

Evidence for Concerted Acid Hydrolysis of Alkyl Nitrites

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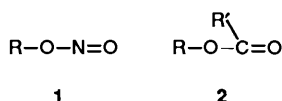
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The results of studying the acid hydrolysis of methyl, ethyl, isopropyl, butyl, *tert*-butyl, pentyl, 2-bromoethyl, 2-chloroethyl and 2-ethoxyethyl nitrites in water show that the reaction is not, as widely accepted in the literature, catalysed by nucleophiles (Cl^- , Br^- , *etc.*), but is however subject to general acid catalysis. These findings, and the observed values of the solvent isotope effect, suggest that the substrate is protonated in the rate-controlling step of the reaction. Further, the relative reactivities of the various substrates investigated suggest a concerted mechanism in which the proton transfer occurs concurrently with the breaking of the O–N bond *via* a slightly imbalanced transition state.

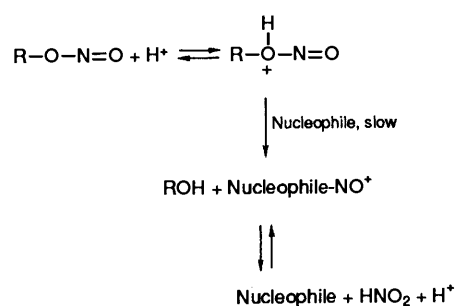
The chemistry of alkyl nitrites has attracted considerable interest in recent years, due in part to the intriguing problem of the relative reactivities of the isoelectronic $\text{N}=\text{O}$ and $\text{C}=\text{O}$ groups. In principle, it ought to be possible to consider alkyl nitrites (**1**) as related to carboxylic esters (**2**).



However, the fact that nitrogen is more electronegative than carbon and has a lone pair is probably the explanation for the significant differences between the chemistry of alkyl nitrites and that of carboxylic esters: whereas carboxyl chemistry is dominated by the formation of tetrahedral intermediates, the $\text{N}=\text{O}$ group has been regarded as being transferred intact,¹ no convincing evidence having been brought forward for addition reactions involving migration of the double bond, at least as regards reaction in water. Quantitative and often paradoxical differences in chemical behaviour are also observed: for example, alkyl nitrites react with OH^- much more slowly than carboxylic esters,² but exhibit considerable reactivity towards amines.^{3–6} Attempts have been made to explain this difference in terms of the theory of hard and soft acids and frontier orbital theories,⁷ $\text{N}=\text{O}$ being treated as a soft electrophile that reacts preferentially with soft nucleophiles, whereas the contrary is assumed to hold for carboxylic esters.^{2,3} Some authors have also noted a relationship between the reactivities of certain nucleophiles with $\text{N}=\text{O}$ and their vertical ionization potentials,^{3,8} and a similar relationship has recently been observed for the addition of nucleophiles to carboxylic esters,⁹ suggesting that in both types of compound an important part of the activation process may consist of single electron transfer during attack by the nucleophile.

The hydrolysis of alkyl nitrites to the parent alcohol and nitrous acid in acid media (a reversible reaction) is much faster than acid hydrolysis of esters, autocatalysis by the nitrous acid resulting in a considerable reaction rate even in the absence of added catalysts. The work of Allen,¹⁰ Battacherjee¹¹ and, in particular, Williams and co-workers¹² led to acceptance^{1,13} of the reaction mechanism shown in Scheme 1.

The chief experimental evidence in favour of this mechanism was that the rate equation was of first order with respect



Scheme 1

to protons, and that the reaction was catalysed by added nucleophiles (Cl^- , Br^- , SCN^- , *etc.*). Some experiments^{10,11} started with the alkyl nitrite, whereas others¹² measured the approach to equilibrium from the alcohol and nitrous acid. The mechanism was also made attractive by its paralleling the accepted mechanism for the denitrosation of *N*-nitrosamines,¹ which allowed the chemical behaviour of simple nitroso compounds to be fitted into a single scheme. Furthermore, Scheme 1 also leads to a single model for nitrosation reactions, since by the principle of microscopic reversibility it implies that the rate-controlling step of the reverse process, the nitrosation of alcohols, ought to be reaction between the alcohol and the nitrosating reagent (NO^+ or H_2NO_2^+ in simple aqueous solutions; NOCl , NOBr , *etc.* in the presence of halides), as in the nitrosation of amines, enols, thiols and other compounds.

However, when studying the acid hydrolysis of alkyl nitrites in micellar media, we were unable to detect the catalysis by nucleophiles required from the above mechanism. This led us to re-examine the reaction in water. Our experimental results are at odds with the mechanism of Scheme 1, and instead suggest a concerted mechanism in which protonation and the breaking of the O–N bond occur in the same step.

