N-Nitroso Compounds. Part 1. Structure and Decomposition of *N*-Nitroso-2-arylimidazolines in Aqueous Acidic Media

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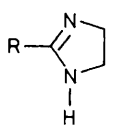
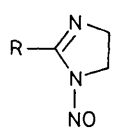
Kinetic measurements for the acid-catalysed decomposition of *N*-nitroso-2-arylimidazolines are reported. Reactions are first-order in both [substrate] and [H^+]. Two products are formed; an oxazoline, which is the product of hydrolysis of the amidine moiety, and the parent imidazoline formed by denitrosation of the substrate. These products arise from two competing pathways both of which are acid catalysed. The solvent isotope effects for the denitrosation, $k_{NO}^{D^+}/k_{NO}^{H^+}$, and amidine hydrolysis, $k_A^{D^+}/k_A^{H^+}$, are 3.1 and 3.5, respectively. The denitrosation pathway, but not amidine hydrolysis, is catalysed by nucleophilic anions, and a value of 1.7 for the Swain–Scott constant, *s*, is obtained. In the absence of nucleophilic anions, amidine hydrolysis is preferred over denitrosation, $k_A^{H^+}$ being twice as large as $k_{NO}^{H^+}$ at 25 °C. Substitutents in the 2-aryl ring affect the rate of decomposition giving Hammett ρ values of 0.7 for denitrosation and 1.0 for amidine hydrolysis, which reflect the proximity of the reacting centres to the substituents. Values of the activation parameters are $\Delta H_{NO}^{\ddagger}$ 74 kJ mol^{-1}, $\Delta H_A^{\ddagger}$ 74 kJ mol^{-1}, $\Delta S_{NO}^{\ddagger}$ −48 J K^{-1} mol^{-1} and $\Delta S_A^{\ddagger}$ −43 J K^{-1} mol^{-1}. The data are interpreted in terms of a fast equilibrium protonation of the substrate, followed by competitive attack at the protonated substrate, either of water or nucleophilic anions at the nitroso nitrogen atom, or of water at the amidine carbon atom. Protonation is required to activate the substrate, the substrate being recovered from neutral or alkaline solutions unchanged. The mechanism is discussed with reference to the analogous reactions of *N*-nitrosoamines and *N*-nitrosoamides.

Imidazolines [*e.g.* (**1**)] are cyclic amidines that have a variety of biological effects.[1] For example, fenmetozole (**2**) and dazadrol (**3**) are examples of antidepressive imidazolines, whereas tolazoline (**4**) and phentolamine (**5**) are known vasodilators.[1–3] Many of these actions are known to lie in the ability of the imidazolines to bind to the α_1/α_2-adrenergic receptors.[3] Amidines, like guanidines, are generally more basic than aliphatic amines, and are capable, therefore, of undergoing nitrosation, as has been reported for the guanidine anti-ulcer drug, cimetidine.[4] As far as we are aware, no such nitrosated imidazolines have yet been reported. Indeed, few nitrosoamidines have been studied. *N*-Nitrosochlordiazepoxide (**6**) the nitroso derivative of Librium (**7**), is known to undergo displacement of the *N*-nitroso-*N*-methylamino moiety by alcohols, hydrazine, and hydroxide ion,[5,6] but in hydrochloric acid it also undergoes competitive denitrosation (Scheme 1).[6]

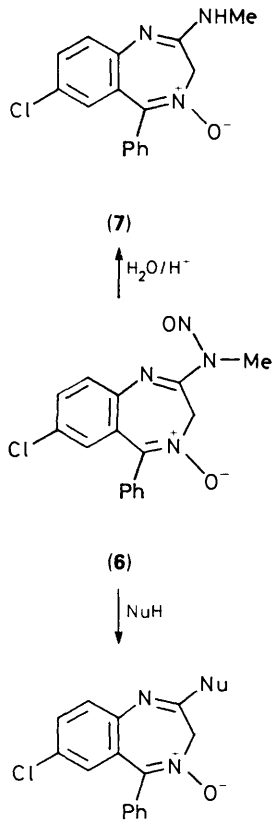


(**1**) R = H
(**2**) R = 3,4-$Cl_2C_6H_3OCH_2$
(**3**) R = Ph(OH)(2-C_5H_4N)C
(**4**) R = $PhCH_2$
(**5**) R = Ph(3-HOC_6H_4)NCH_2



(**8**) R = 4-MeC_6H_4
(**9**) R = Ph
(**10**) R = 4-ClC_6H_4
(**11**) R = 4-$NO_2C_6H_4$

We were therefore interested in studying the chemistry of *N*-nitrosoimidazolines in order to investigate further these two modes of decomposition and to determine whether or not such compounds might generate mutagenic alkylating agents. Herein we report the synthesis of the nitrosoimidazolines (**8**)–(**11**),



Scheme 1.

discuss their structure and describe their decomposition in aqueous acidic solutions.

