The Chemistry of Nitroso-compounds. Part VIII.[1] Denitrosation and Deamination of *N*-n-Butyl-*N*-nitrosoacetamide in Aqueous Acids

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Decomposition of *N*-n-butyl-*N*-nitrosoacetamide in aqueous acid at 25 °C involves both deamination and denitrosation. Both reactions occur concurrently *via* different conjugate acid intermediates, with denitrosation becoming predominant at high acidity. Acidity dependences, activation parameters, and solvent deuterium isotope effects [$k(H_2SO_4)/k(D_2SO_4)$ *ca.* 0·74] show that deamination involves rate-limiting attack by H_2O on an *O*-conjugate acid, formed in a rapid pre-equilibrium. For denitrosation, proton transfer to the amide nitrogen atom is considered rate limiting because of the substantial solvent deuterium isotope effects [$k(H_2SO_4)/k(D_2SO_4)$ *ca.* 1·9] and general acid catalysis [$k(H_2SO_4) > k(HClO_4)$]: the *N*-conjugate acid formed breaks down rapidly to products. The unusual slow proton transfer to nitrogen observed is related to the very low basicity of this atom (pK_A *ca.* −15). These results are discussed in relation to carcinogenesis by *N*-nitroso-compounds and it is shown further that the nitrosation of amides cannot be catalysed by nucleophilic species (*e.g.* Cl^-) as hitherto supposed.

SECONDARY *N*-nitrosamides are relatively unstable compounds most commonly met as intermediates in the conversion of amides to carboxylic acids with nitrous acid and as precursors to either diazoalkanes or phenyl radicals. More recently, they have been recognised as powerful carcinogens [2] and this has stimulated interest in their chemical properties.

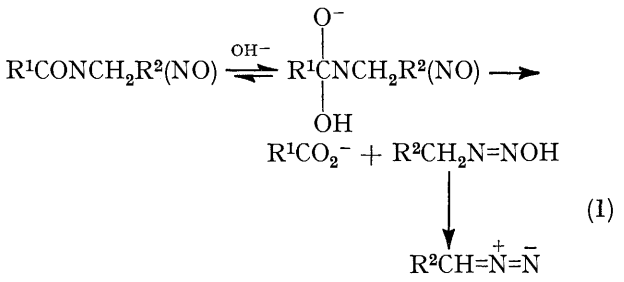
Under basic conditions, *N*-alkylnitrosamides are often used to generate diazoalkanes,[3] presumably by a hydrolytic addition–elimination pathway similar to that of amides themselves. The diazoalkane reagent would

[1] Part VII, B. C. Challis and R. J. Higgins, *J.C.S. Perkin II*, 1973, 1597.

[2] H. Druckrey, R. Preussmann, S. Ivankovic, and D. Schmail, *Z. Krebsforsch.*, 1967, **69**, 103.

[3] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, London, 1967, p. 191.

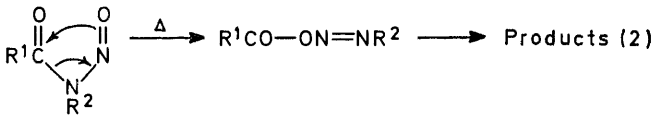
then derive from the primary diazo-hydroxide that is expelled from the tetrahedral intermediate [equation (1)].



(1)

However, a different pathway has been proposed recently for diazoalkane formation from *N*-nitrosoureas.[4]

Much interest, and also some long standing controversy, has been evoked by the thermal decomposition processes, both in respect of deamination of *N*-alkylnitrosamides and the synthesis of biaryl compounds from *N*-nitrosoacetanilide. Details of the reactions are given in several excellent reviews [5] and it is sufficient to mention here that it is now generally agreed that the *N*-nitrosamide thermally rearranges to a diazo-ester [equation (2)], which then decomposes to various



(2)

products depending on both the substrate structure and the reaction conditions.

Much less is known about the behaviour of secondary *N*-nitrosamides under acidic conditions. Their formation is said to be reversible, which implies release of nitrous acid on dissolution in acidic media: this expectation is tentatively confirmed by quantitative regeneration of the parent amide on treating *N*-nitrosamide with gaseous HBr in CCl_4.[6] However, as a reflection of their amide properties, *N*-nitrosamides in aqueous solution should readily undergo acid catalysed hydrolysis.[7]

Our interest in the chemistry of nitrosamides stems from their carcinogenic properties,[2] and those of *N*-nitrosamines,[8] too. The physiological activity of both classes of compounds has been widely attributed to their properties as alkylating agents,[2,8] but recently we have shown that some secondary *N*-nitrosamines may act as proximate carcinogens by direct transnitrosation of other bases.[9] With this in mind our investigation has been extended to *N*-nitrosamides, and *N*-n-butyl-*N*-nitrosoacetamide, in particular, because this is one of the more thermally stable compounds.[6a] A preliminary account of our findings has been published.[10]