Experimental

Isopropyl, butyl, *tert*-butyl, pentyl, 2-ethoxyethyl, 2-chloroethyl and 2-bromoethyl nitrites were synthesized by treating the corresponding alcohols with sodium nitrite in an acid medium, purified by fractional distillation,¹⁴ and stored over molecular sieves to prevent their hydrolysis. When their hydrolysis was studied by conventional spectrophotometry, the reaction was

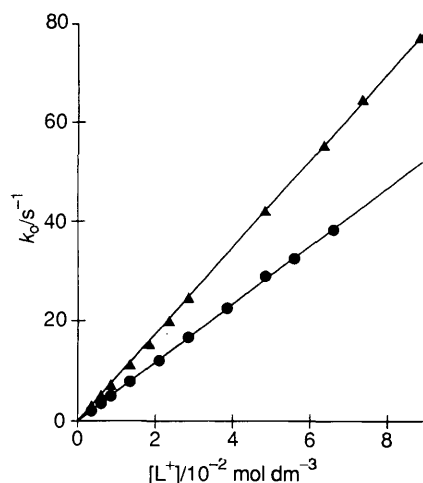


Fig. 1 Influence of the acidity upon the pseudo-first-order rate constant for acid hydrolysis of isopropyl nitrite: (●) in H_2O ; (▲) in D_2O

Table 1 Effects of the concentrations of Cl^- , Br^- and SCN^- on the first-order pseudoconstant k_0 for acid hydrolysis of isopropyl nitrite at a constant ionic strength controlled with NaClO_4

[Nucleophile]/mol dm^{-3}	Nucleophile	k_0/s^{-1}
0.05	Cl^-	23.3 ^a
0.09	Cl^-	23.8 ^a
0.225	Cl^-	23.0 ^a
0.360	Cl^-	22.7 ^a
0.60	Cl^-	22.4 ^a
0.90	Cl^-	21.9 ^a
0	—	5.02×10^{-3b}
1.41×10^{-3}	Br^-	5.17×10^{-3b}
2.83×10^{-3}	Br^-	5.04×10^{-3b}
5.66×10^{-3}	Br^-	5.12×10^{-3b}
1.13×10^{-2}	Br^-	5.15×10^{-3b}
2.26×10^{-2}	Br^-	5.35×10^{-3b}
1.33×10^{-3}	SCN^-	5.06×10^{-3b}
2.66×10^{-3}	SCN^-	4.91×10^{-3b}
5.33×10^{-3}	SCN^-	5.13×10^{-3b}
1.06×10^{-2}	SCN^-	5.15×10^{-3b}
2.13×10^{-2}	SCN^-	5.19×10^{-3b}

^a $[\text{H}^+] = 0.0185 \text{ mol dm}^{-3}$. Ionic strength 1 mol dm^{-3} . ^b $\text{pH} = 5.48$, controlled by an acetate buffer 0.26 mol dm^{-3} . Ionic strength = 0.26 mol dm^{-3} .

initiated by addition to the rest of the reaction mixture of 50 mm^3 of a solution of alkyl nitrite in dioxane. The percentage of dioxane in the final reaction mixture was 1.7% by volume. When the reactions were studied by stopped-flow, a small amount of the alkyl nitrite solution was dissolved in weakly basic $10^{-3} \text{ mol dm}^{-3}$ carbonate buffer, in which they are reasonably stable, and loaded into one syringe, and the appropriate acid and/or salt into the other. There is no discrepancy between the results of the two procedures.

Methyl and ethyl nitrites, which are gases at room temperature, were prepared in aqueous solution by treating known quantities of an aqueous solution of sodium nitrite with excess of the appropriate alcohol in an acid medium. This yielded an equilibrium mixture of alkyl nitrite, alcohol and nitrous acid at about $\text{pH} 2$. Kinetic studies of these nitrites were performed in acetic buffers of $\text{pH} 4.5$ – 5.6 ; when transferred to these media, the alkyl nitrites decomposed irreversibly, since the reverse reaction (the nitrosation of the alcohol) does not take place in this pH range, in which nitrous acid is totally converted to nitrite ion.

Deuterated water (99.77%) was supplied by C.I.E.M.A.T.

(Spain). All other reagents were Merck products of the highest commercially available purity.

The kinetics of the faster reactions were studied using a Hi-Tech SF-61 stopped-flow apparatus, and those of the slower reactions with a Spectronic 3000 Diode-Array UV-VIS spectrophotometer equipped with a multiple cell carrier thermostatted by circulating water. The consumption of alkyl nitrite was followed by recording the absorbance at 250–265 nm. The concentration of alkyl nitrite used was $(0.4\text{--}3.0) \times 10^{-3} \text{ mol dm}^{-3}$. All experiments were performed at 25°C . Some experiments were carried out starting from methanol and nitrous acid, as previously,¹² using the stopped-flow procedure.

