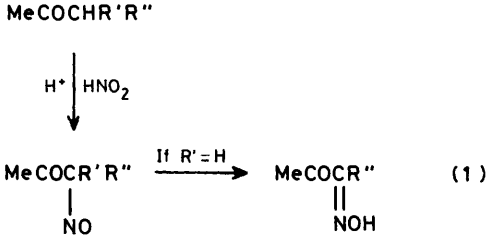
Nitrosation of Ketones: Clear Evidence for the Involvement of the Enol Tautomers

J. Ramón Leis,† M. Elena Peña,† D. Lyn H. Williams,* and, in part, Simon D. Mawson
Chemistry Department, University Science Laboratories, South Road, Durham DH1 3LE

Nitrosation of acetone and ethyl methyl ketone in the presence of a fairly high concentration of Cl^-, Br^-, or SCN^- is first-order in [ketone] and $[H^+]$ and zero-order in $[HNO_2]$ and $[Cl^-]$, $[Br^-]$, and $[SCN^-]$. This demonstrates that reaction occurs by nitrosation of the enol form of the ketone, and that under these conditions, enolisation is rate-limiting. The measured rate constant for enolisation in the nitrosation experiments is in excellent agreement with that obtained earlier for halogenation and for hydrogen-exchange reactions. The same behaviour occurs with 1,3-dichloroacetone, except that here the enolisation is not acid-catalysed — again this agrees with the bromination work. With lower concentrations of added nucleophiles, for all four ketones, the rate equation includes terms first-order in $[HNO_2]$ and also in $[Cl^-]$ or $[Br^-]$, showing that the reaction of the enol with the nitrosating species is now rate-limiting. There is a very close analogy with the kinetic behaviour found in the halogenation of ketones. Analysis of the kinetic data reveals the reactivity sequence NOCl > NOBr > NOSCN (well known in *N*-nitrosation), and the reactivity of the enols is as expected for electrophilic addition. With acetylacetone, the rate-limiting step is always the reaction of the enol, due in part to the lower reactivity of the enol. In the absence of added nucleophiles, both acetone and ethyl methyl ketone react with N_2O_3, whereas the less-reactive 1,3-dichloroacetone and acetylacetone react preferentially with $H_2NO_2^+$ or NO^+ — a similar trend occurs in *N*-nitrosation of amines.

It has long been known that ketones react with a variety of nitrosating agents to give nitroso ketones or keto oximes, depending on whether the substituted group is a primary or secondary structure [see equation (1)]. The reaction is quite

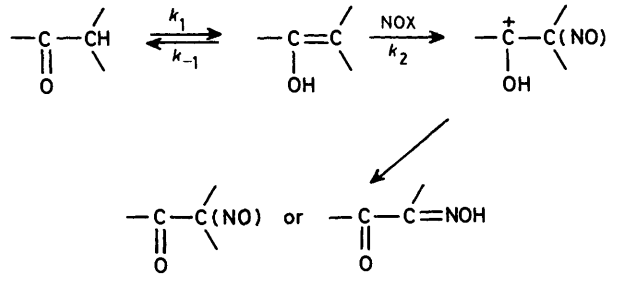


(1)

general, not only for simple ketones, but also for other carbonyl-containing compounds such as β-keto acids, β-keto esters, malonic acids and esters, and arylacetic acids and esters. Aliphatic nitro compounds react similarly to give nitro-nitroso (pseudonitrole) or nitro-oxime (nitrolic acid) products. Reaction occurs quite readily at room temperature using nitrous acid, alkyl nitrites, nitrosyl halides, or dinitrogen trioxide. In the case of alkyl nitrites reaction occurs both in acid and alkaline solution. There is a comprehensive account[1] of these reactions which covers the literature up to 1953. However, although these reactions are so well known, and have been and continue to be much used synthetically, very little indeed is known of the reaction mechanisms. This situation contrasts markedly with *N*-nitrosation (and also to a lesser extent with *O*- and *S*-nitrosation), where much effort has been successfully directed at establishing the details of the various reaction pathways. The results of a number of kinetic studies have been particularly useful in this context.

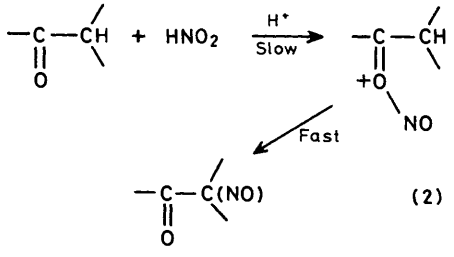
† *Permanent address:* Departmento de Quimica, Fisica, Facultad de Quimica, Universidad de Santiago, Santiago de Compostela, Spain.