Experimental

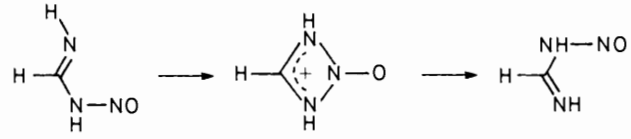
Substrates.—2-Phenylimidazoline (Aldrich) was purified by chromatography. Suitable substituted 2-arylimidazolines were synthesised by known procedures.[7] *N*-Nitroso-2-arylimidazolines were prepared from the parent imidazolines by standard nitrosation procedures with N_2O_4.[8] Prepared in this way were (**8**) m.p. 62–64 °C, ν_{max} 3 000, 1 610, 1 450, 1 170, 1 000, 950, and 770 cm^{-1}; δ($CDCl_3$) 4.0 (2 H, t), 4.20 (2 H, t), 7.28 (2 H, d, *J* 8 Hz), and 7.80 (2 H, d, *J* 8 Hz) (Found: C, 63.0; H, 6.1; N, 21.5. Calc. for $C_{10}H_{11}N_3O$: C, 63.5; H, 6.1; N, 22.0%); (**9**) m.p. 58–60 °C, ν_{max} 1 600, 1 000, and 850 cm^{-1}; δ($CDCl_3$) 3.80 (2 H, t), 4.30 (2 H, t), and 8.00 (5 H, m) (Found: C, 61.6; H, 5.1; N, 24.0. Calc. for $C_9H_9N_3O$: C, 61.7; H, 5.2; N, 24.0%); (**10**) m.p. 98–100 °C, ν_{max} 1 600, 1 220, 1 000, and 830 cm^{-1}, δ($CDCl_3$) 4.00 (2 H, t), 4.20 (2 H, t), 7.38 (2 H, d, *J* 8.5 Hz), and 7.70 (2 H, d, *J* 8.5 Hz) (Found: C, 51.3; H, 3.8; N, 20.2. Calc. for $C_9H_8N_3OCl$: C, 51.5; H, 3.8; N, 20.0%); (**11**) m.p. 118–120 °C, ν_{max} 1 590, 1 240, 1 000, and 830 cm^{-1}; δ($CDCl_3$) 4.10 (2 H, t), 4.20 (2 H, t), 8.25 (2 H, d, *J* 9 Hz), and 8.38 (2 H, d, *J* 9 Hz) (Found: C, 49.2; H, 3.8; N, 25.0. Calc. for $C_9H_8N_4O_3$: C, 49.1; H, 3.6; N, 25.0%).

Products.—Two products were detected by t.l.c. from the acid-catalysed decomposition of the *N*-nitrosoimidazoline (**9**). These were isolated by neutralisation of the reaction mixture, extraction into $CHCl_3$, and chromatography. One corresponded to the parent imidazoline (confirmed by comparison with the standard material), the other to the 2-phenyloxazoline (**14**; Ar = Ph) which had *m/z* 147, δ(CD_3OD) 3.5 (2 H, t), 3.75 (2 H, t), and 7.4–7.7 (5 H, m); ν_{max} 3 000, 1 600, and 1 100 cm^{-1}.