The influence of buffer concentration was studied by adding various quantities to mixtures that, in order to guarantee constant pH at all buffer concentrations (including the low ones), already contained the quantity of acid required to achieve the desired pH . In addition, at the end of each reaction, the pH was always measured using a Radiometer 82 pH meter with a GK-2401C combined electrode (in experiments with heavy water, pD was calculated by adding 0.4 pH units to the measured value).¹⁵

The absorbance–time data of all the kinetic experiments were in perfect agreement with first-order integrated equations. In what follows, k_0 denotes the observed first-order pseudoconstant, whose values were usually reproducible to within 3%.

Results and Discussion

The influence of acidity (controlled with HCl) on the acid hydrolysis of isopropyl nitrite leads to the linear relationship implied by eqn. (1). Fig. 1 shows no indication of the upward

$$k_0 = k_{\text{H}}[\text{H}^+] \quad (1)$$

curvature to be expected were catalysis by Cl^- to occur. To determine whether the apparent absence of catalysis was due to the low concentration of HCl used ($<0.1 \text{ mol dm}^{-3}$), the concentration of Cl^- was increased to 0.9 mol dm^{-3} by adding NaCl , acidity and ionic strength being kept constant (the latter by the addition of NaClO_4). The results (Table 1) show that the reaction rate constant was totally unaffected by Cl^- concentration.

Since catalysis by nucleophiles was the main evidence in favour of the mechanism in Scheme 1, we performed a similar series of experiments under various experimental conditions using Br^- and SCN^- , which, owing to their greater nucleophilicity, generally catalyse denitrosation reactions better than Cl^- .¹ In neither case was catalysis observed, although these nucleophiles are very effective (even at lower concentrations than those used in this work) in the acid decomposition of other nitroso compounds (the catalytic efficiencies of Cl^- , Br^- and SCN^- in the denitrosation of *N*-methyl-*N*-nitrosoaniline, for example, are in the ratio 1:50:5500).¹⁶

In two of the studies in which, in apparent contradiction to the above results, the hydrolysis of alkyl nitrites has been reported as being catalysed by nucleophiles, the occurrence of catalysis may have been due to the reactions being carried out in media that were *ca.* 70% dioxane.^{10,11} We have recently found^{17,18} that the mechanism of nitrosation reactions can depend on the medium (in one of our studies,¹⁷ the mechanism of the nitrosation of ureas was observed to change precisely at dioxane concentrations of 70–75%), and Williams and co-workers have also reported that denitrosation¹⁹ and nitrosation²⁰ mechanisms observed in water do not necessarily hold in other solvents. We therefore investigated whether changing the medium similarly affected the kinetic characteristics of the hydrolysis reactions considered in the present work. We found (Fig. 2) that increasing the dioxane content of the medium

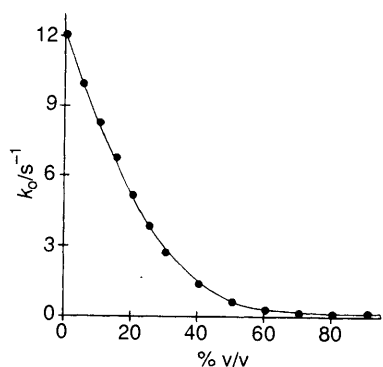


Fig. 2 Influence of the percentage of dioxane in the medium upon k_0 for the acid hydrolysis of isopropyl nitrite ($[HCl] = 2.1 \times 10^{-2} \text{ mol dm}^{-3}$)

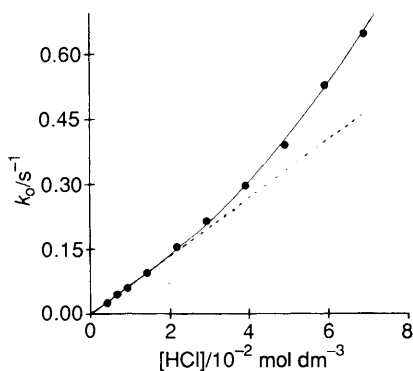


Fig. 3 Influence of the concentration of HCl upon k_0 for the acid hydrolysis of isopropyl nitrite at 72% dioxane

reduced the reaction rate (at a dioxane concentration of 72%, for example, the reaction was 80 times slower than in water). When the influence of HCl-controlled acidity on the reaction rate was investigated with 70% dioxane as the medium, the k_0 - $[H^+]$ plot curved upwards (Fig. 3), suggesting that, as a result of the low polarity and relative permittivity of the medium, the reaction mechanism now involved the occurrence of catalysis by Cl^- .