The obvious expectation is that nitrosation of ketones occurs by an electrophilic addition to the enol form of the ketone. This is by analogy with other reactions of ketones with electrophilic species, notably in halogenation and hydrogen-atom exchange reactions, where reaction of the enol form has been well established.[2] The corresponding mechanism for nitrosation is outlined in the Scheme. This has been proposed as a likely



Scheme.

sequence[3] but there is in act no experimental evidence in its favour. Indeed the results of the only published account[4] of the kinetics of nitrosation of ketones indicate otherwise. It has been claimed that the rate of nitrosation of acetone (using nitrous acid) is faster than the enolisation rate (under the same conditions) by a factor of *ca.* 7. These authors[4] proposed an alternative mechanism [equation (2)], whereby



(2)

Table 1. Variation of k_0 with $[Me_2CO]$ for the nitrosation of Me_2CO[a]

$[Me_2CO]$/M	$10^5\ k_0$/mol l^{-1} s^{-1}
0.389	0.494
0.583	0.720
0.777	0.942
0.971	1.17
1.166	1.37
1.360	1.74

[a] $[Br^-]$ = 0.634M, $[H^+]$ = 0.317M, $[HNO_2]$ = 7.3 × 10^{-3}M; ionic strength = 2M ($NaClO_4$)

Table 2. Variation of k_0 with $[H^+]$ for the nitrosation of Me_2CO[a]

$[H^+]$/M	$10^5\ k_0$/mol l^{-1} s^{-1}
0.073	0.400
0.153	0.815
0.234	1.27
0.314	1.64
0.394	2.04

[a] $[Br^-]$ = 0.634M, $[Me_2CO]$ = 1.36M, $[HNO_2]$ = 7.3 × 10^{-3}M; ionic strength = 2M ($NaClO_4$).

electrophilic nitrosation occurs at the carbonyl oxygen atom, and that this is followed by a rapid internal rearrangement of the nitroso group to an adjacent carbon atom. More recently[5] it has been claimed that 'it is reasonable to assume that the reaction involves electrophilic attack of the nitrosating species on the double bond of the enol present in equilibrium'; such a scheme was the basis of an explanation of the rather unusual products obtained by the nitrosation of cyclohexanone in liquid sulphur dioxide, in the presence of alcohols and hydrogen chloride.

It seemed to us that a large gap exists in our understanding of the mechanism of aliphatic (and alicyclic) *C*-nitrosation, and we have set out to attempt to establish various mechanistic features. It is clearly important to resolve the uncertainty regarding the involvement, or otherwise, of the enol tautomers of ketones. A further point of interest is the question of whether nucleophilic catalysis (by halide ion, thiocyanate ion *etc.*), which is common in *N*-nitrosation of amines, also occurs in aliphatic *C*-nitrosation. Additionally it was hoped to establish gross structure–reactivity patterns. We chose initially to examine the kinetics of the four ketones, acetone, (Ac), ethyl methyl ketone (EMK), 1,3-dichloroacetone (DCA), and acetylacetone (AcAc) (pentane-2,4-dione); typical substrates showing a range of structural features and a large range in the keto ⇄ enol equilibrium constant. Our results are presented in this paper; some of the conclusions have been given in an earlier preliminary communication.[6]

Results

(a) *Reactions in the Presence of Added Nucleophiles.*—(i) *Acetone* (Ac) *and ethyl methyl ketone* (EMK). In the presence of quite high bromide ion concentrations (~0.5M) the nitrosation of both Ac and EMK in acid solution with [ketone] ≫ $[HNO_2]$ gave perfectly linear absorbance–time plots (at 385 nm where HNO_2 absorbs) up to at least 80%, showing zero-order kinetics. Under these conditions the product is the keto oxime, which is formed in quantitative yield for both ketones. The variation of the observed zero-order rate constant (k_0) with both [ketone] and $[H^+]$ are shown in Tables 1 and 2 for Ac. Similar behaviour was found for EMK. Plots of k_0 *vs.* [ketone] at constant $[H^+]$,

Table 3. Values of k_e [equation (3)] from the nitrosation of EMK at various $[Br^-]$ and $[SCN^-]$[a]

$[Br^-]$/M	$10^5\ k_e$/l mol^{-1} s^{-1}
0.211	4.9
0.317	4.5
0.423	4.7
0.634	4.9
5.1 × 10^{-2}M SCN^-	4.4

[a] $[H^+]$ = 0.401M, [EMK] = 0.717M, $[HNO_2]$ = 7.33 × 10^{-3}M; ionic strength = 2M ($NaClO_4$)

Table 4. Dependence upon $[Cl^-]$ in the nitrosation of Me_2CO, when the reaction is first-order in $[HNO_2]$[a]

10^2 $[Cl^-]$/M	$10^4\ k_{obs}/s^{-1}$
2.09	1.82
3.48	3.42
4.87	4.08
6.26	6.53

[a] $[H^+]$ = 0.400M, $[Me_2CO]$ = 2.50M, $[HNO_2]$ = 1.95 × 10^{-3}M; ionic strength = 2M ($NaClO_4$).

and of k_0 *vs.* $[H^+]$ at constant [ketone] are linear for both ketones thus establishing rate equation (3). For Ac the two values

$$\text{Rate} = k_e[H^+][\text{Ketone}] \quad (3)$$

of k_e obtained in this way were 3.90 × 10^{-5} l mol^{-1} s^{-1} and 3.76 × 10^{-5} l mol^{-1} s^{-1}. Similar values were obtained at other $[Br^-]$. The corresponding values for EMK were 4.8 × 10^{-5} and 5.1 × 10^{-5} l mol^{-1} s^{-1}. The clear explanation is that under these experimental conditions nitrosation takes place *via* the enol form, and that the enolisation reaction is rate-limiting. Values of k_e (the enolisation rate constant) are independent of the concentration of $[Br^-]$ and of $[SCN^-]$ at these quite high concentrations as shown in Table 3 for the reactions of EMK.