Kinetics.—All reagents were either of Analar grade or purified by recrystallisation or distillation prior to use. Deionised water was used throughout this study. Kinetic runs were carried out in thermostatted cuvette cells, and were initiated by injecting a small aliquot (30 mm^3) of a dioxane solution of the appropriate *N*-nitrosoimidazoline into the reaction medium. The initial concentration of *N*-nitrosoimidazoline in these reactions was *ca.* 6×10^{-5} mol dm^{-3}. Reactions were monitored by u.v. spectrophotometry and exhibited clean isosbestic points. Kinetic data were obtained by monitoring reactions at fixed wavelength, usually λ_{max}. Pseudo-first-order rate constants, k_{obs}, determined by this procedure were reproducible to ±5%. Reactions were first-order up to five half-lives. Product ratios were determined at the end of kinetic runs by determining the concentration of NO_2^-, liberated by the denitrosation reaction, using the modified method of Shinn.[9] Since NO_2^- is unstable in acidic media, we routinely constructed calibration curves using solutions containing known nitrite concentrations (at levels similar to those released by the denitrosation of the nitrosoamidine) that had been aged for times comparable to the reaction mixtures. In general, the value of log ε (at λ_{max} 541) of 4.53, calculated from the standard curves, is smaller than the literature value of 4.71.[10] This is evidence that nitrite does indeed decompose during the lifetime of the reactions, but the use of standard curves enables us to allow for such loss. Concentrations of NO_2^- were accurate to ±10%. However, in several reactions we also determined the concentrations of the product imidazoline and oxazoline by h.p.l.c. using a C18 reversed-phase system. The concentrations determined by the two methods agreed to within ±15%, so we routinely employed the colourimetric procedure. Errors in the rate constants for denitrosation, k'_{NO}, and hydrolysis, k'_A, are therefore ±15% for k'_{NO} and 10–30% for k'_A.

Results and Discussion

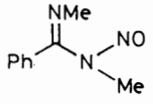
Structure of N-*Nitrosoimidazolines.*—We recently reported the rearrangement of imidoyl nitrites to *N*-nitrosoamides.[11] This reaction involves a [1,3]-nitroso-group migration and we were interested in the possibility that the analogous *N*-nitrosoamidines might be nitrosotopic. Theoretical calculations have been reported for acyclic *N*-nitrosoamidines and these show that a fast, reversible [1,3]-shift of the nitroso group between the two amidine nitrogen atoms should be observable.[12] The reaction is predicted to proceed *via* a mesoionic intermediate (**12**) (Scheme 2).



(**12**)

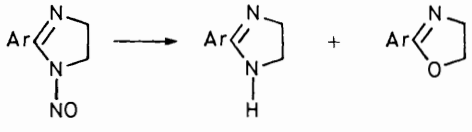
Scheme 2.

Such a migration requires an *E,syn* orientation of the nitrosoamidine to enable the imine-nitrogen lone pair to attack the nitroso nitrogen atom. Clearly, nitrosoimidazolines are constrained to adopt a *Z,syn* orientation making it impossible for the reacting centres to achieve the correct alignment for an intramolecular nitroso-group migration. The ^1H n.m.r. spectra of the four nitrosoimidazolines used in the present work all exhibit two distinct triplets for the two imidazoline CH_2 groups at room temperature (see the Experimental section). This signifies that the nitroso group is not migrating rapidly on the timescale of the ^1H n.m.r. experiment. Corroboration of this comes from the ^{13}C n.m.r. spectra which show two signals for the CH_2 carbon atoms at *ca.* 45 and 53 ppm. Raising the temperature to 100 °C (in chlorobenzene solvent) does not reveal any broadening or coalescing of peaks in either the ^1H or ^{13}C n.m.r. spectra. The nitroso group does not therefore appear to be nitrosotopic, even intermolecularly, under these conditions. To establish whether or not this was related to conformation, we briefly studied the acyclic *N,N'*-dimethyl-*N*-nitrosobenzamidine (**13**). This compound displays methyl singlets at δ2.95 and 3.23 at 25 °C and these do not change up to 100 °C.



(**13**)

Hydrolysis of N-*Nitrosoimidazolines.*—*N*-Nitrosoimidazolines are stable in both neutral and basic solutions, and can be recovered unchanged from 0.01 mol dm^{-3} sodium hydroxide solutions after 12 h. In acidic solution, however, *N*-nitrosoimidazolines decompose to give two different compounds, (**1**) and (**14**), which are not interconvertible under the conditions of the experiments (Scheme 3).



(**1**) (**14**)

Scheme 3.