In the other study¹² whose findings included the occurrence of catalysis by halides in water, the observed catalysis was slight even at high catalyst concentration: a 0.8 mol dm^{-3} concentration of Br^- , for example, only doubled the reaction rate and the effects of Cl^- and Br^- were very similar, contrasting markedly with their normal pattern of reactivity as nucleophiles. Since this would seem to be an abnormally low catalytic efficiency in comparison with other reactions in which the nitroso group is removed, it seems possible that the slight catalysis observed may actually have been a salt effect, ionic strength not having been kept constant in these experiments. The results of experiments in which ionic strength was controlled with $NaClO_4$ under a variety of experimental conditions (Table 2) show that the reaction rate does indeed increase almost linearly with ionic strength (in fact, as pointed out by one referee, a straight line is found when plotting $\log k_0$ vs. $I^{1/2}$). We have repeated the earlier experiments¹² now at constant ionic strength. The results (Table 3) show clearly that there is no catalysis by Cl^- , Br^- or SCN^- . We conclude that the nucleophilic catalysis upon which the mechanism of Scheme 1 was largely based was in fact an effect of ionic strength which was misinterpreted owing to the almost linear relationship between k_0 and the quantity of salt present.

To investigate whether the reaction studied is susceptible to general acid catalysis, we carried out experiments at constant pH in acetic acid/acetate buffers of various concentrations,

Table 2 Influence of ionic strength ($I/\text{mol dm}^{-3}$) (controlled with $NaClO_4$) on the first-order pseudoconstant k_0 for acid hydrolysis of isopropyl nitrite

$[H^+] 0.022 \text{ mol dm}^{-3}$		$[H^+] 0.0085 \text{ mol dm}^{-3}$		pH = 5.34 (acetate buffer 0.13 mol dm^{-3})	
I	k_0/s^{-1}	I	k_0/s^{-1}	I	$k_0/10^{-3} s^{-1}$
0.06	13.7	0.06	4.90	0.12	3.79
0.18	15.5	0.18	5.79	0.15	4.01
0.30	16.9	0.30	6.44	0.22	4.26
0.42	18.0	0.42	7.09	0.31	4.64
0.54	19.9	0.78	9.39	0.52	5.28
0.78	22.1	1.20	12.7	0.92	6.29

Table 3 Effect of Cl^- , Br^- and SCN^- concentration (mol dm^{-3}) on the rate constants for $MeOH + HNO_2 \rightleftharpoons MeONO + H_2O$. $[MeOH] = 0.593 \text{ mol dm}^{-3}$, $[H^+] = 0.032 \text{ mol dm}^{-3}$, $[HNO_2] = 0.02 \text{ mol dm}^{-3}$

$I = 1 \text{ mol dm}^{-3}$		$I = 1 \text{ mol dm}^{-3}$		$I = 0.1 \text{ mol dm}^{-3}$	
$[Cl^-]$	k_0/s^{-1}	$[Br^-]$	k_0/s^{-1}	$[SCN^-]$	k_0/s^{-1}
0	42	0	45	0.02	25
0.2	40	0.2	48	0.04	24
0.4	38	0.4	50	0.06	27
0.6	40	0.6	54	0.08	27
0.8	42	0.8	58	0.10	26
1.0	44				

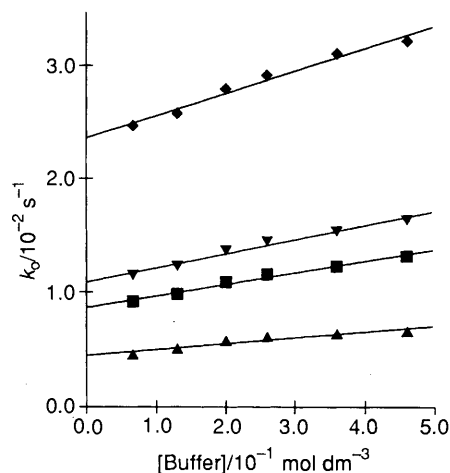


Fig. 4 Influence of the concentration of acetic acid/acetate ion buffer upon k_0 for the acid hydrolysis of isopropyl nitrite. Ionic strength = 0.5 mol dm^{-3} ($NaClO_4$). $T = 25^\circ\text{C}$. pH (\blacktriangle) 5.48; (\blacksquare) 5.16; (\blacktriangledown) 5.04; (\blacklozenge) 4.56.

ionic strength being kept constant at 0.50 mol dm^{-3} . In all cases there was moderate catalysis (Fig. 4) in accordance with eqn. (2) or, in terms of the total concentration of buffer, eqn. (3) where

$$k_0 = k_H[H^+] + k_{HA}[\text{Acetic acid}] \quad (2)$$

$$k_0 = k_H[H^+] + k_{HA}[H^+][\text{Buffer}]/(K_a + [H^+]) \quad (3)$$

K_a is the acidity constant of acetic acid. The observed linear dependence of the intercepts at the origin of Fig. 4 on $[H^+]$ yields a value of k_H , $920 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, that agrees well with the values determined at greater acidities at the same ionic

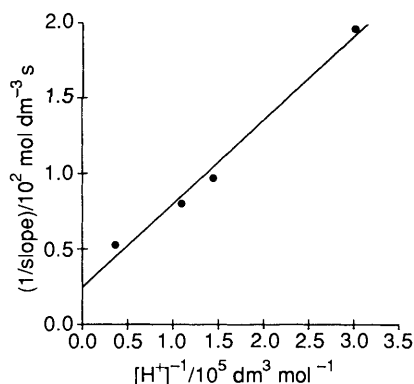


Fig. 5 Linearization of the slopes from Fig. 4 according to eqn. (4)

