All k_2 values are indeed at or close to the expected diffusion limit. These results suggest that any rate constant changes due to the solvent change upon the introduction of up to 30% dioxane into water, are quite small and can be ignored in any discussion of major reactivity differences consequent upon structural changes in the reactants.

Table 1 Values of k_2 [*i.e.* for $XNO + {}^-CH(CN)_2 \rightarrow$ oxime] as a function of solvent composition for reaction at pH 3.1

	$X^- = Br^-$	$X^- = SCN^-$
Solvent	k_2/dm^3 mol^{-1} s^{-1}	k_2/dm^3 mol^{-1} s^{-1}
Water[3]	1.1×10^{10}	4.2×10^9
15% Dioxane–water	—	7.3×10^{9}[a] 6.8×10^{9}[b]
30% Dioxane–water	7.4×10^{9}[a] 2.5×10^{9}[b]	7.0×10^{9}[a] 6.7×10^{9}[b]

[a] From $[X^-]$ variation at constant [MN]. [b] From [MN] variation at constant $[X^-]$.

Both ECA and DEM reacted smoothly with nitrous acid under the kinetic conditions (with [ECA] or [DEM] $\gg$ $[HNO_2]$) to give the corresponding oximes. Throughout, good first-order behaviour was found. In the absence of an added nucleophilic catalyst X^- (such as halide ion) the reactions were not sufficiently rapid to allow the competing decomposition reaction of nitrous acid to be ignored. Quantitative information therefore was not reliable in this case. The same is true of the chloride-ion catalysed reactions, where although chloride-ion catalysis clearly occurs, the decomposition side reaction cannot be ignored. Fortunately this was not a problem for the bromide- and thiocyanate-ion catalysed reactions. Table 2 shows the kinetic results for these processes for reactions of both ECA and DEM. There is a reasonably good linear dependence of k_0 upon $[Br^-]$ and $[SCN^-]$ for both substrates and there is a good first-order dependence upon [ECA] (similar results were found for DEM).

Information concerning the nature of the intermediate can often be obtained from a study of the dependence of k_0 on the acidity of the medium. Reactions of both ECA and DEM were studied for the thiocyanate catalysed reaction in the pH range 1.25–3.5. Here it is necessary to allow for the nitrous acid ionisation to nitrite ion (an inactive form) since the relevant pK_a is 3.15. We have chosen to 'correct' the k_0 values by multiplying by the factor $([H^+] + K_N)/[H^+]$, where K_N is the acid dissociation constant of nitrous acid (7.1×10^{-4} mol dm^{-3}) to give k_0' values. The results are presented in Figs. 1 and 2 for ECA and DEM, respectively, as plots of k_0' *vs.* $[H^+]$. In both cases acid catalysis is evident but there is a substantial positive

Table 2 Catalytic effect of Br^- and SCN^- in the nitrosation of ECA at pH 3.2 and DEM at pH 2.8

Substrate	Concentration/mol dm^{-3}	$[Br^-]$/mol dm^{-3}	$[SCN^-]$/mol dm^{-3}	$k_0/10^{-4}$ s^{-1}
ECA	0.25	0.10	—	0.44
	0.25	0.14	—	0.49
	0.25	0.19	—	0.52
	0.25	0.24	—	0.60
	0.25	0.38	—	0.70
	0.25	0.76	—	1.06
DEM	0.125	0.10	—	0.53
	0.125	0.15	—	0.66
	0.125	0.20	—	0.78
	0.125	0.30	—	1.19
	0.125	0.40	—	1.51
	0.125	0.75	—	2.59
ECA	0.25	—	0.08	4.90
	0.25	—	0.14	6.76
	0.25	—	0.19	8.88
	0.25	—	0.24	11.5
	0.25	—	0.38	20.2
	0.25	—	0.76	40.0
DEM	0.125	—	0.20	4.48
	0.125	—	0.30	5.20
	0.125	—	0.40	6.97
	0.125	—	0.75	13.2
ECA	0.15	—	0.24	7.47
	0.20	—	0.24	10.2
	0.25	—	0.24	12.8
	0.30	—	0.24	14.8
	0.40	—	0.24	20.2