EXPERIMENTAL

Substrates and Reagents.—*N*-n-Butyl-*N*-nitrosoacetamide was prepared by the nitrosation of the parent amide following one of White's [6a] procedures. *N*-n-Butylacetamide (1·15 g, 0·01 mol) in CH_2Cl_2 (100 ml) at −10° in the presence of NaOAc (2·46 g, 0·03 mol) was treated with gaseous N_2O_4 (Matheson; 1·38 g, 0·015 mol). The solution was stirred for 30 min at −10° and then washed repeatedly with aqueous $NaHCO_3$ and water. After drying the separated organic fraction, CH_2Cl_2 was removed under vacuum at room temperature. The residual yellow liquid was distilled under high vacuum to give *N*-n-butyl-*N*-nitrosoacetamide (*ca.* 1·2 g), b.p. 30° at 0·4 Torr (lit.,[6a] 35—37° at 0·1 Torr) (Found: C, 50·1; H, 8·2; N, 19·6; O, 22·1. Calc. for $C_6H_{12}N_2O_2$: C, 50·0; H, 8·4; N, 19·4; O, 22·2%), n_D^{22} 1·4440 (lit.,[6a] n_D^{25} 1·4425); $\nu_{max.}$ (thin film) 1739 and 1515 cm^{-1}, $\lambda_{max.}$ (EtOH) 244 (log ε 4·01) and 409 nm (1·80), τ (CCl_4) 6·25 (2H, t), 7·25 (3H, s), and 8·80 (7H, m).

AnalaR H_2SO_4, $HClO_4$, HCl, NaCl, NaBr, NaI, $NaNO_2$, and $NaClO_4$ were used without further purification other than vacuum drying where appropriate. D_2SO_4 was prepared by distilling SO_3 from 20% oleum (SO_2 being removed by prior heating for 10 h under reflux over CrO_3) into 99·7% D_2O (Prochem).

Kinetics.—Decomposition rates were measured by two independent analytical procedures for the loss of the substrate (u.v. method) and the formation of HNO_2 (Shinn's method), respectively.

U.v. method. The u.v. absorption of the reaction solution (at either 244 or 409 nm using a Unicam SP 1800 spectrophotometer) proved a convenient way of estimating the concentration of unchanged substrate. Depending on the half-life, either portions of the reaction solution were assayed at timed intervals, or the reaction solution in a thermostatted silica cell was monitored continuously. Regular measurements were taken for at least three half-lives and an 'infinity' after 10 half-lives: the latter invariably had zero absorbance.

Data in Table 1 for a typical kinetic experiment in

TABLE 1

Decomposition of *N*-n-butyl-*N*-nitrosoacetamide in 6·03M-$HClO_4$ at 25°: initial [$MeCONBu^n(NO)$] *ca.* $1·6 \times 10^{-4}$M

t/min	A_t*	Reaction (%)	$10^3k_0/s^{-1}$
0	1·60	0	
2	1·29	20·1	1·88
4	1·04	36·4	1·88
6	0·83	50·0	1·93
8	0·67	60·4	1·93
10	0·54	68·8	1·95
14	0·36	80·5	1·95
22	0·18	92·2	1·93
∞	0·06		

* At 244 nm.

6·03M-$HClO_4$ at 25° show the observed decomposition rate has a first-order dependence on [*N*-n-butyl-*N*-nitrosoacetamide] and equation (3) therefore applies. Values of

$$\text{Rate} = k_0[MeCONBu^n(NO)] \quad (3)$$

k_0 were usually obtained from the slopes of the plots of

[4] S. M. Hecht and J. W. Kozarich, *Tetrahedron Letters*, 1972, 5147.

[5] E. H. White and D. J. Woodcock, 'Chemistry of the Amino Group,' ed. S. Patai, Wiley, London, 1968, p. 407; J. I. G. Cadogan, *Accounts Chem. Res.*, 1971, **4**, 186.

[6] (*a*) E. H. White, *J. Amer. Chem. Soc.*, 1955, **77**, 6008; (*b*) R. Huisgen, *Annalen*, 1951, **573**, 163.

[7] B. C. Challis and J. A. Challis, 'Chemistry of Amides,' ed. J. Zabicky, Wiley, London, 1970, p. 733.

[8] P. N. Magee and J. M. Barnes, *Adv. Cancer Res.*, 1967, **10**, 163.

[9] B. C. Challis and M. R. Osborne, *J.C.S. Perkin II*, 1973, 1526.

[10] C. N. Berry and B. C. Challis, *J.C.S. Chem. Comm.*, 1972, 627.

log $(A_t - A_\infty)$ *versus* time, where A_t and A_∞ are the absorbance at time t and ∞, respectively; they were reproducible to $\pm 4\%$.