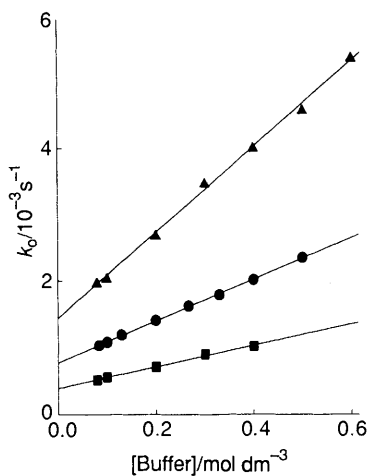


Fig. 6 Influence of the concentration of $\text{PO}_4\text{H}_2^-/\text{PO}_4\text{H}^-$ buffer upon k_0 for the acid hydrolysis of isopropyl nitrite. Ionic strength = 1 mol dm^{-3} (NaClO_4). $T = 25^\circ\text{C}$. pH (\blacktriangle) 6.05; (\bullet) 6.45; (\blacksquare) 6.96.

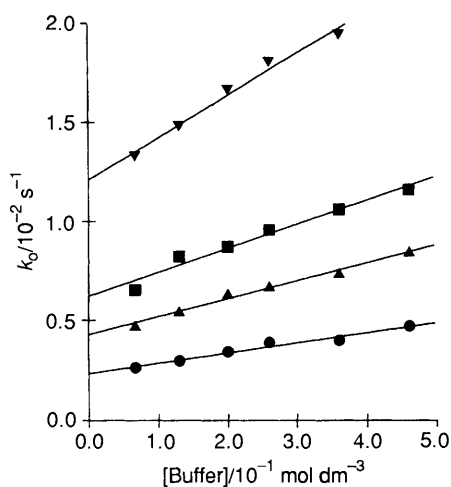


Fig. 7 Influence of the concentration of acetic acid/acetate ion buffer upon k_0 for hydrolysis of methyl nitrite. Ionic strength = 0.5 mol dm^{-3} (NaClO_4). $T = 25^\circ\text{C}$. pH (\bullet) 5.36; (\blacktriangle) 5.01; (\blacksquare) 4.91; (\blacktriangledown) 4.52.

strength and in the absence of buffers. Eqn. (3) implies that in Fig. 4 the reciprocal of the slope depends linearly on the reciprocal of $[\text{H}^+]$ [eqn. (4)] and the plot of this equation (Fig.

$$1/\text{slope} = 1/k_{\text{HA}} + K_{\text{a}}/(k_{\text{HA}}[\text{H}^+]) \quad (4)$$

5) yields a value of $4.16 \times 10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for k_{HA} and a $\text{p}K_{\text{a}}$ of 4.6 for acetic acid, in good agreement with the value expected at the working ionic strength.²¹

General acid catalysis was also effected by monochloroacetic acid buffers: a series of experiments (not shown) at three different pH values afforded a value of k_{HA} of $1.5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. Following one referee's suggestion we tried to find more conclusive evidence for the existence of general acid catalysis. This could be achieved by carrying out some experiments using phosphate buffers. The results obtained (Fig. 6) show quite large enhancements of reaction rate by PO_4H_2^- ($\text{p}K_{\text{a}} = 6.5$ at $I = 1 \text{ mol dm}^{-3}$ and 25°C). A value of k_{HA} of $7 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ was obtained for phosphate monoanion acting as a general acid. At the low acidities employed in this new set of experiments, reaction with water as the general acid could probably be detected, as suggested by the fact that a plot of the intercepts at the origin of the lines in Fig. 6 *vs.* $[\text{H}^+]$ was linear, with a small but significant intercept corresponding to an 'uncatalysed' process. The rate constants for the H_3O^+ , acetic acid, monochloroacetic acid and phosphate monoanion reactions lead, using the appropriate statistical factors, to a linear Brønsted plot with $\alpha = 0.62$ ($r = 0.995$), suggesting that protonation is involved in the rate-controlling step of the reaction, rather than constituting a prior step as in Scheme 1. To investigate this possibility further, the reaction was studied in deuterated water, in the presence of either DCl (under conditions analogous to those for Fig. 1) or acetic buffers. The observed solvent isotope effect, $k(\text{H})/k(\text{D})$, was 0.67 for hydrolysis by the hydronium ion in the absence of buffer, and 1.65 for the acetic acid catalytic term. These values rule out the possibility of protonation preceding the rate-controlling step, since in that case the fact that acids are more dissociated in water than in deuterated water would lead to an isotope effect of 0.2–0.4.²² The reason for the low value of the solvent isotope effect when the reagent is H_3O^+ is understandable in terms of the fractionation factor theory,²³ as being due merely to the low value (0.69) of the fractionation factor of the protons in the hydronium ion.²⁴