The reactions can be monitored by ultraviolet spectroscopy and they exhibit clear isosbestic points. Thus, the products (**1**)

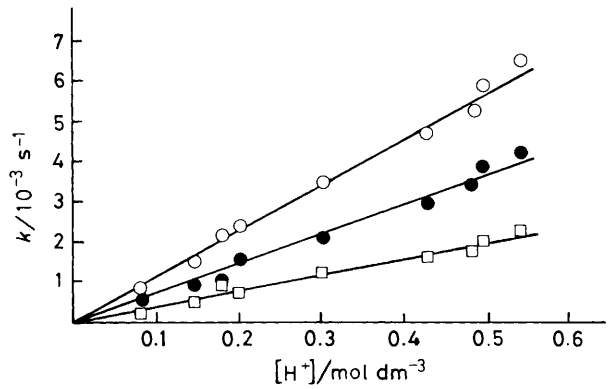


Figure. Plot of k_{obs}, k'_{NO}, and k'_{NO} *versus* [H$^+$] for the decomposition of (**9**) at 25 °C. μ = 1 mol dm^{-3}.

Table 1. Values of the rate constants k_{NO}^{H+} and k_A^{H+} for (**8**)–(**11**) at 25 °C, μ = 1 mol dm^{-3}.

Compound	$k_{NO}^{H+}/10^{-3}$ dm^3 mol^{-1} s^{-1}	$k_A^{H+}/10^{-3}$ dm^3 mol^{-1} s^{-1}
(**8**)	3.0	7.2
(**9**)	4.0	7.95
(**10**)	4.9	14.0
(**11**)	16.0	70.2

and (**14**) arise from two concurrent competing pathways; (**1**) is the product of simple denitrosation, whereas (**14**) is the product of hydrolysis of the nitrosoamidine group. In perchloric acid solutions, the decomposition of compounds (**8**)–(**12**) follows first-order kinetics [equation (1)], from which it follows that

$$\text{Rate} = k_{obs}[\text{substrate}] \quad (1)$$

both the denitrosation and hydrolysis reactions are also first-order. The Figure shows that the value of k_{obs} increases linearly with the acid concentration which indicates that the reaction is acid catalysed. The lack of an intercept verifies the earlier observation that the compounds are stable in neutral solutions [equation (2)].

$$\text{Rate} = k'[\text{substrate}][H^+] \quad (2)$$

The pseudo-first-order rate constants for denitrosation, k'_{NO}, and hydrolysis, k'_A, can be obtained from the values of k_{obs} and the ratio of the products as described in the Experimental section. That both k'_A and k'_{NO} also depend on [H$^+$] can be clearly seen from the Figure. This strongly suggests that denitrosation and nitrosoamidine hydrolysis arise from competitive decomposition of a protonated nitrosoamidine moiety. Under these conditions, the hydrolysis reaction is the preferred process, k'_A being some 1.9 times k'_{NO}. However, as discussed below, denitrosation can become the dominant reaction.

Substituent Effects.—From plots such as the Figure, it is possible to obtain the rate constants k_{NO}^{H+} and k_A^{H+}, for the acid-catalysed denitrosation and hydrolysis reactions, respectively, for each of the compounds (**8**)–(**11**). Such values are contained in Table 1. For both reactions, electron-withdrawing groups in the 2-aryl ring facilitate the reaction, and approximate values for the Hammett parameter $\rho_A^{H'}$ and $\rho_{NO}^{H'}$ of 1.0 ± 0.1 and 0.7 ± 0.1, respectively can be calculated from the limited data set available. These values are inconsistent with the influence of the substituent on substrate protonation, where a negative ρ value would be expected. They do reflect, however, the ability of the substituent in the aromatic ring to enhance nucleophilic attack (in this instance, by water) at the nitroso group or the amidine carbon atom. Indeed, if the reaction proceeds *via* a rapid protonation of the substrate, as we argue later, then the experimentally determined ρ values contain components for both protonation and nucleophilic attack. Since ρ for protonation should be negative, $\rho_A^{H^+}$ and $\rho_{NO}^{H^+}$ must be larger than the values reported here. The slightly greater susceptibility of the hydrolysis reaction to substituent effects, if real, probably relates to the relative proximity of the amidine group, as compared with the nitroso group, to the substituent.