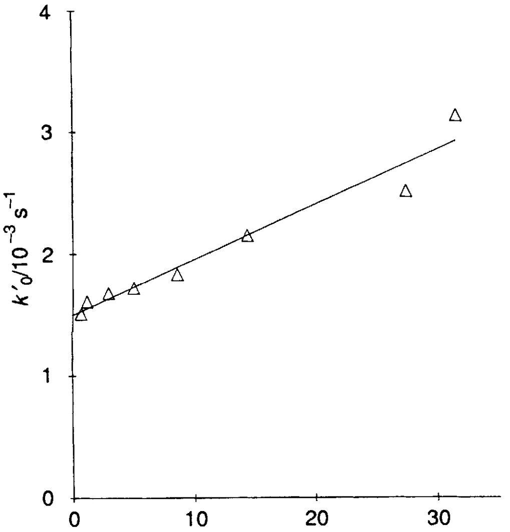


Fig. 1 Plot of k_0' *vs.* $[H^+]$ for the reaction of ECA (0.247 mol dm^{-3}) with nitrous acid (5×10^{-3} mol dm^{-3}) in the presence of thiocyanate ion (0.190 mol dm^{-3})

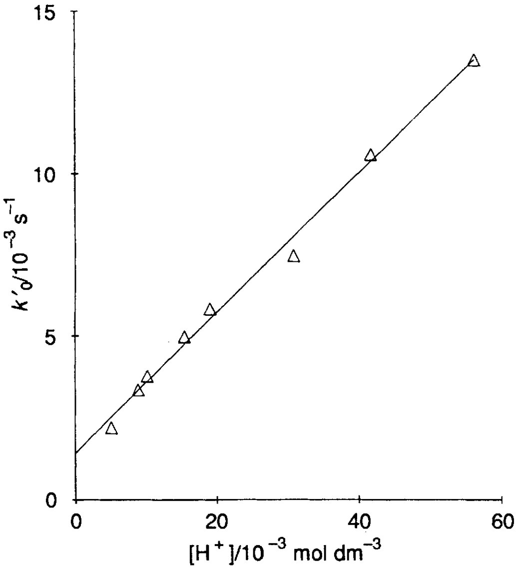


Fig. 2 Plot of k_0' *vs.* $[H^+]$ for the reaction of DEM (0.125 mol dm^{-3}) with nitrous acid (5×10^{-3} mol dm^{-3}) in the presence of thiocyanate ion (0.400 mol dm^{-3})

intercept to the plot which is much larger for ECA than for DEM.

Catalysis by thiourea was also noted for both substrates, and the results are presented in Table 3.

Discussion

Throughout this work, under the experimental conditions chosen there was always a good first-order dependence upon $[HNO_2]$ indicating that the rate-limiting step is one of nitrosation and not the formation of some reactive intermediate such as an enol or carbanion. Similarly, reactions were also first order in [substrate], so that we do not have a situation of rate-limiting XNO formation. Examples are known elsewhere in the literature of nitrosation where XNO formation[10] or some reactive intermediate formation,[1] is the rate-limiting process.

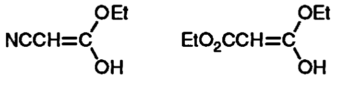
Nucleophilic catalysis by added X^- was observed as expected for Cl^-, Br^-, SCN^- and $SC(NH_2)_2$ and was quantified for each nucleophile except Cl^-. It is clear then that the attack of XNO is the rate-limiting step.

Table 3 Thiourea catalysis in the nitrosation of ECA and DEM

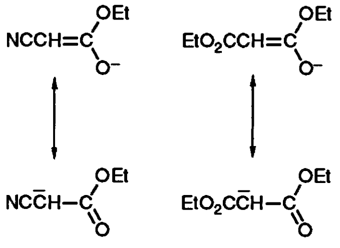
	ECA[a]	DEM[b]
$[SC(NH_2)_2]$/mol dm^{-3}	10^2k_0	10^2k_0
0.10	0.76	—
0.14	1.05	
0.19	1.07	
0.20	—	1.38
0.23	1.51	—
0.30	—	3.01
0.38	2.05	—
0.40	—	3.95
0.75	—	5.83

[a] [ECA] 0.25 mol dm^{-3}, pH 3.2. [b] [DEM] 0.125 mol dm^{-3}, pH 2.8.

The possibility exists for both ECA and DEM that the reactive intermediates are the corresponding enol tautomers **1** and **2**, which was not possible for MN. Acid dissociation of the enol forms allows the possibility of enolate (or carbanion) formation **3** and **4**. It is to be expected that **1**, **2**, **3** and **4** would be very reactive species towards electrophilic addition (such as in nitrosation) with the enolate species being the more reactive.