For both ketones the k_e values determined in this way agree reasonably well with those obtained earlier (2.8 × 10^{-5} l mol^{-1} s^{-1} for Ac and 4.8 × 10^{-5} l mol^{-1} s^{-1} for EMK) from the kinetics of halogenation[7] and of hydrogen-isotope exchange,[8] all in aqueous acid solution at 25 °C.

At much lower halide ion concentration the kinetic pattern is changed. For both chloride ion (2—6 × 10^{-2}M for Ac and 2 × 10^{-3}—2 × 10^{-2}M for EMK), and bromide ion (4—7 × 10^{-3}M for Ac and 4 × 10^{-4}—2 × 10^{-3}M for EMK) the rate equation now contains two terms, the first is first-order in $[HNO_2]$ and also first-order in $[Cl^-]$ or $[Br^-]$, and the second is second-order in $[HNO_2]$ [see equation (4)]. The second term

$$\text{Rate} = k_4[\text{Ketone}][NO_2][H^+][Cl^-] + k_3[\text{Ketone}][HNO_2]^2 \quad (4)$$

clearly represents reaction *via* dinitrogen trioxide N_2O_3 and will be dealt with more fully in part (b) of this discussion. The obvious mechanistic explanation of the first term in equation (4) is that under these conditions the rate-limiting step is now the attack of the nitrosating species NOX on the enol form. This occurs when (in the Scheme) $k_2[NOX] \ll k_{-1}$ *i.e.* when the concentration of NOX is reduced by the reduction in $[X^-]$ (Cl^- or Br^-). The kinetic $[Cl^-]$ and $[Br^-]$ dependence is shown in Tables 4 and 5 for Ac and EMK respectively. The reactions are necessarily slower than those at higher $[Br^-]$, and some of the rate measurements (particularly for EMK as in Table 5) were determined by the initial-rate method. Thiocyanate catalysis also occurs, the data for EMK are in Table 6.

Table 5. Dependence upon $[Br^-]$ in the nitrosation of EMK when the reaction is first-order in $[HNO_2]$[a]

10^3 $[Br^-]$/M	10^8 Rate/mol l^{-1} s^{-1}
0	0.10
0.37	0.612
0.74	0.825
1.11	1.19
1.48	1.50
1.85	1.86
2.22	2.02

[a] $[H^+]$ = 0.562M, [EMK] = 5.58 × 10^{-3}M, $[HNO_2]$ = 2.69 × 10^{-3}M; ionic strength = 2M ($NaClO_4$).

Table 6. Thiocyanate catalysis in the nitrosation of EMK[a]

10^4 $[SCN^-]$/M	10^8 Rate/mol l^{-1} s^{-1}
0	0.40
3.0	4.77
6.0	6.30
9.0	7.40
12.0	7.70

[a] $[H^+]$ = 0.141M, [EMK] = 1.67 × 10^{-2}M, $[HNO_2]$ = 2.69 × 10^{-3}M; ionic strength = 2M ($NaClO_4$).

Table 7. Values of k_2 for the reaction of NOCl, NOBr and NOSCN with the enol of Ac and EMK

	k_2(l mol^{-1} s^{-1})	
Nitrosating agent	Ac	EMK
NOCl	1.4 × 10^8[a]	4.6 × 10^9
	1.5 × 10^9[b]	
NOBr	7.0 × 10^7[a]	3.8 × 10^9
	7.4 × 10^8[b]	
NOSCN	—	~3.0 × 10^8

[a] Using pK_E = 7.2. [b] Using pK_E = 8.22.

From the slopes of the observed first-order rate constant or the initial rate *vs.* $[Cl^-]$, $[Br^-]$, or $[SCN^-]$ it is possible to obtain a value for k_2, the rate constant for attack by NOX. The full equation is given in equation (5). This assumes that the

$$\text{Rate} = k_2K_EK_{NOX}[H^+][X^-][HNO_2][\text{Ketone}] \quad (5)$$

extent of enol formation is very small and the equilibrium constant for enolisation is K_E (= k_1/k_{-1} in the Scheme). We have taken the published values[9] for K_{NOX} (1.1 × 10^{-3} l^2 mol^{-2} and 5.1 × 10^{-2} l^2 mol^{-2} for NOCl and NOBr respectively at 25 °C). There is more of a problem with the K_E values. For both Ac and EMK K_E is very small. A number of different approaches have been used (which are basically either kinetic or thermochemical), most of which rely on some assumption. Consequently a range of values exists in the literature[10,11] for K_E typically from 2.5 × 10^{-6}—1.6 × 10^{-9} for Ac. We will use two recently determined values for Ac, one determined by Guthrie[10] (K_E = 6.3 × 10^{-8}) and one by Kresge and co-workers[11] (K_E = 6.0 × 10^{-9}). Both refer to the enolisation in water at 25 °C. The latter value has the merit of having been determined by a direct method, requiring no numerical assumptions. For EMK we use the most recent value published by Guthrie[12] (K_E = 5 × 10^{-9}). The kinetic analysis leads to values of k_2 shown in Table 7. The situation for SCN^- catalysis is a little more complex than that for Cl^- and Br^- in that over the range studied k_o *vs.* $[SCN^-]$ is not linear, but tends to level off at the higher $[SCN^-]$. This suggests

