The Chemistry of Nitroso-compounds. Acid-catalysed Decomposition of *N*-n-Butyl-*N*-nitrosoacetamide—An Unusual Slow Proton Transfer to Nitrogen

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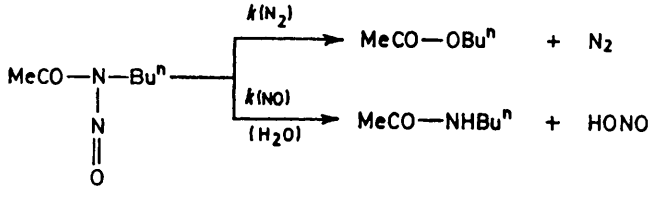
Summary The decomposition of *N*-n-butyl-*N*-nitrosoacetamide at 25° involves both deamination and denitrosation; for the latter pathway, proton transfer to the amide-nitrogen is rate-limiting.

WE have recently shown that some secondary *N*-nitrosamines may act as proximate carcinogens by direct nitrosation of other bases[1] and with this in mind our investigations have been extended to *N*-nitrosamides. In non-polar solvents, secondary *N*-nitrosamides regenerate the amide quantitatively with HBr[2] and undergo thermal deamination,[3] but little is known about their behaviour in aqueous acids.



SCHEME. *Decomposition of* N-*n-butyl*-N-*nitrosoacetamide in aqueous acid.*

Our initial investigation has concerned *N*-n-butyl-*N*-nitrosoacetamide, one of the more thermally stable compounds.[2] In aqueous acids at 25°, decomposition proceeds readily by two concurrent pathways which can be regarded as the release of either nitrogen [$k(N_2)$] or nitrous acid [$k(NO)$] as shown in the Scheme. Understandably, both the ester and amide products accompanying decomposition are further hydrolysed under our conditions.

We have measured the overall decomposition rate [$k_0 = k(N_2) + k(NO)$] in two ways: from the disappearance of the nitrosamide (λ 244 nm, log ϵ 4·01) in accordance with equation (1) and, secondly, from the *in situ* diazotisation of sulphanilamide (*cf.* Shinn's[4] method) which is proportional to the formation of nitrous acid. Values of k_0 obtained by

$$v = k_0[\mathrm{MeCONBu^n(NO)}] \quad (1)$$

each method show excellent agreement ($\pm 5\%$). The individual contributions from $k(NO)$ and $k(N_2)$ to k_0 have been deduced from the amount of denitrosation after 10 half lives [$k(NO) = k_0\{\%[HNO_2]_\infty/100\}$]. Representative values of these coefficients are listed in the Table and they show several characteristic features. At low acidities, $k(N_2) > k(NO)$, but the inequality is reversed at high acidities, showing that acid catalysis is more important for denitrosation than deamination. Furthermore, $k(NO)$ is independent of the added sulphanilamide and added chloride ion; thus neither release of nitrous acid nor its attack on the sulphanilamide can be kinetically significant. This implies that an earlier step is rate-limiting for denitrosation and direct evidence to this effect comes from measurements in deuteriated solvents (Figure). At the same molar acidity, $k(NO)$ in D_2SO_4 is *ca.* 2·3 times less than in H_2SO_4, showing that proton transfer from the solvent to the nitrosamide must be slow. We note that an *inverse* solvent isotope effect pertains to deamination [$k(N_2)(H_2SO_4)/k(N_2)(D_2SO_4)$] = 0·7, so this reaction must involve a rapid pre-equilibrium protonation.

It is not firmly established which atom is undergoing rate-limiting protonation for the denitrosation pathway, but several considerations point to the amide nitrogen atom (I). In particular, protonation of either nitroso- or carbonyl-oxygen atoms would probably lead to a common hydrogen-bonded conjugate acid (II). Since deamination and denitrosation should then result from H_2O attack on either the carbonyl carbon atom or the nitroso nitrogen atom of (II), it is difficult to reconcile this with the marked differences of kinetic acidity dependence and solvent isotope effect. Furthermore, the observation that the solvent isotope effect lies in an opposite sense for denitrosation and deamination irrespective of the relative magnitudes of $k(N_2)$ and $k(NO)$ (Figure), precludes any mechanism involving a common conjugate acid for the two decomposition pathways.