Shinn's method. Sulphanilamide is readily diazotised under acidic conditions and the resultant diazonium ion may be coupled with *N*-1-naphthylethylenediamine to give an azo-dye, $\lambda_{max.}$ 541 nm (log ε 4·71). This method, an adaptation [11] of that first described by Shinn,[12] was suitable for estimating the HNO_2 released on decomposition. To prevent reversal of the denitrosation of the substrate, excess of sulphanilamide (*ca.* $2{\cdot}5 \times 10^{-2}$M) was added to the solution prior to adding the substrate. Portions were taken at timed intervals and, after dilution with H_2O to quench the reaction partially, added to 0·1% *N*-1-naphthylethylenediamine dihydrochloride (1 ml) in a volumetric flask. After volume adjustment with H_2O, the dye absorption was measured on a Unicam SP 1800 spectrophotometer at 541 nm. Values of k_0 {equivalent to equation (1) but measured from the increase in $[HNO_2]$ with respect to time} were obtained from the slopes of the plots of log $(A_\infty - A_t)$ *versus* time, where A_∞ and A_t are the absorbance of the azo-dye at time ∞ and t, respectively.

Experience showed that values of k_0 obtained from Shinn's method were inherently less accurate than those from the direct u.v. assay of the reaction solution, possibly because of the extra volumetric handling required and certainly because denitrosation continued, albeit at a much slower rate, in the coupled azo-dye solution. The Shinn method was therefore used only to prove the existence of two concurrent first-order decomposition reactions and for product analysis (see below) where further denitrosation in the coupled azo-dye solution was not a problem. Independent experiments established that (i) diazotised sulphanilamide is quite stable under the reaction conditions (*ca.* 0·175% decomposition h^{-1} at 25° and 2M-HCl to *ca.* 0·3% decomposition h^{-1} at 25° and 8M-HCl) and (ii) that the nitrite assay was independent of [sulphanilamide].

Reactions in D_2SO_4 were followed by similar procedures using scaled down quantities. In all cases, the acidity of the reaction solution was ascertained volumetrically on completion of the kinetic experiment.

Product Analysis.—To evaluate the contribution from various decomposition pathways to the overall rate, accurate product analysis had to be made for each kinetic experiment, usually by measuring the total amount of HNO_2 released from a known initial substrate concentration by Shinn's technique. In practice, it was found convenient, when k_0 was determined by the u.v. method, to run duplicate experiments to one of which sulphanilamide had been added. From this solution, several portions were then assayed for HNO_2 after 10 half-lives. By making the assay on completion of the reaction, errors arising from further denitrosation in the coupled azo-dye solution were eliminated. The agreement between individual assays was $\pm 2\%$.

Other products were assayed by t.l.c.; both acetic acid and *N*-n-butylacetamide, but not n-butyl acetate, were identified. A few experiments were also carried out with the reaction flask connected to a gas burette. The expected amounts of N_2 were obtained, but this method was more tedious and less accurate than HNO_2 assay for the purpose of product analysis.

[11] N. F. Kershaw and N. S. Chamberlin, *Ind. Eng. Chem. Analyt.*, 1942, **14**, 312.
[12] M. B. Shinn, *Ind. Eng. Chem. Analyt.*, 1941, **13**, 33.

RESULTS

Evidence given in Table 1 and elsewhere [13] shows first-order dependence on [*N*-n-butyl-*N*-nitrosoacetamide] for the overall rate of decomposition [equation (1)]. The products imply decomposition by two independent reactions and the amino-products, in particular (N_2 *versus* HNO_2 + *N*-n-butylacetamide), suggest these occur concurrently rather than consecutively. Conclusive proof of this deduction comes from the well known kinetic relationship that the overall rate (k_0) of the concurrent first-order processes may be ascertained from either removal of the substrate or formation of any one of the products [*i.e.* equation (4)].[14]

$$-\mathrm{d}[\mathrm{MeCONBu^n(NO)}]/\mathrm{d}t = \mathrm{d}[\mathrm{HNO_2}]/\mathrm{d}t \qquad (4)$$

Data in Figure 1 show values of k_0 obtained by each of the kinetic methods described above plotted as a function

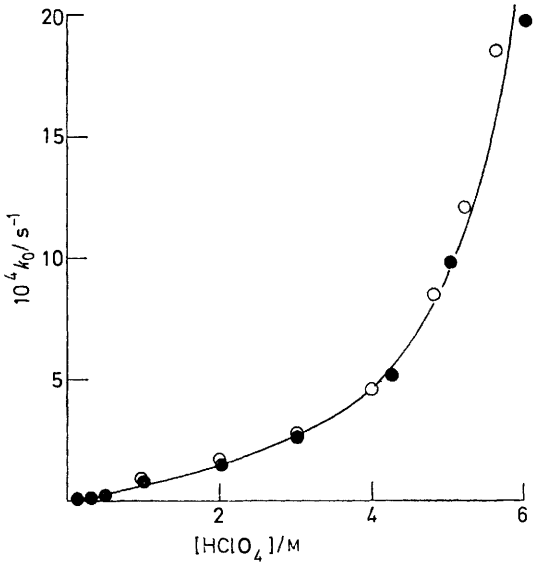
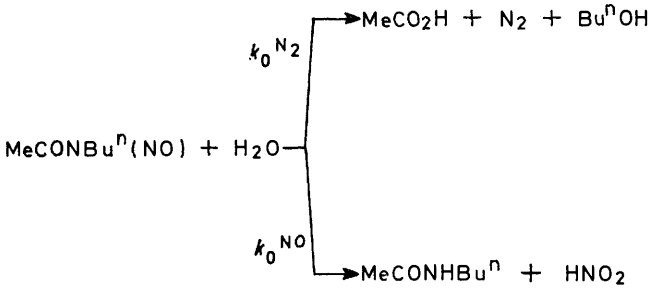