Table 8. Cl^-, Br^- and SCN^- catalysis in the nitrosation of AcAc. $[H^+]$ = 0.138M, [AcAc] = 0.0487M, $[HNO_2]$ = 2.1 × 10^{-3}M. Ionic strength = 0.5M ($NaClO_4$)

Cl^-/M	k_{obs}/s^{-1}	Br^-/M	k_{obs}/s^{-1}	SCN^-/M	k_{obs}/s^{-1}
0.0	0.0397	0.0	0.0397	0.0	0.0397
0.0487	0.0512	0.0218	0.0717	1.0 × 10^{-3}	0.0572
0.146	0.0573	0.0654	0.0970	3.0 × 10^{-3}	0.0995
0.244	0.0703	0.109	0.128	5.0 × 10^{-3}	0.130
0.341	0.0833	0.153	0.176	7.0 × 10^{-3}	0.170
0.414	0.0942	0.218	0.224	1.0 × 10^{-2}	0.208

Table 9. Thiourea (TU) catalysis in the nitrosation of AcAc[a]

10^3 [TU]/M	k_{obs}/s^{-1}	$k_{obs}(1 + K_{NOTU}[H^+][TU])$
0.378	0.071	0.078
0.945	0.136	0.165
1.70	0.180	0.255
2.27	0.223	0.340
2.83	0.266	0.442

[a] $[H^+]$ = 0.467M, [AcAc] = 0.0974M, $[HNO_2]$ = 2.1 × 10^{-3}M; ionic strength = 0.5M ($NaClO_4$).

that neither enolisation nor reaction of the enol is fully rate-limiting, but that an intermediate situation prevails. An analysis in these terms involving a double reciprocal plot yields a values of ~3.0 × 10^8 l mol^{-1} s^{-1} for k_2 for the reaction of NOSCN (using K_{NOSCN} = 30 l^2 mol^{-2}), and also a value of 4.2 × 10^{-5} l mol^{-1} s^{-1} for k_e [equation (3)] which agrees well with the earlier values obtained from the zero-order experiments.

(ii) *Acetylacetone* (AcAc). For the nitrosation of AcAc, even in the presence of high nucleophile catalyst concentrations, the reactions were always kinetically first-order in $[HNO_2]$, as well as being first-order in [AcAc], $[H^+]$, and [nucleophile catalyst]. The experimental results for Cl^-, Br^-, SCN^-, and $SC(NH_2)_2$ catalysis are given in Table 8 and 9. The rate constants were all obtained by stopped-flow spectrophotometry. For Cl^-, Br^- and SCN^- plots of the observed first-order rate constants k_{obs} (with [AcAc] ≫ $[HNO_2]$) against [nucleophile] were all linear with a small positive intercept representing the uncatalysed reaction. From the slopes, rate constants (k_2) for attack of the enol by NOCl, NOBr and NOSCN were readily obtained as 1.02 × 10^5, 1.44 × 10^4, and 500 l mol^{-1} s^{-1} respectively. For thiourea the corresponding plot was not linear. This arises because a substantial fraction of the stoicheiometric nitrous acid concentration is now tied up as the *S*-nitrosothiourea derivative, because of the large equilibrium constant for the *S*-nitrosation.[13] To allow for this it is necessary to multiply k_{obs} by $(1 + K_{NOTU}[H^+][TU])$ where K_{NOTU} is the equilibrium constant for the formation of the *S*-nitrosothiourea species, and [TU] is the thiourea concentration. This 'corrected' value is now a linear function of [TU] and the rate constant for nitrosation of the enol by the *S*-nitrosothiourea species is determined as 38 l mol^{-1} s^{-1}. For AcAc we have no direct evidence that reaction occurs *via* the enol form, since we are unable to obtain the rate-limiting enolisation form. However this is likely to be the case, by analogy with Ac, EMK, and 1,3-dichloroacetone (see later). There is no problem in measuring K_E for AcAc since the value is many orders of magnitude greater than it is for Ac and EMK, and we have used K_E = 0.2.[14]