1 **2**



3 **4**

In principle it should be possible to distinguish reaction pathways *via* the enol forms from those *via* the enolates by the acidity dependence of the rate constant. This has previously been achieved in the nitrosation of dimedone[2] and for a related system in benzenesulfinic acid.[11] Scheme 2 shows the outline mechanism for concurrent reaction pathways *via* the enol (E) and enolate (E^-) for a general substrate SH. The form of the expression for k_0 is thus given by eqn. (5); the experimental results

$$k_0 = k^E K_E K_{XNO}[SH][X^-][H^+] + k^C K_a K_{XNO}[SH][X^-] \quad (5)$$

confirm the expected dependence upon [SH], $[X^-]$ and $[H^+]$. The value of K_{XNO} is known[12] for ONSCN (30 dm^6 mol^{-2} at 25 °C) and values of K_a have been reported for both ECA[13] and DEM[14] (1.8×10^{-12} and 1.4×10^{-13} mol dm^{-3}, respectively).

$$HNO_2 + H^+ + X^- \rightleftharpoons XNO + H_2O \qquad K_{XNO}$$

$$SH \rightleftharpoons E \qquad K_E$$

$$E \rightleftharpoons E^- + H^+ \qquad K_a$$

$$E + XNO \xrightarrow{k^E} \text{Product}$$

$$E^- + XNO \xrightarrow{k^C} \text{Product}$$

Scheme 2

Table 4 Values of k^C and $k^E K_E$ for reactions of ECA and DEM with ONSCN

	k^C/dm^3 mol^{-1} s^{-1}	$k^E K_E$/dm^3 mol^{-1} s^{-1}
ECA	6.1 (±0.1) × 10^8	2.5 (±0.1) × 10^{-2}
DEM	5.4 (±0.8) × 10^9	1.4 (±0.1) × 10^{-1}
MN[a]	4.2 × 10^9	

[a] From ref. 3.

This enables values of $k^E K_E$ and k^C to be obtained from the slopes and intercepts, respectively, of Figs. 1 and 2. So we can obtain values of the rate constant for reaction of XNO with the enolate but since K_E is not known reliably for either substrate it is not possible to determine k^E values. Table 4 shows the results of such an analysis. For DEM the value of k^C is very close to that found earlier[3] for the reaction of the carbanion of MN which is believed to be at the diffusion limit. The somewhat lower value of k^C for ECA is consistent with the greater electron-withdrawing power of the CN group compared with the CO_2Et group. If the assumption is made that the *enol* form of DEM also reacts at the diffusion limit (which is probably not the case), then we can estimate a minimum value for K_E for DEM of *ca.* 2 × 10^{-11}. Bell and Yates[15] have reported an estimated K_E value of 6 × 10^{-7} for DEM based on the assumption[16] that the pK_a of the enol is in the range 8–10.

Other values of k^C for both ECA and DEM can be obtained from our results for ONSCN reactions (and also for reactions with BrNO) from the results given in Table 2 reporting the variation of k_0 with SCN^- and Br^-, if it is assumed that at these pH values (2.8 and 3.2) reactions occur entirely *via* the enolate. Inspection of Figs. 1 and 2 reveal that this is a reasonable assumption particularly for ECA. In this way we obtain values of 8.3 × 10^8 and 8.5 × 10^9 dm^3 mol^{-1} s^{-1}, respectively for ECA and DEM which are in reasonable agreement with the k^C values given in Table 4. A similar analysis gave values of 8.5 × 10^9 and 5.2 × 10^{11} dm^3 mol^{-1} s^{-1} for the BrNO reactions with the enolates derived from ECA and DEM respectively. This confirms for these substrates the now well-established[17] trend of reactivity BrNO > ONSCN. The value for DEM is of course a little above that expected for the diffusion limit. This is probably due to experimental error deriving from a small component of these reactions resulting in the spontaneous decomposition of HNO_2.

Thiourea catalysis also occurs (see Table 3), due to the formation and subsequent reaction of $ON\overset{+}{S}C(NH_2)_2$—now a familiar pathway. Analysis of the data, again assuming that at these very low acidities the reactive forms of the substrates are the enolates, yields values of k^C of 4.3 × 10^7 and 2.3 × 10^9 dm^3 mol^{-1} s^{-1}, respectively, for ECA and DEM. These results confirm (*a*) the greater reactivity of the enolate derived from DEM and (*b*) the reactivity trend of the nitrosating species BrNO > ONSCN > $ON\overset{+}{S}C(NH_2)_2$ except when values reach the diffusion limit as is apparent for all three reagents in reaction with the enolate from DEM, which makes this species along with the carbanion derived from MN[3] the most reactive of substrates in nitrosation reactions.

Conclusions

It is clear that both ECA and DEM react with electrophilic nitrosating agents *via* both their enol and enolate forms. A similar conclusion had earlier been reached for halogenation reactions of DEM.[18] As expected, a larger component of the reaction occurs *via* the enolate than the enol for the more acidic of the two substrates ECA. The enolate from DEM is the more reactive as expected from the relative electronic effects of the substituents, with all reactions with XNO species taking place at or near the diffusion limit.

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