FIGURE 1 Decomposition rate (k_0) of *N*-n-butyl-*N*-nitrosoacetamide in $HClO_4$ at 25°: ● u.v. method; ○ Shinn's method



SCHEME 1 Concurrent deamination and denitrosation of *N*-n-butyl-*N*-nitrosoacetamide in acidic media

of $[HClO_4]$. The agreement between each set of data is very satisfactory, showing that the decomposition can be represented by Scheme 1, where $k_0^{N_2}$ and k_0^{NO} are the observed rates of deamination and denitrosation, respectively.

Rate coefficients for each decomposition pathway were evaluated from k_0 and the product ratio for each kinetic

[13] C. N. Berry, Ph.D. Thesis, London, 1973.
[14] See A. A. Frost and R. G. Pearson, ' Kinetics and Mechanism,' Wiley, London, 1961, 2nd edn., p. 160.

run [*i.e.* by solving equations (5) and (6)]. In practice, it

$$k_0 = k_0^{N_2} + k_0^{NO} \quad (5)$$

$$k_0^{NO}/k_0^{N_2} = [HNO_2]_t/[N_2]_t \quad (6)$$

was convenient to evaluate equation (6) on completion of the reaction (*i.e.* when $t = \infty$) from the total amount of HNO_2 released and the initial substrate concentration [equation (7)]. From equation (5) and equation (7), it

$$\frac{k_0^{NO}}{k_0^{N_2}} = \frac{[HNO_2]_\infty}{[MeCONBu^n(NO)]_0 - [HNO_2]_\infty} \quad (7)$$

follows that k_0^{NO}, for example, is given by equation (8).

$$k_0^{NO} = k_0\%[HNO_2]_\infty/100 \quad (8)$$

Values of k_0 and $\%[HNO_2]_\infty$ for reaction in aqueous $HClO_4$ at 25 °C are listed in Table 2 together with the calculated values of k_0^{NO} and $k_0^{N_2}$.

TABLE 2

Decomposition rates (k_0, k_0^{NO}, and $k_0^{N_2}$) and product ratio for *N*-n-butyl-*N*-nitrosoacetamide in $HClO_4$ at 25°: initial [MeCONBu^n(NO)] *ca.* 1·4—2·0 × 10^{-4}M: [sulphanilamide] = 2·4 × 10^{-2}M

$[HClO_4]$/M	10^4k_0/s^{-1}	$[HNO_2]_\infty$ (%)	$10^4k_0^{NO}$/s^{-1}	$10^4k_0^{N_2}$/s^{-1}
1·00	1·40	8·8	0·12	1·28
2·00	2·05	17·6	0·36	1·69
3·00	3·42	27·9	0·95	2·47
4·02	4·53	41·9	1·90	2·63
4·80	8·05	52·1	4·20	3·85
5·20	12·0	53·9	6·49	5·56
5·60	18·7	60·3	11·3	7·43

Acidity Dependence.—It is apparent from Table 2 that deamination predominates at low $[HClO_4]$, but this reaction

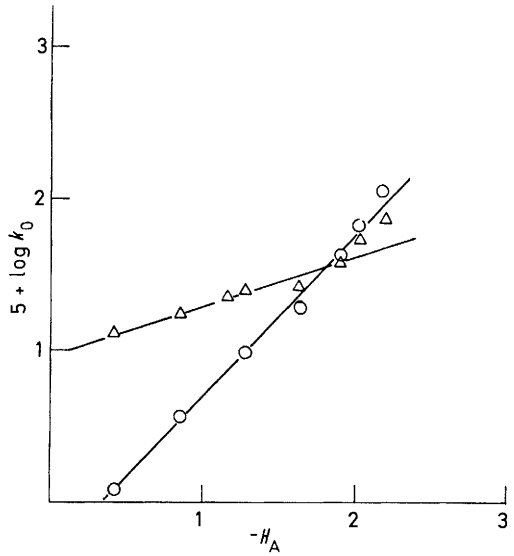


FIGURE 2 Plots of log k_0^{NO} (○) and log $k_0^{N_2}$ (△) *versus* ($-H_A$) for the decomposition of *N*-n-butyl-*N*-nitrosoacetamide in $HClO_4$ at 25°

is overtaken by denitrosation at $[HClO_4] \gtrsim 4·8$M. It follows that denitrosation is more strongly acid catalysed than deamination. This difference is more forcefully illustrated by the plot of log k_0^{NO} and log $k_0^{N_2}$ *versus* the H_A acidity function [15] in Figure 2. The plot is reasonably linear for denitrosation with slope 1·08; for deamination, the best straight line through points showing substantial scatter has slope *ca.* 0·37. Similar results are evident for catalysis by aqueous H_2SO_4 at 25°: here, the slope of log k_0^{NO} *versus* ($-H_A$) is 1·13 and, significantly, k_0^{NO} is *ca.* 2·5-fold faster in H_2SO_4 than in $HClO_4$ of the same H_A value; $k_0^{N_2}$ is also larger in H_2SO_4 than $HClO_4$, but again the slope for the plot of log $k_0^{N_2}$ *versus* ($-H_A$) is lower than for log k_0^{NO}.

