Carbanion Nitrosation. Reaction of Malononitrile with Nitrous Acid

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Malononitrile reacts readily with nitrous acid in aqueous acid buffer solutions, particularly in the presence of nucleophilic catalysts X [$\mathrm{Br^-}$, $\mathrm{SCN^-}$, and $\mathrm{SC(NH_2)_2}$] to give the corresponding oxime product $\mathrm{C(CN)_2{=}NOH}$. In the absence of catalysts and also with $\mathrm{Cl^-}$ as catalyst, reaction is slow and competes with the spontaneous decomposition of nitrous acid. The rate equation at one acidity for the catalysed reaction is established as rate = $k_1[\mathrm{CH_2(CN)_2}][\mathrm{HNO_2}][\mathrm{X}]$, which suggests that reaction occurs by rate-limiting attack of the XNO species. In the pH range 2–4.5 the dependence of k_1 upon acidity varies from being approximately first order in $[\mathrm{H^+}]$ at low acidities to being approximately zero order in $[\mathrm{H^+}]$ at higher acidities. All the results are consistent with a mechanism involving a rate-limiting reaction between XNO and the carbanion $^-\mathrm{CH(CN)_2}$. Analysis of the kinetic results reveals that the second-order rate constants k_2 for this step are, respectively, 1.1×10^{10}, 4.2×10^9, and 5.0×10^9 dm^3 mol^{-1} s^{-1} (at 25 °C) for the BrNO, ONSCN, and $\mathrm{ON\overset{+}{S}C(NH_2)_2}$ reactions. Thus each of these nitrosating species appears to react at the diffusion-controlled limit. Comparison with literature values of other substrate nitrosations shows that this carbanion is the most reactive substrate studied in nitrosation. There are no other reported examples where (the less reactive) ONSCN and $\mathrm{ON\overset{+}{S}C(NH_2)_2}$ species react upon encounter. Reaction also occurs in aqueous acetic acid solutions, again at convenient rates only in the presence of catalysts X, *i.e.* involving reaction *via* XNO.

It is well known that compounds containing strongly electron-withdrawing groups (such as $>$C=O, $-\mathrm{NO_2}$, and $-$CN) readily undergo conventional aliphatic electrophilic reactions at carbon. Halogenation,[1] hydrogen-isotope exchange, nitrosation,[2] and racemisation are the most widely known reactions in this context. Carbonyl compounds react *via* the enol or enolate forms, and the mechanism is well understood, based on the pioneering work of Lapworth.[3] Either the formation of the enol or its subsequent reaction (conventional electrophilic addition to an alkene) can be the rate-limiting step, depending upon the reaction conditions and the structure of the carbonyl compound. The nitrosation of ketones *etc.*, although much used synthetically, has only recently been shown to be of the same mechanistic type.[4] In a similar way aliphatic nitro compounds react by electrophilic addition to the C=N function in the tautomeric nitronic acids. In this case however, the formation of the nitronic acid in acid solution is so slow as to make the reaction of little use in nitrosation. A better procedure[5] is to generate the nitronic acid by acidification of the nitronate anion formed by reaction of the nitro compound with base (possibly *via* the carbanion). The nitronic acid is sufficiently stable in solution, relative to the nitro tautomer, to enable addition reactions to be carried out. Bromo- and nitroso-nitroalkanes are conveniently prepared by this method. Nitrosation of some nitronic acids have recently been examined kinetically by this procedure.[6] Less is known mechanistically about the corresponding reactions of aliphatic nitriles. Halogenation occurs readily, since bromomalononitrile is easily made by the addition of bromine to an aqueous solution of malononitrile at room temperature [equation (1)]. Similarly some nitriles give oxime products when treated with nitrous acid in acid solution [equations (2) and (3)].[2] Most reported synthetic procedures for the nitrosation of nitriles involve reactions with alkyl nitrites in alcohol solvents under basic conditions. These reactions probably involve direct attack by the alkyl nitrite at the carbanion, but this has never been shown to be the case. We have concentrated in this work on acid solutions, since under basic conditions the kinetics are complicated by a competing hydrolysis reaction. The reactions of the alkyl cyanoacetates [equation (2)] could in principle occur *via* the enol form, but no such possibility exists for malononitrile [equation (3)], so we elected to examine its nitrosation mechanistically. Although enolisation is not possible, and the most likely intermediate is the carbanion, another possibility exists in the tautomeric ketenimine, *e.g.* HC(CN)=C=NH, which is claimed to exist.[7] A detailed kinetic study should distinguish between these alternatives.