To investigate further the mechanism and transition state of the reaction, we carried out experiments with other alkyl nitrites. For those for which k_{H} values have been published previously, these published values agree reasonably well with those we determined (Table 4): for methyl and ethyl nitrites, Williams *et al.*^{12a} reported values of respectively 576 and 282 $\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at low ionic strength; and published values for *tert*-butyl and isopropyl nitrite²⁵ coincide almost exactly with the values we obtained when ionic strength was not controlled. Other kinetic results are also in keeping with those obtained for isopropyl nitrite, showing positive salt effects, moderate general acid catalysis (with satisfactory determinations of the $\text{p}K_{\text{a}}$ of the acid), and no catalysis by nucleophiles (Tables 5 and 6 and Fig. 7 show typical data obtained in these experiments). The Brønsted slope obtained from data for catalysis by H_3O^+ and acetic acid (after statistical correction) was 0.62 for methyl nitrite, 0.66 for ethyl nitrite and 0.66 for 2-ethoxyethyl nitrite. For 2-bromoethyl nitrite and 2-ethoxyethyl nitrite, we also determined the solvent isotope effects: the values found, 0.8 and 0.66 respectively, once more imply that no protonated intermediate is formed prior to the rate-controlling step of the reaction. In addition, the solvent isotope effect upon the acetic acid catalytic term in the case of the 2-ethoxyethyl derivative was found to be 1.4, a value similar to that measured for isopropyl nitrite. One can therefore appreciate a remarkable similarity in the kinetic features (solvent isotope effects, Brønsted slopes) irrespective of the nature of the substrate employed.

When comparing reactivity of the different alkyl nitrites, one observes a trend for tertiary substrates to hydrolyse somewhat faster than secondary ones and primary ones, but the effects are rather small. The most striking feature of Table 4 is that the reactivity of the alkyl nitrites increases slightly with the

Table 4 Values of k_H and k_{HA} obtained at 25 °C for acid hydrolysis of alkyl nitrites RONO

R	$k_H/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ($I = 0.5 \text{ mol dm}^{-3}$)	$k_H/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ($I < 0.1 \text{ mol dm}^{-3}$)	k_H/k_D	$k_{HA}/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ($I = 0.5 \text{ mol dm}^{-3}$)	k_{HA}/k_{DA}
CH ₃	420 ^{a,c}	—	—	4.00×10^{-2a} (acetic acid)	—
CH ₃ CH ₂	620 ^{a,c}	—	—	3.65×10^{-2a} (acetic acid)	—
(CH ₃) ₂ CH	845 ^b	584 ^b	0.66	4.2×10^{-2a} (acetic acid)	1.68 ^d
				1.5 ^a (Monochloroacetic acid)	
				7×10^{-3} (Phosphate monoanion) ^e	
CH ₃ (CH ₂) ₃	779 ^b	556 ^b	—	—	—
(CH ₃) ₃ C	1351 ^b	953 ^b	—	—	—
CH ₃ (CH ₂) ₄	739 ^b	531 ^b	—	—	—
EtOCH ₂ CH ₂	1216 ^b	860 ^b	0.66	6.79×10^{-2a} (Acetic acid)	1.4 ^d
BrCH ₂ CH ₂	1874 ^b	1314 ^b	0.83	—	—
ClCH ₂ CH ₂	2170 ^b	1869 ^b	—	—	—

^a Measured by conventional spectrophotometry. ^b Measured by stopped-flow. ^c Extrapolated to zero buffer concentration. ^d Referred to catalysis by acetic acid. ^e $I = 1 \text{ mol dm}^{-3}$.

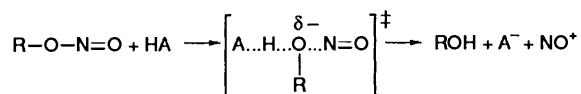
Table 5 Influence of ionic strength on the acid hydrolysis of methyl nitrite at pH 5.36 (controlled with 0.13 mol dm⁻³ acetate buffer)

$I/\text{mol dm}^{-3}$	$k_0/10^{-3} \text{ s}^{-1}$
0.115	2.03
0.215	2.40
0.315	2.52
0.465	2.90
0.615	3.08
0.865	3.36
1.12	3.75