Effect of Added Nucleophiles. We mentioned above that release of HNO_2 was independent of the added [sulphanilamide]. Details of these experiments are given in Table 3 for decomposition in aqueous HCl at 25°. Clearly a 10-fold increase in the concentration of the HNO_2 trap has a negligible effect on either k_0^{NO} or $k_0^{N_2}$. This is a surprising result because other nitrosating agents (*e.g.* RONO, NOCl) invariably react in a bimolecular manner.[15]

The matter was further examined by comparing catalysis by NaCl with $NaClO_4$ (Table 4). Generally, halide ions act as powerful nucleophiles towards nitrosating agents whereas ClO_4^- does not.[16] The data, however, show no evidence for nucleophilic catalysis by Cl^-: on the contrary, ClO_4^-, itself, appears to be a slightly better catalyst than Cl^-. Thus addition of 2·0M-$NaClO_4$ and 2·0M-NaCl to 2·0M-$HClO_4$ increase k_0^{NO} at 25° by 86 and 72%, respectively, and the trend is similar for addition of

TABLE 3

Effect of added sulphanilamide on the decomposition rates of *N*-n-butyl-*N*-nitrosoacetamide in 2·0M-HCl at 25°: initial [MeCONBu^n(NO)] *ca.* 1·7 × 10^{-4}M

10^2[Sulphanilamide]/M	10^4k_0/s^{-1}	$[HNO_2]_\infty$ (%)	$10^4k_0^{NO}$/s^{-1}	$10^4k_0^{N_2}$/s^{-1}
0·24	3·00	8·62	0·26	2·74
2·4	3·08	7·42	0·23	2·77

TABLE 4

Effect of added salts on the decomposition rates of *N*-n-butyl-*N*-nitrosoacetamide in $HClO_4$ at 25°: initial [MeCONBu^n(NO)] 1·6—2·0 × 10^{-4}M

$[HClO_4]$/M	[Salt]/M	10^4k_0/s^{-1}	$[HNO_2]_\infty$ (%)	$10^4k_0^{NO}$/s^{-1}	$10^4k_0^{N_2}$/s^{-1}
1·00		1·40	8·8	0·12	1·28
1·00	1·0-$NaClO_4$	1·68	12·3	0·21	1·47
1·00	1·0-NaCl	1·37	10·9	0·15	1·22
1·00	0·1-NaBr	0·95			
1·00	0·1-NaI	1·07			
2·00		2·05	17·6	0·36	1·69
2·00	1·0-$NaClO_4$	2·05	26·6	0·55	1·50
2·00	1·0-NaCl	2·17	23·0	0·50	1·67
2·00	2·0-$NaClO_4$	2·63	29·3	0·77	1·86
2·00	2·0-NaCl	2·83	21·8	0·62	2·21
2·00	3·0-$NaClO_4$	3·10	33·3	1·03	2·07
2·00	3·0-NaCl	3·50	24·1	0·84	2·66

1·0M- and 3·0M-salts at other acidities. Both $NaClO_4$ and NaCl also increase the value of $k_0^{N_2}$: catalysis by $NaClO_4$ is again stronger than NaCl, but in both cases the effect is less marked than for k_0^{NO}. The accelerative effect of $NaClO_4$ may seem surprising in view of our comment above, but it probably stems in this instance from a salt effect on the acidity (H_A value) of the medium. Significantly, $NaClO_4$ is known to have a similar effect to NaCl

[15] K. Yates, H. Wai, G. Welch, and R. A. McClelland, *J. Amer. Chem. Soc.*, 1973, **95**, 418.
[16] J. H. Ridd, *Quart. Rev.*, 1961, **15**, 418.

on the acidity of $HClO_4$,[17] and the rate of deamination has a lower acidity dependence than that of denitrosation.