$$\mathrm{CH_2(CN)_2 + Br_2 \longrightarrow CHBr(CN)_2 + HBr} \qquad (1)$$

$$\mathrm{NCCH_2CO_2R + HNO_2 \xrightarrow{H^+} NCC({=}NOH)CO_2R + H_2O} \qquad (2)$$

$$\mathrm{CH_2(CN)_2 + HNO_2 \xrightarrow{H^+} (CN)_2C{=}NOH + H_2O} \qquad (3)$$

Experimental

Malononitrile was purified by sublimation, dried in a vacuum desiccator and generally used within 24 h, otherwise the solid became yellow. Solutions of malononitrile in water were found to be unstable over a period of days, when a new absorbance appeared at 278 nm in the u.v. spectrum, probably due to a hydrolysis product. However, solutions in dilute perchloric acid and also in 50% aqueous acetic acid were stable over many days, and the u.v. spectrum remained unchanged. All other materials were of the highest purity grade available, and were used as such. The product $\mathrm{(CN)_2C{=}NOH}$ was isolated as follows. To malononitrile (0.45 g) in an acetic acid–acetate buffer at pH 3.3 was added slowly sodium nitrite (0.3 g). The solution became dark yellow very rapidly. After *ca.* 5 min no nitrous acid remained and a slight excess of silver nitrate was added as an aqueous solution. The yellow precipitate was filtered, washed, and dried. The same product was obtained in lower yield from nitrosation carried out in 50% aqueous acetic acid (Found: C,

Table 1. Value of k_{obs} for the nitrosation of $CH_2(CN)_2$ in 46.7% acetic acid–water as a function of $[CH_2(CN)_2]$ at constant $[Br^-]$ (0.42 mol dm^{-3}) and $[HNO_2]$ (1.3×10^{-3} mol dm^{-3})

$[CH_2(CN)_2]$/ mol dm^{-3}	$10^3k_{obs}/s^{-1}$
0.089	0.494
0.150	0.730
0.210	1.03
0.300	1.39
0.440	2.09
0.680	2.98

Table 2. Value of k_{obs} for the nitrosation of $CH_2(CN)_2$ in 46.7% acetic acid–water as a function of $[Br^-]$ at constant $[CH_2(CN)_2]$ (0.44 mol dm^{-3}) and $[HNO_2]$ (1.3×10^{-3} mol dm^{-3})

$[Br^-]$/ mol dm^{-3}	$10^3k_{obs}/s^{-1}$
0.083	0.458
0.120	0.629
0.170	0.888
0.250	1.34
0.420	2.09
0.580	2.84
0.830	4.00
1.08	5.59

Table 3. Value of k_{obs} for the nitrosation of $CH_2(CN)_2$ as a function of solvent composition: $[CH_2(CN_2]$ 0.44 mol dm^{-3}, $[Br^-]$ 0.51 mol dm^{-3}, and $[HNO_2]$ 1.0×10^{-3} mol dm^{-3}

% Acetic acid v/v	$10^3k_{obs}/s^{-1}$
13.5	0.77
23.7	1.30
37.3	2.00
47.4	2.57

18.3; N, 21.0; H, 0.0. Calc. for C_3AgN_3O: C, 17.8; N, 20.8; H, 0.0%). An attempt was made to obtain the pure oxime by dissolving the silver salt in nitric acid and extracting with ether. A pale yellow oil was obtained after solvent removal, which quickly became dark orange and later gave off nitrogen dioxide on standing. However, the u.v. spectrum in water was the same as that observed in the kinetic experiments, and approximate measurements of the extinction coefficient at 310 nm showed it to be pH dependent (no doubt due to protonation equilibria), increasing somewhat over the pH range 2–4.