(iii) 1,3-*Dichloroacetone* (DCA). This ketone behaved kinetically much like Ac and EMK, in that when high concentrations of *e.g.* bromide ion are present, then reaction is zero-order in $[HNO_2]$ and enolisation is rate-limiting. There is one significant difference however, in that initially there is a faster reaction which occurs (for *ca.* 20% reaction under our conditions), which

is not zero-order in $[HNO_2]$. This probably corresponds to the reaction of the enol content, already present in the system. From the amount of nitrous acid consumed initially in this way we can estimate K_E to be 3.2×10^{-3}. This compares with the value of 1×10^{-2} estimated by Guthrie,[12] who used a method using rate–equilibrium correlations. Under these conditions that part of the reaction which is zero-order in $[HNO_2]$ (the bulk of the reaction), is also as expected first-order in [DCA], but, unusually, is not acid-catalysed. Rate data giving the zero-order rate constant at different acidities are shown in Table 10. The first-order rate constant for enolisation (k_e in Rate = k_e[DCA]) has an average value of $3.2 (\pm 0.1) \times 10^{-6}$ s^{-1}, which agrees very well with the value of 3.2×10^{-6} s^{-1} found by Bell and Harisson[15] from bromination kinetics. These authors also found that enolisation is not acid-catalysed; the mechanism is believed to involve proton abstraction by a water molecule from the non-protonated form of the ketone. The protons are, of course, much more acidic than are those in acetone. As expected the observed rate constant under these conditions is independent of the bromide ion concentration in the range 0.1—0.6M, giving an average value again of $3.2 (\pm 0.1) \times 10^{-6}$ s^{-1} for k_e.

At much lower nucleophile concentrations (for both Cl^- and Br^-) the reaction order in $[HNO_2]$ changes from 0 towards 1. It was not possible under our conditions to change completely to the pure first-order situation. However, the data analysed well for a mixed zero-(k_0) and first-(k_1) order reaction, where neither enolisation nor nitrosation of the enol is fully rate-limiting. This analysis was used successfully for a number of different halide ion concentrations. We have used equation (6) for this analysis, which is that deduced by Dubois *et al.*[16] for an analogous situation (intermediate order) encountered in the iodination of carbonyl compounds. We always used [DCA] ≫ $[HNO_2]$ in these experiments and k_0 is the zero-order rate constant and k_1 the first-order rate constant at any one acidity. From the experiments with varying $[Cl^-]$ this procedure gives an average value for k_e of 3.1×10^{-6} s^{-1} and similarly a value of 3.1×10^{-6} s^{-1} from experiments at different $[Br^-]$, in good agreement with earlier values. This analysis also gave values of 1.2×10^4 and 2.8×10^3 l mol^{-1} s^{-1} for the second-order rate constant (k_2) for the attack of NOCl and NOBr respectively at the enol of DCA. These values are based on the Guthrie value[12] for K_E; using our measured K_E value, the corresponding rate constants are 3.8×10^4 and 8.8×10^3 l mol^{-1} s^{-1}, *i.e.* they are greater by a factor of *ca.* 3.

$$\frac{t' - t}{[HNO_2]_t - [HNO_2]_{t'}} = \frac{1}{k_0} + \frac{1}{k_1} \frac{\ln ([HNO_2]_t/[HNO_2]_{t'})}{[HNO_2]_t - [HNO_2]_{t'}} \quad (6)$$

Table 10. Influence of acidity on the nitrosation of DCA under zero-order conditions[a]

$[H^+]$/M	$10^6 k_0$/mol l^{-1} s^{-1}
0.161	1.11
0.241	0.97
0.321	1.15
0.482	1.14
0.642	1.10
0.987	1.30
Average value	1.13

[a] [DCA] = 0.359M, $[Br^-]$ = 0.634M, $[HNO_2] = 3.3 \times 10^{-3}$M; ionic strength = 1.3M ($NaClO_4$).

(b) *Reactions without Added Nucleophile Catalysts.*—For all four ketones studied, nitrosation also occurs without added nucleophiles, but at a much slower rate. In some cases this results in complications arising from hydrolysis of the oxime product, a reaction which also yields hydroxylamine which consumes nitrous acid. This is particularly true for the reactions of Ac and EMK. Under these conditions the kinetic results are complex and do not fit simple rate equations or even simple combinations of these equations. The yield of the oxime product was measured as a function of time for the reaction of EMK. The value increased initially approximately as expected for a first-order process, but then levelled off at *ca.* 65% and thereafter fell away.

This problem was avoided in the case of the EMK reactions by using the initial-rate method for the kinetic measurements. The rate was found to be proportional to $[HNO_2]^2$ and not to $[HNO_2]$, as is shown clearly in the Figure. This is readily interpreted as a nitrosation reaction involving dinitrogen trioxide N_2O_3 as the effective reagent. From the data in the Figure and also from the observed linear dependence of the rate upon [EMK], it is clear that the rate-limiting step is the attack by N_2O_3 rather than its formation. It is likely, by comparison with the earlier results with added nucleophiles, that the enol form is again the reactive entity, although we are not able to obtain conditions where the enolisation is rate-limiting. Using the most recent value[17] for the equilibrium constant for N_2O_3 formation (3.0×10^{-3} l mol^{-1} at 25 °C) and the published value[12] for K_E, we can deduce the second-order rate constant for attack by N_2O_3 ($k_{N_2O_3}$) as 2.7×10^9 l mol^{-1} s^{-1} from the data in the Figure, and as 3.3×10^9 l mol^{-1} s^{-1} from the variation of the rate with [EMK]. Further values of 2.2×10^9 and 2.2×10^9 l mol^{-1} s^{-1} were also obtained from the intercepts