The most remarkable aspect of these results is that proton transfer from solvent to nitrogen is rate-limiting for denitrosation. This may be associated with the extremely low basicity of the nitrosamide molecule (our data give $pK_{BH^+} = ca. -15$ assuming deprotonation is diffusion controlled). One factor contributing to this low basicity may be extensive conjugation of the lone-pair nitrogen electrons with either the carbonyl- or nitroso-groups and, in this respect, nitrosamides may resemble carbon bases such as nitroalkane anions.[5] The phenomenon should be general for other oxygen and nitrogen bases where lone-pair electrons are delocalized and experiments are in hand to check this hypothesis. Two other important conclusions come from our results. The first is that, contrary to earlier reports,[6] the nitrosation of amides cannot be catalysed by chloride ion. This is confirmed by preliminary examination of neutral salt effects on the nitrosation rate ($v = k_2$-$[MeCONH_2][HNO_2]$) of acetamide at 0° in 1M-$HClO_4$ [k_2(1M-$NaClO_4$) = $4{\cdot}8 \times 10^{-3}$ min^{-1} $mol^{-1}l$; k_2(1M-NaCl) = $1{\cdot}2 \times 10^{-3}$ min^{-1} $mol^{-1}l$] and by more extensive investigations by Stedman and his colleagues.[7] The second is that transnitrosation from *N*-nitrosamides to other amines occurs readily, but the present results do not show whether or not this involves the intermediacy of nitrous acid.

Decomposition rates of N-*n-butyl*-N-*nitrosoacetamide at* 25°. *Initial* [$MeCONBu^n(NO)$] ca. 2×10^{-4}M

[Acid]/M	$10^2 \times$ [Sulphanilamide]/M	[Salt]/M	$10^2 \times k_0/min^{-1}$	(% HNO_2)∞	$10^2 \times k(NO)/min^{-1}$	$10^2 \times k(N_2)/min^{-1}$
0	2·4	—	0·031	0	—	0·031
1·00 $HClO_4$	2·4	—	0·84	8·8	0·074	0·766
2·00 $HClO_4$	2·4	—	1·23	17·6	0·211	1·22
4·02 $HClO_4$	2·4	—	2·72	41·8	1·14	1·58
6·00 $HClO_4$	2·4	—	14·73	66·8	9·84	4·89
2·00 HCl	0·24	—	1·79	8·6	0·154	1·64
2·00 HCl	2·4	—	1·84	7·9	0·145	1·69
1·00 $HClO_4$	2·4	1·00 $NaClO_4$	1·01	12·3	0·124	0·886
1·00 $HClO_4$	2·4	1·00 NaCl	0·82	10·9	0·089	0·731

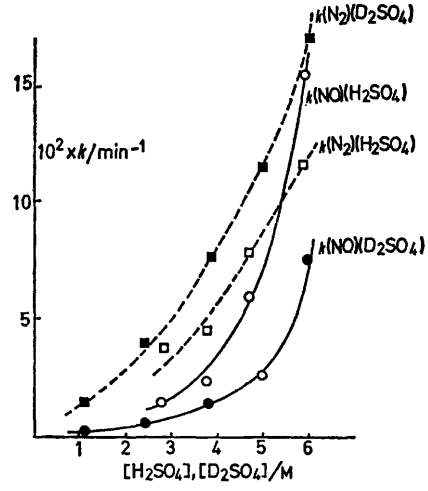
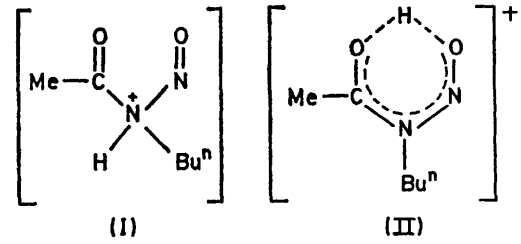


FIGURE. *Solvent isotope effects for the decomposition of* N-*n-butyl*-N-*nitrosoacetamide in sulphuric acids at* 25°.



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