Kinetic Measurements.—These were carried out at 25 °C in the cell of a recording spectrophotometer, noting the increasing absorbance at 310 nm due to the product. In the presence of Br^-, SCN^-, or $SC(NH_2)_2$ the reactions were quite rapid and the rate of decomposition of nitrous acid is negligible. Reactions were all carried out under first-order conditions with $[CH_2(CN)_2]_0 \gg [HNO_2]_0$. Typical reaction conditions were $[CH_2(CN)_2]_0$ 0.44 mol dm^{-3}, $[HNO_2]_0$ 3.3×10^{-3} mol dm^{-3}, $[Br^-]$ 0.12 mol dm^{-3}. Most experiments were carried out at constant ionic strength with pH buffers. Some experiments were also carried out in acetic acid–water solvents. Throughout, good first-order kinetic behaviour was found and values of the first-order rate constant k_{obs} was reproducible to within ±2%, for reactions followed to *ca.* 80% reaction.

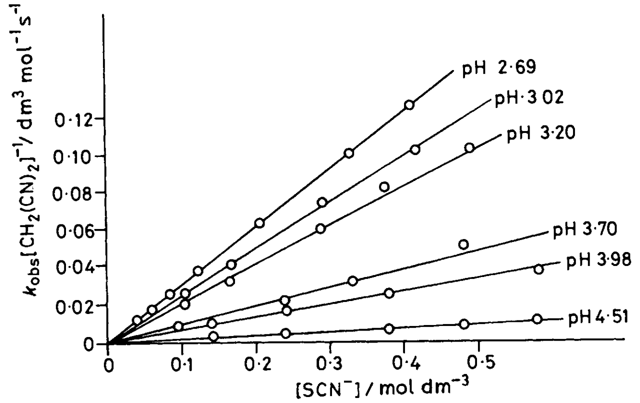

Figure 1. Thiocyanate catalysis for the nitrosation of malononitrile at different pH values in the range 2.69–4.51

Note added in proof.—Since the manuscript was prepared we became aware of a paper by Kresge and *et al.** who examined the kinetics of the bromination (and hydrogen exchange) of malononitrile. Under their conditions both the carbon acid ionisation and the bromination of the carbanion were partly rate-limiting. In the case of nitrosation, although the rate constants for nitrosation of the carbanion are in the diffusion-controlled region, the actual rate of nitrosation must be significantly less than the rate of reprotonation of the carbanion, since the actual concentration of XNO is much less than the stoicheiometric $[HNO_2]$. Strict first-order behaviour in $[HNO_2]$ was found throughout, so that in our experiments ionisation of malononitrile was not rate-limiting.

Results

We have confirmed an earlier report by Longo[8] that malononitrile undergoes nitrosation in dilute acid solution to give the dicyano oxime [equation (3)]. Although an accurate extinction coefficient has not been obtained, the indications are that the reaction is quantitative under the kinetic conditions employed.

Tables 1 and 2 show the results of reactions carried out in 46.7% v/v acetic acid–water, in the presence of bromide ion as catalyst. Plots of k_{obs} *versus* $[CH_2(CN)_2]$ and also of k_{obs} *versus* $[Br^-]$ are both excellent straight lines. The former plot shows a very small positive intercept on the y axis, suggesting that the reaction may be reversible. However, the extent is so small that we have ignored the effect. The plot of k_{obs} *versus* $[Br^-]$ has no measurable intercept at $[Br^-] = 0$, which indicates that the uncatalysed component of the reaction is indeed negligibly small. These data establish the rate equation (4). Values of k_1,

$$\text{Rate} = k_1[CH_2(CN)_2][HNO_2][Br^-] \qquad (4)$$

the third-order rate constant, from the two sets of results (Tables 1 and 2) are 1.02×10^{-2} and 1.13×10^{-2} dm^6 mol^{-2} s^{-1}, and are in very good agreement. The same rate equation has been established for reactions carried out in other acetic acid–water mixtures, and also for reactions in aqueous buffer solutions. The reaction is also first order in SCN^- and $SC(NH_2)_2$ when these are used as catalysts in place of Br^-. The solvent effect is shown for four different solvent compositions in Table 3. The measured rate constant k_{obs} increases a little with increasing percentage acetic acid in the solvent. This could be an acid catalysis effect, or perhaps in the light of later results, this may be a solvent medium effect.