Effect of Added Anions.—It is well known that the denitrosation of nitrosoamines is catalysed by ions such as Cl$^-$, Br$^-$, I$^-$, and SCN$^-$.[13] We therefore studied the effect of added Cl$^-$, Br$^-$, and SCN$^-$ on the decomposition of the nitrosamidine (**9**), and the data are collected in Table 2. From the values of k_{obs}, it is clear that SCN$^-$, Br$^-$, and, to a lesser extent, Cl$^-$, catalyse the decomposition of (**9**). The nature of this catalysis becomes apparent on inspection of the values of k'_A and k'_{NO}; the denitrosation is catalysed by the added anion but the hydrolysis of the amidine function is not. The small apparent increase of k'_A as [SCN$^-$] or [Br$^-$] is increased almost certainly results from the inaccuracy in determining the product NO_2^- concentration; since k'_A and k'_{NO} are determined by difference, errors become magnified. The data in Table 3 show that the reaction is insensitive to the ionic strength of the medium. From plots of k'_{NO} *versus* [SCN$^-$], [Br$^-$], or [Cl$^-$], catalytic rate constants for the denitrosation of (**9**) by these ions, k_{NO}^{SCN}, k_{NO}^{Br}, and k_{NO}^{Cl}, respectively, were determined. Values of k_{NO}^{SCN} 4.04 dm^3 mol^{-1} s^{-1}, k_{NO}^{Br} 1.8 × 10^{-2} dm^3 mol^{-1} s^{-1}, and k_{NO}^{Cl} 2 × 10^{-3} dm^3 mol^{-1} s^{-1}

Table 2. Effect of Cl$^-$, Br$^-$, and SCN$^-$ on k'_A and k'_{NO} for the decomposition of (**9**) at 25 °C. μ = 1 mol dm^{-3}.

[Cl$^-$]/mol dm^{-3} [a]	$k_{obs}/10^{-3}$ s^{-1}	$k'_A/10^{-3}$ s^{-1}	$k'_{NO}/10^{-3}$ s^{-1}
0	4.85	3.15	1.70
0.2	5.40	3.24	2.16
0.5	5.90	3.22	2.68
0.7	6.30	3.26	3.04
0.9	6.80	3.06	3.74

[SCN$^-$]/mol dm^{-3} [b]	$k_{obs}/10^{-3}$ s^{-1}	$k'_A/10^{-3}$ s^{-1}	$k'_{NO}/10^{-3}$ s^{-1}
0	6.9	4.0	2.9
0.002	15.5	4.4	11.1
0.004	27.7	6.6	21.1
0.007	35.6	6.9	28.7
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[Br$^-$]/mol dm^{-3} [c]	$k_{obs}/10^{-3}$ s^{-1}	$k'_A/10^{-3}$ s^{-1}	$k'_{NO}/10^{-3}$ s^{-1}
0	3.00	2.05	0.95
0.2	6.24	2.54	3.70
0.4	10.0	3.0	7.0
0.6	14.6	3.5	11.1

[a] [H$^+$] = 0.42 mol dm^{-3}. [b] [H$^+$] = 0.5 mol dm^{-3}. [c] [H$^+$] = 0.25 mol dm^{-3}.

Table 3. Effect of the ionic strength on the decomposition of (**9**) at 25 °C in 0.2 mol dm^{-3} H^+.

$\mu(NaClO_4)$	$k_{obs}/10^{-3}$ s^{-1}
0.3	2.0
0.5	1.8
0.75	2.2
1.00	2.2

are obtained. These values give a Swain–Scott susceptibility constant, *s*, of 1.7, which compares with the value of 2.1 previously reported for the denitrosation of *N*-methyl-*N*-nitrosoaniline.[13] Thus, the nucleophilic reactivity of the anion towards the nitroso nitrogen atom in (**9**) has a significant influence on the outcome of the reaction. In aqueous acid containing the non-nucleophilic ClO_4^- ion, amidine hydrolysis is the favoured reaction pathway, with (**14**) accounting for *ca.* 65% of the reaction products. In the presence of SCN^-, the denitrosation pathway rapidly becomes the major pathway and (**1**) can account for >90% of the reaction products.