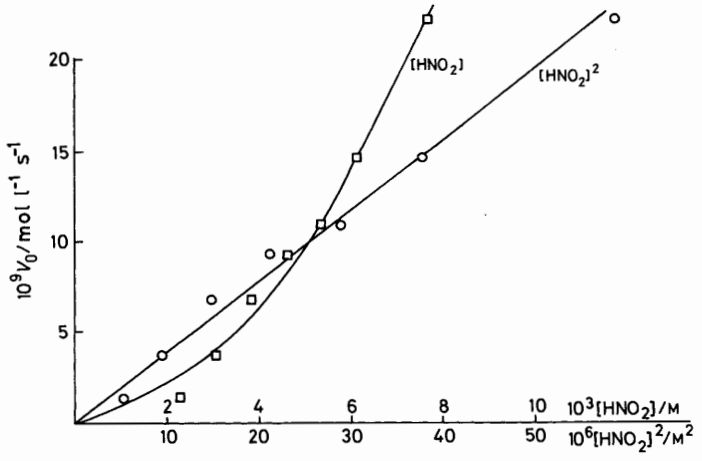


Figure. Rate dependence upon $[HNO_2]$ and $[HNO_2]^2$ in the nitrosation of EMK with no added nucleophilic catalysts

of the plots of rate constants *vs.* $[Cl^-]$ and $[Br^-]$ from the results in (a).

A different approach was used for the reactions of Ac. Small amounts of Cl^- and Br^- catalysts were used and the kinetic results satisfactorily analysed in terms of a mixed-order rate equation [equation (7)], again with [ketone] ≫ $[HNO_2]$ and

$$\text{Rate} = k_1^1[HNO_2] + k_2^1[HNO_2]^2 \qquad (7)$$

at constant acidity. To obtain k_1^1 and k_2^1 we used the integrated form of (7) given in equation (8) and determined the integral

$$\frac{1}{t}\ln\frac{[HNO_2]_0}{[HNO_2]_t} = k_1^1 + k_2^1\int_0^t [HNO_2]\,dt \qquad (8)$$

graphically. Consistent results were obtained yielding values for $k_{N_2O_3}$ of 1.4×10^9 l mol^{-1} s^{-1} and 1.0×10^9 l mol^{-1} s^{-1} from experiments in the presence of low concentrations of Cl^- and Br^- respectively. In one experiment with very low $[Cl^-]$ ($\sim 1 \times 10^{-2}$M), catalysis by Cl^- was negligible and the absorbance–time data fitted exactly a second-order rate equation when a plot of $(A_t - A_\infty)^{-1}$ *vs.* t is linear with a positive slope and intercept.

The AcAc reactions in the absence of added nucleophiles were all simple first-order reactions in each of $[HNO_2]$, [AcAc] and $[H^+]$. This is consistent with nitrosation *via* $H_2NO_2^+$ or NO^+. We shall refer to this as the NO^+ reaction, though no distinction is intended. If K_{NO^+} is the equilibrium constant for NO^+ formation and k_{NO^+} the second-order rate constant for its reaction with the enol of AcAc then we obtain values of 38.7 and 33.2 l^2 mol^{-2} s^{-1} for the product $K_{NO^+}k_{NO^+}$, from the acidity and ketone dependence respectively. Again it appears, as for the catalysed reaction discussed in (a), that the reaction of the enol is not sufficiently fast to make enolisation rate-limiting. Data from (a) also yield values of $K_{NO^+}k_{NO^+}$ (from the intercepts of rate constant–[nucleophile] plots) of 37, 40, and 38 l^2 mol^{-2} s^{-1}, from the Cl^-, Br^-, and SCN^- plots. The reaction of AcAc was also examined under conditions where the initial concentrations of AcAc and HNO_2 were the same. Rate measurements were obtained both for the disappearance of HNO_2 (at 385 nm) and for the appearance of the oxime product (at 330 nm). In both cases good linear second-order plots were obtained resulting in values of 39 and 36 l^2 mol^{-2} s^{-1} respectively for the product $K_{NO^+}k_{NO^+}$.

Reactions of DCA with nitrous acid in the absence of added nucleophiles also showed a clear first-order dependence upon $[HNO_2]$, indicating that here the nitrosating agent is again $H_2NO_2^+$ or NO^+. Values of $K_{NO^+}k_{NO^+}$ of 2.4 l^2 mol^{-2} s^{-1} (using the Guthrie value for K_E[12]) or of 7.5 l^2 mol^{-2} s^{-1} (using our own K_E value) were obtained. Similar values were obtained from the intercepts of the plots involving Cl^- and Br^- catalysis.