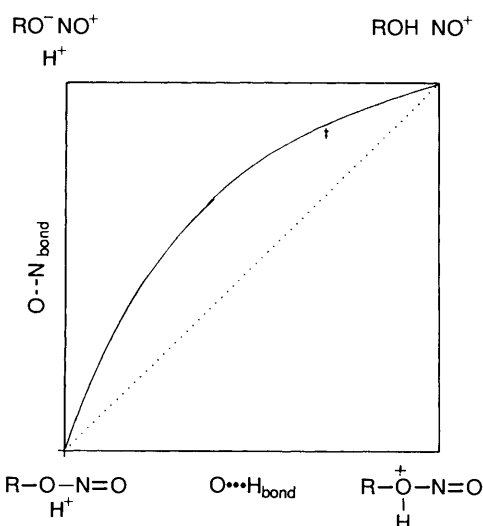
Table 6 Influence of concentration of Cl⁻ on k_0 for acid hydrolysis of methyl nitrite in 0.13 mol dm⁻³ acetate buffer of pH 5.36 ($I = 0.5 \text{ mol dm}^{-3}$)

[Cl ⁻]/mol dm ⁻³	$k_0/10^{-3} \text{ s}^{-1}$
0	2.85
0.05	2.92
0.1	2.88
0.15	2.98
0.23	3.09
0.30	3.06
0.38	3.10

electron-withdrawing capacity of the group R; the more electronegative its O-substituents, the faster the hydrolysis of the alkyl nitrite. This behaviour means that the slow step of the reaction cannot be a simple proton transfer, which would be speeded up by increasing the basicity of the oxygen atom. Rather, it suggests a concerted mechanism involving both proton transfer and the breaking of the N–O bond, the latter facilitated by the presence of electron-withdrawing groups. Our results do not support the existence of perfect synchronization between the proton and N–O breaking processes, the observed behaviour can be explained in terms of an imbalanced transition state in which a slight negative charge on the O atom is stabilized by the presence of electron-withdrawing groups (Scheme 2).

**Scheme 2**

The observed value of the Brønsted parameters show that in the transition state proton transfer must have reached a fairly advanced stage, and the observed values of the isotope effects are also typical of concerted processes in which proton transfer and the breaking of the bonds between heavy atoms take place

**Fig. 8** Qualitative reaction coordinate energy diagram for the acid-catalysed hydrolysis of alkyl nitrites. The horizontal axis measures the extent of proton transfer and the vertical axis the extent of O–N bond. The solid line shows an approximate reaction coordinate.

concurrently. The negative charge on O in the transition state nevertheless implies that the breaking of the N–O bond must be at an even more advanced stage than protonation. Non-perfect synchronization between different processes is well documented in many cases,²⁶ interesting and striking examples occurring for example in the dehydration of carbinolamines²⁷ and, in particular, the ionization of nitroalkanes.²⁸ The situation can be appropriately represented by reaction-coordinate diagrams of the kind described by Jencks²⁹ and More O'Ferrall³⁰ (Fig. 8) in which one axis represents the protonation process and the other the bond-breaking process. The dashed straight line in Fig. 8 represents a balanced concerted mechanism in which the two processes are perfectly synchronized, whereas the solid curve represents the process suggested by our data, in which, possibly because of the high electronegativity of the oxygen atom, N–O bond breaking somewhat leads protonation.

The equilibrium constant for the process $\text{RONO} + \text{H}^+ \rightleftharpoons \text{ROH} + \text{NO}^+$ can be estimated by combining the equilibrium constants for the nitrosation of the alcohol (K_4) and the formation of NO^+ by protonation of nitrous acid (K_5).



For methyl nitrite, for example, $K_4 = 3.5 \text{ dm}^3 \text{ mol}^{-1}$,³¹ and

though K_5 is more uncertain, a number of results support the spectrophotometrically determined value of $3 \times 10^{-7} \text{ dm}^3 \text{ mol}^{-1}$.^{32,33} The combination of these values suggests a value of *ca.* 40 kJ mol⁻¹ for the thermodynamic barrier ΔG^\ddagger , only 18 kJ mol⁻¹ below the value of 58 kJ mol⁻¹ calculated for ΔG^\ddagger from the observed value of 420 dm³ mol⁻¹ s⁻¹ for k_H (Table 3). This is in keeping with a transition state that occurs late along the reaction coordinate and that resembles the products, as expected from Hammond's postulate for highly endoenergetic reactions.

It remains to answer the question of why alkyl nitrites are hydrolysed *via* a concerted mechanism and not *via* the stepwise mechanism of Scheme 1, which is somewhat similar to the A_{AC}^2 mechanism by which acid hydrolysis of simple carboxylic esters takes place. The reason would appear to be that the protonated alkyl nitrite ROHNO^+ must be highly acidic, for, as Jencks notes,³⁴ the boundary between concerted and stepwise mechanisms is determined by the stability of the intermediates. Protonated alkyl nitrites must be very acidic species. Substitution of a hydrogen atom by a N=O group lowers the pK_a of amines by at least 10 units³⁵ (probably more since *N*-nitrosoamines are thought to be protonated at the NO oxygen atom rather than at the nitrogen bearing the NO group). Assuming a similar effect in the case of the alcohols, the pK_a of protonated methyl nitrite, for example, may be estimated as < -13 , since protonated methanol has³⁶ a pK_a of *ca.* -2.2 . The pK_a of MeOHNO^+ is thus much less than that of protonated carboxylic esters (*ca.* -7),³⁷ suggesting that the nitroso group withdraws charge much more effectively than the carbonyl group; this conclusion is in keeping with the fact that alkyl nitrites, but not esters, exhibit a *cis-trans* isomerism at room temperature,³⁸ and with the large value of ρ for the equilibrium $\text{ROH} + \text{NOCl} \rightleftharpoons \text{RONO} + \text{HCl}$.³⁹ The great acidity of protonated alkyl nitrites means that they can hardly be considered as conventional intermediates, for Eigen's theory⁴⁰ implies that, as oxyacids, their reaction with water must be diffusion-controlled (the pK_a of the hydronium ion being -1.74), from which it follows that they cannot be equilibrated by diffusion through the solvent.