Solvent Deuterium Isotope Effects.—Rates of decomposition and product ratios at 25° were also measured in D_2SO_4 to evaluate the solvent deuterium isotope effect by comparison with H_2SO_4. Values of k_0^{NO} and $k_0^{N_2}$ in both acids are plotted against the acid concentration in Figure 3. It is clear that $k_0^{NO}(D_2SO_4) < k_0^{NO}(H_2SO_4)$ for any given acidity whereas the order is reversed for deamination, *i.e.* $k_0^{N_2}(D_2SO_4) > k_0^{N_2}(H_2SO_4)$. Interpolated values of the

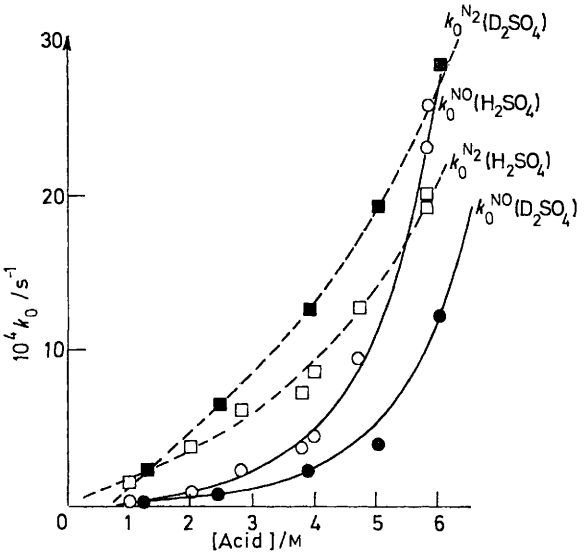


FIGURE 3 Solvent deuterium isotope effects for the decomposition rates of *N*-n-butyl-*N*-nitrosoacetamide in sulphuric acid at 25°. Initial [MeCONBu^n(NO)] 1·6—2·0 × 10^{-4}M, [sulphanilamide] 2·4 × 10^{-2}M

isotopic rate ratios are summarised in Table 5 for 2—5M-D_2SO_4.

TABLE 5

Interpolated values (Figure 3) of the solvent deuterium isotope effects for the decomposition rates of *N*-n-butyl-*N*-nitrosoacetamide in sulphuric acids at 25°

[Acid]/M	$k_0^{NO}(H_2SO_4)/k_0^{NO}(D_2SO_4)$	$k_0^{N_2}(H_2SO_4)/k_0^{N_2}(D_2SO_4)$
2·0	1·8	0·77
3·0	1·83	0·71
4·0	2·0	0·71
5·0	2·05	0·75

Activation Parameters.—The effect of temperature (0—25°) on both deamination and denitrosation was measured for 5M-$HClO_4$, where the contribution from each pathway is about equal and so experimental errors are minimised. These data are given in Table 6. From the corresponding

TABLE 6

Temperature dependence of decomposition rates for *N*-n-butyl-*N*-nitrosoacetamide in 5·0M-$HClO_4$: initial [MeCONBu^n(NO)] 1·6—2·0 × 10^{-4}M; [sulphanilamide] = 2·4 × 10^{-2}M

T/K	$10^4 k_0$/s^{-1}	[HNO_2] (%)	$10^4 k_0^{NO}$/s^{-1}	$10^4 k_0^{N_2}$/s^{-1}
273·3	0·53	34·4	0·18	0·35
281·15	1·50	41·2	0·62	0·88
289·15	3·50	42·6	1·49	2·01
298·0	9·46	45·7	4·33	5·13

Arrhenius plots of either log k_0^{NO} or log $k_0^{N_2}$ against $1/T$, activation energies and entropies were calculated for 16°. In turn, these gave values of $\Delta F^{\ddagger}$ 89·9 and 89·3 kJ mol^{-1} for

	E_a/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
Denitrosation	88·3	−13·5
Deamination	74·1	−60·8

the free energy of activation for denitrosation and deamination, respectively.

DISCUSSION

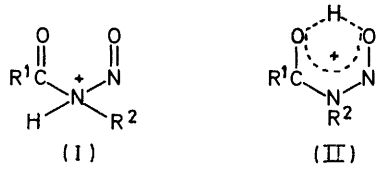
Both the products and the experimental dependences of $k_0^{N_2}$ and k_0^{NO} show that decomposition of *N*-n-butyl-*N*-nitrosoacetamide proceeds by at least two concurrent pathways, each of which has first-order dependence on substrate concentration. At low acidities, $k_0^{N_2} > k_0^{NO}$, but the inequality reverses at high acidity because acid catalysis is more important for denitrosation than deamination. This conclusion is borne out by the acidity function plots (Figure 2), where the lower slope for deamination suggests that H_2O is involved in the rate limiting step.

Another important mechanistic observation is the independence of k_0^{NO} on either added sulphanilamide or chloride ion, which implies that neither release of nitrous acid (NO^+) nor its attack on sulphanilamide is kinetically significant. Instead an earlier step on the reaction path must be rate limiting and direct evidence to this effect comes from the solvent deuterium isotope effects. Thus, at the same molar acidity, $k_0^{NO}(H_2SO_4)/k_0^{NO}(D_2SO_4)$ *ca.* 1·8—2·0, which shows that proton transfer from the solvent to the nitrosamide must be slow. The solvent isotope effects, in concert with the different acidity dependences for deamination and denitrosation noted above, exclude a common rate-limiting step for both reactions. Since an *inverse* solvent isotope effect [$k_0^{N_2}(H_2SO_4)/k_0^{N_2}(D_2SO_4)$ *ca.* 0·74] is found for deamination, formation of the conjugate acid must occur in a rapid pre-equilibrium step rather than be rate limiting.