The effect of acidity, and hence the question of possible reaction *via* the carbanion is best established by reaction in aqueous buffer solutions. We have examined the kinetics over

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* M. Hojatti, A. J. Kresge, and W.-H. Wang, *J. Am. Chem. Soc.*, 1987, **109**, 4023.

Table 4. Values of k_1 [equation (4)] in dm^6 mol^{-2} s^{-1} for the nitrosation of $CH_2(CN)_2$ in the presence of Br^-, SCN^-, and $SC(NH_2)_2$ as a function of pH

Br^{-a}		SCN^{-b}		$SC(NH_2)_2{}^c$	
pH	10^3k_1	pH	$10k_1$	pH	k_1
2.19*	2.13	2.69*	3.12	2.19*	68.8
2.48*	1.95	3.02*	2.62	2.65*	53.5
3.31	1.15	3.20*	2.15	3.20*	36.0
3.46	0.98	3.32	1.92	3.45	33.1
3.76	0.56	3.70	1.05	3.70	19.6
		3.98	0.63	4.07	8.80
		4.51	0.19	4.35	4.50

* Chloroacetic–chloroacetate buffers, the remainder are acetic acid–acetate buffers. [a] Ionic strength 1.2 ($NaClO_4$). [b] Ionic strength 1.1 ($NaClO_4$). [c] Ionic strength 0.71 ($NaClO_4$).

Table 5. Effect of buffer concentration on the thiourea-catalysed nitrosation of malononitrile at pH 4.35

$[CH_2(CN)_2]$/ mol dm^{-3}	[Acetic acid]/ mol dm^{-3}	k_{obs}/s^{-1}	$k_{obs}/[CH_2(CN)_2]$
0.73	1.97	1.51×10^{-3}	2.07×10^{-3}
0.44	0.70	8.61×10^{-4}	1.96×10^{-3}
0.24	0.43	5.11×10^{-4}	2.13×10^{-3}

$[HNO_2]$ 3.3×10^{-4} mol dm^{-3}, thiourea 3.75×10^{-4} mol dm^{-3}, ionic strength ($NaClO_4$) 0.71 mol dm^{-3}.

the pH range 2–4.5 using acetic acid–acetate and chloroacetic acid–chloroacetate buffers for each of the catalysts Br^-, SCN^-, and $SC(NH_2)_2$. The results are presented as the variation of k_{obs} with [catalyst] at each pH value, at constant ionic strength. A set of results for the thiocyanate catalysed reactions over the pH range 2.69–4.51 is shown in Figure 1. Similar plots were obtained for both bromide ion and thiourea catalysis, and the results are summarized in Table 4. The catalytic efficiency is clearly in the sequence $(NH_2)_2CS > SCN^- > Br^-$. This is a well known sequence, well established in nitrosation chemistry, and arises principally from the decreasing value of the equilibrium constant K_{XNO} for XNO formation along this series.[9] The acidity dependence of k_1 is shown in Figure 2 again for the thiocyanate-catalysed reactions, but similar plots were obtained for both of the other catalysed reactions. It is evident that at low acidity acid catalysis occurs, which disappears as $[H^+]$ is increased.

There is no kinetic effect arising from buffer catalysis as is clear from the results in Table 5 where $k_{obs}/[CH_2(CN)_2]$ values are constant within experimental error, for experiments carried out at constant pH, whilst varying the buffer ratio over about a five-fold range. These results refer to the thiourea-catalysed reactions at pH 4.35.