The impossibility of protonated alkyl nitrites acting as intermediates may be considered as being due essentially to their high energy. The pK_a of protonated methyl nitrite for example, which was estimated above as < -13 , implies a free energy change of 74 kJ mol⁻¹, which is much greater than the free energy of activation that was determined for the hydrolysis of MeONO , 58 kJ mol⁻¹ (*vide supra*). The protonated alkyl nitrite, if our estimation is correct, may therefore be completely ruled out as a possible intermediate, since it would have to react faster than the diffusion rate in order to achieve the observed overall reaction rate. This is not the case for protonated *N*-nitrosamines, for which one can estimate much higher pK_a values, therefore allowing them to be real intermediates in denitrosation reactions. However, the avoidance of highly unstable intermediates is probably the reason why denitrosation mechanisms change in the case of other *N*-nitroso compounds, whose protonated intermediates would be too acidic. This is the case for amides and related compounds, and for some indoles. In these cases, reaction takes place involving other nucleophilic centres of the molecule (amidic oxygen, indolic C-3)^{41,42} therefore avoiding the formation of the very acidic protonated *N*-nitroso compounds.

All these arguments support a concerted mechanism. Furthermore, the hydrolysis of alkyl nitrites fulfils Jencks'²⁹ criteria for the possibility of proton transfer occurring concertedly with the formation or breaking of covalent bonds; briefly, that the site of protonation undergo a large change in pK during the course of the reaction, and that the pK of the catalyst lie between the initial and final pK 's of the protonation site. The hydrolysis of

alkyl nitrites under the conditions we employed certainly satisfies these criteria, since the pK of the O atom changes from *ca.* -13 to *ca.* 15 and the catalyst is H_3O^+ (pK_a -1.74) or a carboxylic acid.

The high acidity and instability of protonated alkyl nitrites probably also explains why the nitrosation of nucleophiles such as amines, thiols or thioureas by alkyl nitrites in acid media does not take place directly *via* the protonated alkyl nitrite, but instead *via* acid hydrolysis, the effective nitrosating agent being NO^+ .²⁵ This mechanism would seem to be incompatible with that of Scheme 1, in which direct nitrosation of weak nucleophiles such as the chloride ion is postulated. A doubtful explanation, that the protonated alkyl nitrite is an abnormally weak electrophile for N or S nucleophiles, is no longer necessary if the mechanism of Scheme 1 is accepted as being ruled out by our findings. One can alternatively say that the putative intermediate protonated alkyl nitrite does not meet the requirements to be considered as a real intermediate, since its lifetime is incompatible with its diffusion through the solvent to transmit the nitroso group.

The question arises as to why, looking at the reaction from the reverse direction, other nitrosating agents (NOBr *etc.*) do not compete with NO^+ in the nitrosation of alcohols. It is clear that the oxygen atom in alcohols generally is a poor nucleophile, certainly compared with the nitrogen atom in amines, and the sulfur atom in thiols. Rate constants for the reaction of thiols with some NOX species are known.⁴³ If we assume that alcohols are less reactive by at least a factor of 10 (probably much more) we can estimate rate constants for NOBr attack on methanol. A straightforward calculation reveals that the NO^+ reaction is faster than the NOBr reaction by at least a factor of 40. In short, the oxygen atom in alcohols is so weakly nucleophilic that reaction will only occur with the most powerful electrophiles, *e.g.* NO^+ .

Finally, it is interesting to compare the mechanism of the hydrolysis of alkyl nitrites with those of related compounds. Though normal esters are hydrolysed by a stepwise process, hydrolysis of the related orthoesters probably involves an $A-S_E2$ mechanism in which proton transfer is in some way concerted with the breaking of the C-O bond.⁴⁴ There is a similar mechanistic difference between the hydrolysis of simple acetals and ketals, which takes place stepwise, and that of derivatives with highly polar substituents and very low basicity, which exhibits kinetics similar to those of orthoesters.⁴⁴ The concerted mechanism inferred for the hydrolysis of alkyl nitrites may therefore be seen as in keeping with a general tendency to such mechanisms among compounds of sufficiently low basicity.

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