The solvent isotope effect and activation parameters also eliminate any mechanisms in which both deamination and denitrosation occur *via* a common conjugate acid intermediate. If formation of this conjugate acid is to be slow for denitrosation, but some subsequent higher energy step rate-limiting for deamination, as the solvent isotope effect implies, then the common conjugate acid intermediate would preferentially decompose *via* the lower energy pathway to products, to give *N*-n-butylacetamide and nitrous acid (NO^+) exclusively. This deduction is nicely confirmed by the activation parameters, in particular the almost identical values of $\Delta F^{\ddagger}$ for denitrosation (89·9 kJ mol^{-1}) and deamination (89·3 kJ mol^{-1}). Their similarity unequivocally excludes any shift to a later, more energetic step for the deaminative pathway. We therefore believe that deamination and denitrosation must proceed *via* two independent pathways involving unique conjugate acid intermediates.

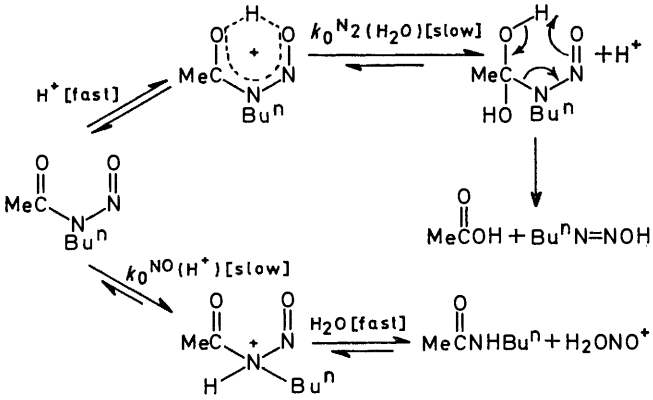
[17] C. H. Rochester, 'Acidity Functions,' Academic Press, London, 1970, p. 101.

The structure of each of these conjugate acids has to be deduced indirectly, because we have been unable to detect substantial protonation of the substrate even in concentrated (7M) $HClO_4$. Only two structures seem feasible for these, however, one from protonation of the amino nitrogen atom (I), the other (II) from protonation of either the carbonyl or nitroso oxygen atoms. For (II), both alternatives should lead to the same mesomeric ion structure as written because of intramolecular hydrogen bonding to the second oxygen atom. Thus the immediate mechanistic problem is that of deciding which of the two conjugate acids is the intermediate on each decomposition pathway.



(I) (II)

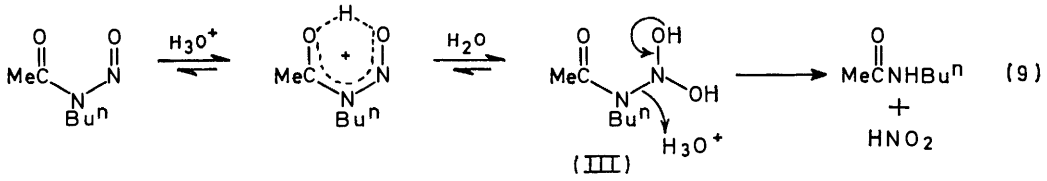
The preferred alternative for several reasons is that described by Scheme 2. The main factor influencing



SCHEME 2 Mechanism for concurrent deamination and denitrosation of *N*-n-butyl-*N*-nitrosoacetamide

our choice is that protonation, leading to denitrosation has to be slow, which suggests that the least stable conjugate acid lies on this pathway. Both these conditions are more effectively met by (I), which lacks the stabilising intramolecular hydrogen bond of (II), and whose rate of formation, as discussed in detail below, will be retarded by extensive delocalisation of the nitrogen lone pair electrons towards the nitroso oxygen atom. Further, release of nitrous acid from (II) may only be effected by nucleophilic (H_2O) attack at the nitroso nitrogen atom to give a tetrahedral intermediate (III), which then collapses to products [equation (9)]. It seems unlikely that nucleophilic species, such as H_2O, would not concurrently attack the carbonyl carbon atom of (II) to effect deaminative hydrolysis, which, in turn, implies a common intermediate for both decomposition pathways. Also, the addition of H_2O across the $-N{=}O$ group to form a tetrahedral intermediate similar to (III) is not observed for the hydrolysis of alkyl nitrites [18] or *N*-nitrosamines.[19] Finally, there is unequivocal evidence that denitrosation of *N*-n-butyl-*N*-nitrosoacetamide is *not* catalysed by various nucleophilic species added to the reaction solutions, so clearly nitrous acid (or NO^+) is released from the conjugate acid intermediate either unimolecularly or by a rapid, bimolecular process. This condition is more likely to be met for denitrosation *via* the conjugate acid (I) than (II).