When working with nitrous acid solutions at pH > 2 it is important to allow for the nitrous acid ionisation to nitrite ion, in addition to the equilibrium formation of XNO. If we assume that reactions in the present system occur by rate-limiting attack of XNO on the carbanion species then the sequence of reactions is that laid out in the Scheme. The predicted rate equation from the Scheme is (5). In this equation k_2 is the

$$\text{Rate} = k_2K_aK_{XNO}[CH_2](CN)_2[X][HNO_2][H^+]/(K_N + [H^+]) \quad (5)$$

second-order rate constant for reaction of XNO with the carbanion, K_a is the dissociation constant of malononitrile, K_{XNO} the equilibrium constant for XNO formation, and K_N the dissociation constant of nitrous acid. The literature values[10–12] are K_a 4.1×10^{-12}, K_{BrNO} 5.1×10^{-2}, K_{ONSCN} 30, $K_{(NH_2)_2C\overset{+}{S}NO}$ 5 000, and K_N 7.1×10^{-4}. This leads to the expression for k_1 [equation (4)] in terms of the acidity given in equation (6). This

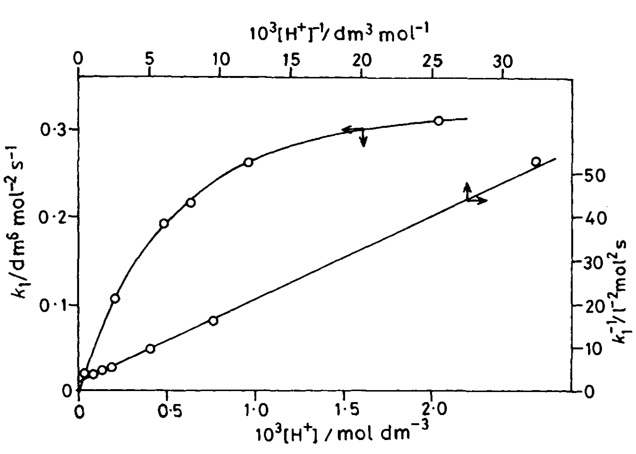

Figure 2. Acid catalysis and a double reciprocal plot for the thiocyanate catalysed nitrosation of malononitrile

$$HNO_2 \rightleftharpoons H^+ + NO_2^- \qquad K_N$$

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

$$CH_2(CN)_2 \rightleftharpoons {}^-CH(CN)_2 + H^+ \qquad K_a$$

$$XNO + {}^-CH(CN)_2 \xrightarrow{k_2} (CN)_2C{=}NOH + X^-$$

Scheme.

$$k_1 = k_2K_aK_{XNO}[H^+]/(K_N + [H^+]) \quad (6)$$

predicts acid catalysis at low acidity and no acid catalysis at high acidity. More quantitatively it is apparent that k_1^{-1} should be directly proportional to $[H^+]^{-1}$. Such a double reciprocal plot is also shown in Figure 2. Similar lines with positive slopes and positive intercepts were also obtained for the Br^- and $SC(NH_2)_2$ catalysed reactions. This implies that the mechanistic ideas are indeed correct. The slope:intercept ratio gives K_N which leads to three (for the three catalysts) values for the pK_a of nitrous acid of 3.26, 3.09, and 3.02 which are in good agreement with the literature value of 3.15. Further, this analysis enables values of k_2 to be obtained from the intercepts of the double reciprocal plots. These are 1.1×10^{10} (BrNO), 4.2×10^9 (ONSCN), and 5.0×10^9 $[(NH_2)_2CSNO]$ dm^3 mol^{-1} s^{-1}. All these values are very close to the calculated limiting value of 7.4×10^9 dm^3 mol^{-1} s^{-1} (at 25 °C) for an encounter- or diffusion-controlled process.