Discussion

The kinetic results show quite clearly for Ac, EMK, and DCA that nitrosation reactions occur *via* their enol forms. Thus nitrosation follows the same pattern as that shown by many other ketone reactions, halogenation, hydrogen-isotope exchange, racemisation, and for a number of oxidation reactions, all usually in acid solution. In all three cases it is possible to arrange the experimental conditions such that the enolisation is rate-limiting. Further, the rate constants k_e thus obtained for the enolisation process agree very well with those in the literature derived from other reactions of ketones, notably halogenation, hydrogen-isotope exchange, and racemisation. These latter reactions have been extensively studied since the pioneering work of Lapworth,[18] who first identified this mechanism. In nitrosation, the limiting conditions of rate-limiting enolisation can only be achieved (for these three ketones) at relatively high concentrations of Cl^-, Br^-, or SCN^- which makes the nitrosation reaction of the enol (*via* NOCl, NOBr, and NOSCN respectively) substantially faster than the enol ⟶ ketone reaction. For AcAc we have not been able to achieve this limit experimentally. This is due in part to the much reduced reactivity of the enol of AcAc compared with that of Ac, which results from the presence of the additional electron-withdrawing COMe group.

The claim by Singer and Vamplew[4] that the rate of nitrosation of acetone is faster than its enolisation by a factor of *ca.* 7 is in fact erroneous. These authors established equation (9) for nitrosation and compared the rate coefficient 2.1×10^{-4} with 2.8×10^{-5} from the enolsation rate equation [equation (10)].

$$\text{Nitrosation rate} = 2.1 \times 10^{-4}[Ac][HNO_2][H^+] \qquad (9)$$

$$\text{Enolisation rate} = 2.8 \times 10^{-5}[Ac][H^+] \qquad (10)$$

This procedure in fact compares a third-order rate coefficient with a second-order one. The correct rate ratio nitrosation: enolisation should in fact be $2.1 \times 10^{-4}[HNO_2]$:$2.8 \times 10^{-5}$. Since $[HNO_2]$ used was $\sim 2 \times 10^{-3}$M, this ratio is in fact ~0.015 and not ~7.

Table 11 gives the average values of all the rate constants obtained for the nitrosation of the four ketones effected by the various reagents NOCl, NOBr, NOSCN, $\overset{+}{O}NSC(NH_2)_2$, N_2O_3, and $H_2\overset{+}{N}O_2/NO^+$ as well as the rate constants for enolisation for three of the four ketones. For the nucleophile-catalysed reactions a number of points emerge. For any one substrate, the reactivity sequence is clear NOCl > NOBr > NOSCN > $\overset{+}{O}NSC(NH_2)_2$. This is the expected sequence, and has been observed many times in *N*-nitrosation of amines and also in *O*- and *S*-nitrosation of alcohols and thiols,[19] and also more recently in the *C*-nitrosation of 2-naphthol.[20] For each nitrosating agent the enol reactivity trend is EMK ~ Ac > AcAc > DCA. This is exactly the order expected for an electrophilic addition to alkenes, given the electron-withdrawing

Table 11. Average values of the derived rate constants (l mol^{-1} s^{-1} except where stated)

Reactant	k_e	k_{NOCl}	k_{NOBr}	k_{NOSCN}	k_{TU}	$k_{N_2O_3}$	$K_{NO^+}k_{NO^+}$
Acetone	3.8×10^{-5}	1.4×10^8 [a]	7.0×10^7 [a]	—	—	1.2×10^9 [a]	—
		1.5×10^9 [b]	7.4×10^8 [b]			1.3×10^{10} [b]	—
Ethyl methyl ketone	4.9×10^{-5}	4.6×10^9	3.8×10^9	3.0×10^8	—	2.5×10^9	—
Acetylacetone	—	1.0×10^5	1.4×10^4	500	38	—	36 l^2 mol^{-2} s^{-1}
1,3-Dichloroacetone	3.2×10^{-6} s^{-1}	1.2×10^4 [c]	2.8×10^3 [c]	—	—	—	2.4 [c] l^2 mol^{-2} s^{-1}
		3.8×10^4 [d]	8.8×10^3 [d]				7.5 [d] l^2 mol^{-2} s^{-1}

[a] Using $K_E = 6.3 \times 10^{-8}$. [b] Using $K_E = 6.0 \times 10^{-9}$. [c] Using $K_E = 1.0 \times 10^{-2}$. [d] Using $K_E = 3.2 \times 10^{-3}$.

properties of COMe and also of Cl and CH_2Cl. It is not possible with our data to distinguish clearly between the reactivities of Ac and EMK, for although we would expect the latter to be the more reactive (and this is borne out by most of the data in Table 11), the considerable uncertainty in the K_E values is reflected also in our derived rate constant data. The values of the bimolecular rate constants for the reactions of EMK with NOCl, NOBr, and N_2O_3 and of Ac with NOCl and N_2O_3 are all very close to the value expected for a diffusion-controlled process.[21] This reflects the considerable activating effect of the OH substituent in the enols.