The Denitrosation Pathway.—One remarkable feature of this reaction is the rate-limiting proton transfer from the solvent to the amino nitrogen atom. With the exception of one or two recent examples,[20] proton transfer to both oxygen and nitrogen bases is usually fast, often proceeding on encounter.[21] So, clearly, special factors must be important in our case. The nitroso-group is sufficiently electron withdrawing for *N*-nitroso-compounds to behave as 1,3-dipolar ions.[22] This should considerably reduce the basicity of the amino nitrogen atom and our results confirm this explanation: thus assuming that the proton loss from (I) proceeds at the encounter rate, the pK_A of the amino nitrogen of *N*-n-butyl-*N*-nitrosoacetamide is *ca.* -15, equivalent to ΔF^0 (for ionisation) 86 kJ mol^{-1}. For the denitrosation $\Delta F^{\ddagger}$ *ca.* 89 kJ mol^{-1}, so the transition state for the reaction must be very product-like, with the proton almost completely transferred. This conclusion also satisfies the strong acidity dependence [dlog k_0^{NO}/d($-H_A$) 1·08 for $HClO_4$] and the relatively small $\Delta S^{\ddagger}$ ($-13{\cdot}5$ J K^{-1} mol^{-1}). Because proton transfer is slow for denitrosation, this pathway will be subject to general acid catalysis. In turn this accounts for the faster reaction rate observed in H_2SO_4 relative to $HClO_4$ at a common H_A value.

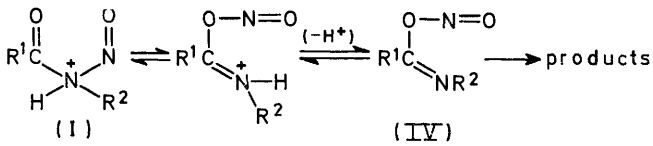


(III) (9)

Firm conclusions about the way in which NO^+ is expelled from (I) cannot be drawn from the kinetic results because this step is post rate-limiting. It cannot be very energetically demanding, however, because ΔF^0

[18] A. D. Allen, *J. Chem. Soc.*, 1954, 1968.
[19] A. J. Buglass, B. C. Challis, and A. D. Gribble, to be published.
[20] M. L. Bade, *J. Amer. Chem. Soc.*, 1971, **93**, 949; F. Hibbert, *J.C.S. Chem. Comm.*, 1973, 463.
[21] M. Eigen, *Angew. Chem.*, 1964, **3**, 1.
[22] A. L. Fridman, F. M. Mukhametshin, and S. S. Novikov, *Russ. Chem. Rev.*, 1971, **40**, 34.

is of similar magnitude to $\Delta F^{\ddagger}$. This condition would be met either by unimolecular expulsion of NO^+ from (I)



or by an intramolecular rearrangement to form the *O*-nitroso-intermediate (IV). The latter explanation is consistent with recent proposals that neutral amides undergo electrophilic attack at the oxygen atom, and then rearrange to the more stable *N*-substituted product.[7]

The Deamination Pathway.—Hydrolytic cleavage of ordinary amides in acidic conditions usually involves rate-limiting attack by water on the conjugate acid, with rapid (or possibly synchronous) expulsion of the amino-fragment.[7] The same mechanism should prevail for *N*-n-butyl-*N*-nitrosoacetamide, particularly as the leaving group (*N*-nitrosamine) is much better in this case. The experimental data support this conclusion. Proton transfer to form (II) is clearly rapid and both $\Delta S^{\ddagger}$ and the reduced acidity dependence [dlog $k_0^{N_2}$/d($-H_A$) *ca.* 0·37 for $HClO_4$] are indicative of slow bimolecular attack by H_2O. An interesting point is that deamination occurs at a significant rate even in neutral solution (*i.e.* the plot in Figure 2 shows a significant intercept). Since deamination of neutral *N*-nitrosamides is also readily effected by various nucleophilic species,[23] the intercepts must represent the 'spontaneous' rate attributable to H_2O, itself, acting as a nucleophile plus a minor contribution from the thermal decomposition pathway.

Conclusions.—Acid catalysed decomposition of *N*-nitrosamides clearly proceeds by two pathways relevant to carcinogenesis. Transnitrosation undoubtedly occurs in dilute acid solution, but it is not possible to deduce whether this occurs directly or *via* HNO_2 intermediates. Significantly, too, concurrent deamination produces a primary *N*-nitrosamine, which may act as an alkylating agent. The results also provide interesting information about the mechanism of amide nitrosation, a reaction that was hitherto thought [24] to be catalysed by halide ions in common with many other nitrosation reactions.[16] The present results, in conjunction with the principle of microscopic reversibility, show that halide ion catalysis cannot occur. We have confirmed this deduction by examining neutral salt effects on the nitrosation rate ($v = k_2[MeCONH_2][HNO_2]$) of acetamide (see Table 6). Addition of NaCl does increase the rate of nitrosation slightly, but the larger effect of $NaClO_4$ shows this arises only from salt effects increasing the acidity of the medium.[17] Further, proton loss from the amino nitrogen atom of (I) must be the rate-limiting step for the nitrosation of amides.

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[4/875 *Received*, 2*nd May*, 1974]

[23] C. N. Berry and B. C. Challis, to be published.
[24] Z. Kricsfalussy and A. Bruylants, *Bull. Soc. chim. belges*, 1964, **73**, 96.