Discussion

The kinetic results clearly show that the reactive species in the nitrosation of malononitrile in dilute acid solution is the carbanion. As far as we are aware, this is the first time that nitrosation in acid solution of a carbanion has been positively established, although it seems likely that the reaction of alkyl nitrites in basic solution with ketones *etc.* probably also involve the corresponding carbanions. In a closely related system, the nitroprusside ion $[Fe(CN)_5NO]^{2-}$ (a carrier of NO^+) reacts in basic solution with some carbon acids to give coloured adducts.[13] In the case of malononitrile the kinetics suggest that in fact reaction occurs not with the singly charged, but with the

Table 6. Rate constants k_2/dm^3 mol^{-1} s^{-1} (Scheme) for nitrosation in water at 25 °C

Reagent	Aniline	4-Aminobenzoic acid	Acetylacetone enol	Malononitrile carbanion
BrNO	1.7×10^9	4.3×10^8	1.4×10^4	1.1×10^{10}
ONSCN	1.9×10^8	1.4×10^6	500	4.2×10^9
$ON\overset{+}{S}C(NH_2)_2$	1.3×10^6	1.8×10^4	38	5.0×10^9

doubly charged carbanion $(CN)_2C^{2-}$. In our work there is no evidence that the latter species is involved.

The carbanion from malononitrile is of course well known and is much used in organic syntheses. Reactions with electrophiles occur readily, including alkylation, acylation, and coupling reactions with diazonium ions. Halogenation also occurs readily and indeed the anion is present in sufficient concentration in aqueous solution to allow the reaction with bromine to proceed rapidly.[14] Kinetic measurements show that the reaction is first order in both reagents,[15] but as far as we are aware no acidity–rate profile has been established which would confirm the carbanion as the reactive species.

The general mechanistic features of nitrosation of the carbanion from malononitrile fit in well with the pattern now well established in nitrosation for reaction at N, O, S, and C sites. Nucleophilic catalysis is very pronounced, and is in the expected reactivity sequence. This work provides another example of the remarkable catalytic effect of thiourea. Since its discovery as a catalyst in amine nitrosation,[16] a number of studies have shown that it does have general applicability. It is likely that other carbanions could undergo nitrosation in this way, even in dilute acid solution, by the use of such a powerful catalyst. In this work thiourea is more effective than is thiocyanate by a factor of *ca.* 170, which is wholly attributable to the differences in K_{XNO} for ONSCN and $(NH_2)_2C\overset{+}{S}NO$. This is a larger factor than for the nitrosation of morpholine since in that case the k_2 values are different, as neither is at the diffusion-controlled limit.

Apart from the identification of the carbanion as the reactive species, the most interesting feature in this work is the fact that all three nitrosating agents appear to react at the diffusion limit. Rate constants in the region of 10^9 dm^3 mol^{-1} s^{-1} have been noted previously in nitrosation, notably for the reactions of both ClNO and BrNO with aromatic primary amines with pK_a > *ca.* 4,[17] and more recently for the reaction of the same two reagents with the enol forms of acetone and ethyl methyl ketone.[4] However, until the present results were obtained there is no report of reactions of either ONSCN or $(NH_2)_2C\overset{+}{S}NO$ taking place at the diffusion limit. Measurements with less reactive species have always shown the reactivity trend BrNO > ONSCN > $(NH_2)_2C\overset{+}{S}NO$. Some typical results are shown in Table 6 for reaction of these species with aniline,[9] 4-aminobenzoic acid,[9] and the enol from acetylacetone,[4] together with the present results for the malononitrile carbanion. Even for aniline, the most reactive substrate hitherto, the rate constant for reaction with ONSCN is *ca.* 10 times smaller than the limiting value, and for $(NH_2)_2C\overset{+}{S}NO$ the factor is *ca.* 10^3. This makes the malononitrile carbanion the most reactive substrate towards electrophilic nitrosation, at least as far as rate measurements reveal. This is perhaps not very surprising, given the fact that carbanions are amongst the most powerful of nucleophiles.

Finally it is worth stressing that all the kinetic evidence points to the carbanion as the reactive species and not the tautomeric form of the nitrile itself, *i.e.* the ketenimine HC(CN)=C=NH. If the reaction occurred by electrophilic addition to the latter species then the acidity dependence of the reaction would be quite different. In particular there would be no levelling off of the rate constant at higher acid concentration, *i.e.* when all the nitrite had been effectively protonated. Thus there is no direct analogy here between the reactions of carbonyl compounds and aliphatic nitriles.

Acknowledgements

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