For the nitrosation reactions carried out in the absence of added nucleophilic catalysts, our kinetic results show quite clearly that over the acid range studied (0.1—0.5M) both Ac and EMK react with dinitrogen trioxide, whilst the less reactive AcAc and DCA react preferentially with $H_2NO_2^+$ or NO^+. This suggests that the enols containing electron-withdrawing groups can only react with the more reactive (and less discriminating) positively charged electrophile ($H_2NO_2^+$ or NO^+). The situation is analogous to that encountered in *N*-nitrosation of amines, where the N_2O_3 pathway is favoured by the more basic (and more reactive) aliphatic amines, whereas $H_2NO_2^+$ or NO^+ is the reagent which more commonly reacts with the less basic (and less reactive) amines. In amine nitrosation it is usually possible to change from one pathway to the other by varying the acidity, but with enol nitrosation, over the rather limited range examined, this does not seem to be the case.

Experimental

Acetone, ethyl methyl ketone, and acetylacetone were purified by distillation. 1,3-Dichloroacetone was recrystallised from light petroleum (b.p. 40—60 °C). Other materials used were of the highest purity grade available and were used as such.

All kinetic measurements were carried out at 25 °C in water, spectrophotometrically, either in a conventional spectrophotometer, or for the more rapid reactions, in a stopped-flow spectrophotometer. In most cases, the decreasing absorption at 385 nm due to nitrous acid was measured as a function of time, but in some cases results were obtained for the increasing absorbance due to the oxime product; both methods gave the same value for the rate constant, within the experimental error. Generally, experimental conditions were chosen such that [ketone] $\gg$ [HNO_2], but a few experiments were carried out with equal reactant conditions; again good agreement was found. Some of the rate constants for the experiments without added nucleophiles were followed by the initial rate method, to avoid complications due to the hydrolysis of the oxime product. These were performed by a discontinuous method, by removing samples which were then added to excess of base, and the absorbance of the oxime product measured at 275 nm.

All four ketones are known[1] to yield the corresponding keto oximes. We observed these directly spectrophotometrically in each case (at ~330 nm). For acetone and ethyl methyl ketone, product formation (for reactions carried out at high [Br^-]) was shown to be virtually quantitative, by measurement of the final absorbance at 268 nm in basic solution, using a published extinction coefficient.[4]

Acknowledgements

We thank the Rectorado of the University of Santiago for financial support to J. R. L. and M. E. P.

References

1 O. Touster, 'Organic Reactions,' ed. R. Adams, Wiley, New York, 1953, vol. 7, ch. 6, pp. 327—377.
2 J. Toullec, *Adv. Phys. Org. Chem.*, 1982, **18**, 1, and references therein.
3 'Sidgwick's Organic Chemistry of Nitrogen,' 2nd edn., Oxford University Press, 1937, p. 171.
4 K. Singer and P. M. Vamplew, *J. Chem. Soc.*, 1957, 3050.
5 M. M. Rogic, J. Vitrone, and M. D. Swerdloff, *J. Am. Chem. Soc.*, 1977, **99**, 1156.
6 J. R. Leis, M. E. Peña, and D. L. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 45.
7 R. P. Bell and O. M. Lidwell, *Proc. R. Soc. London, A*, 1940, **176**. 88.
8 C. Rappe, *Acta Chem. Scand.*, 1966, **20**, 2236; U. L. Haldna, L. E. J. Erreline, and H. J. Kuura, *Org. React. (Tartu)*, 1968, **5**, 86.
9 H. Schmid and E. Hallaba, *Monatsh. Chem.*, 1956, **87**, 560; H. Schmid and M. G. Fouad, *ibid.*, 1957, **88**, 631.
10 J. P. Guthrie, *Can. J. Chem.*, 1979, **57**, 797 and references therein.
11 Y. Chiang, A. J. Kresge, and Y. S. Tang, *J. Am. Chem. Soc.*, 1984, **106**, 460.
12 J. P. Guthrie, *Can. J. Chem.*, 1979, **57**, 1177.
13 K. Al-Mallah, P. Collings, and G. Stedman, *J. Chem. Soc., Dalton Trans.*, 1974, 2469.
14 G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, 1947, **30**, 659; A. S. N. Murthy, A. Balasubramanian, C. N. R. Rao, and T. R. Kasturi, *Can. J. Chem.*, 1962, **40**, 2267.
15 R. P. Bell and J. Harisson, *Proc. R. Soc. London, A*, 1960, **255**, 214.
16 J. E. Dubois, M. El-Alaoui, and J. Toullec, *J. Am. Chem. Soc.*, 1981, **103**, 5393.
17 G. Y. Markovits, S. E. Schwartz, and L. Newman, *Inorg. Chem.*, 1981, **20**, 445.
18 A. Lapworth, *J. Chem. Soc.*, 1904, **85**, 30.
19 D. L. H. Williams, *Adv. Phys. Org. Chem.*, 1983, **19**, 381.
20 A. Castro, E. Iglesias, J. R. Leis, M. Mosquera, and M. E. Peña, *Bull. Soc. Chim. Fr.*, 1987, 83.
21 J. H. Ridd, *Adv. Phys. Org. Chem.*, 1978, **16**, 1.

Received 2nd February 1987; *Paper* 7/175