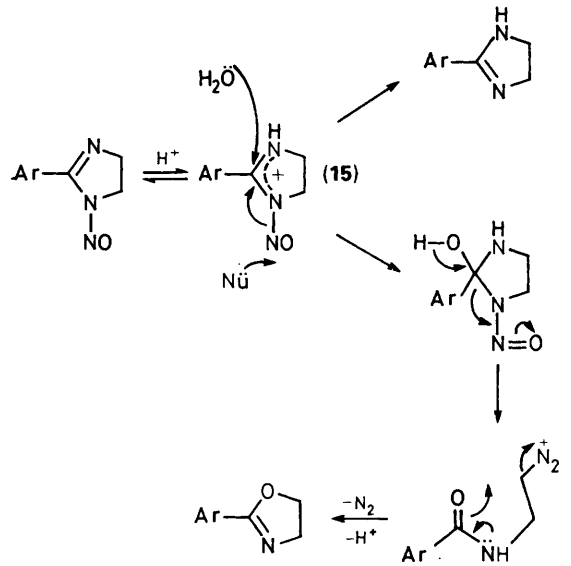
Effect of Temperature.—Data for the hydrolysis of (**9**) at various temperatures in solutions in which $[H^+] = 0.5$ mol dm^{-3} are contained in Table 4. The activation parameters for both denitrosation and amidine hydrolysis are of similar magnitude as expected from the comparable amounts of the two products produced.

Solvent Isotope Effect.—The rate constants for the decomposition of (**9**) in $DClO_4$ solutions were determined at 25 °C (Table 5). Values for $k_{NO}^{D^+}$ and $k_A^{D^+}$ of 12.6×10^{-3} and 27.4×10^{-3} dm^3 mol^{-1} s^{-1}, respectively, were obtained. Comparing these with the values in Table 1 yields an isotope effect of 3.1 for denitrosation and 3.5 for amidine hydrolysis. The similarity and size of these values indicates that both reactions proceed *via* an equilibrium protonation of the substrate.

Mechanism of the Acid-catalysed Decomposition of N-*Nitrosoimidazolines.*—The data presented above are best interpreted in terms of the mechanism outlined in Scheme 4. A rapid equilibrium protonation to form (**15**) is required to activate the substrate to nucleophilic attack; the unprotonated substrate is unreactive to either mode of decomposition. Denitrosation then occurs *via* a nucleophilic attack at the nitroso nitrogen atom to liberate the parent imidazoline (**1**). In the absence of nucleophilic anions, such as Cl^- and SCN^-, solvent water acts as the nucleophile; in their presence these ions act as nucleophiles capable of efficiently bringing about the denitrosation of (**15**). In theory, such a denitrosation should be reversible, and indeed, the imidazolines are easily nitrosated by an excess of NO_2^- ions in acidic media. However, at the concentrations of imidazoline and NO_2^- liberated in these reactions, each *ca.* 3×10^{-5} mol dm^{-3}, we did not observe any nitrosation of (**1**) over the timescale of the decomposition reactions of (**9**), nor did we observe any formation of the oxazoline (**14**). Thus, we can

Table 5. Rate constants, k'_{NO} and k'_A, for the decomposition of (**9**) in $DClO_4$ solutions at 25 °C. $\mu = 1$ mol dm^{-3}.

$[D^+]/10^{-2}$ mol l^{-1}	$k'_{NO}/10^{-3}$ s^{-1}	$k'_A/10^{-3}$ s^{-1}	$k_{NO}^{D^+}/10^{-3}$ dm^3 mol^{-1} s^{-1}	$k_A^{D^+}/10^{-3}$ dm^3 mol^{-1} s^{-1}
4.89	0.66	1.50	13.5	31.7
7.58	0.99	2.31	13.1	30.5
12.3	1.43	3.47	11.6	24.3
13.4	1.65	3.85	12.3	23.3



Scheme 4. Mechanism of the acid-catalysed decomposition of *N*-nitrosoimidazolines.

ignore the possibility that nitrosation of (**1**) takes place during the decomposition of (**9**). Amidine hydrolysis occurs *via* a nucleophilic attack by water at the carbon atom of the protonated nitrosoamidine (**15**). Indeed, the ρ value of +1.0 obtained in this work for nitrosoamidine hydrolysis is similar to that, +1.6, for the hydrolysis of acylic benzamidines.[14] Such attack generates a tetrahedral intermediate which can collapse with the preferential cleavage of the C–N bond to the nitrosoamine moiety. The amide thus formed contains a diazonium ion, and intramolecular trapping of this ion by the amide oxygen atom furnishes the oxazoline (**14**). Amides are well known to react with various alkylating agents, including alkyl diazonium ions, by nucleophilic attack of the oxygen atom,[15] and intramolecular alkylation reactions similar to the one described here are known to be particularly efficient.[16]

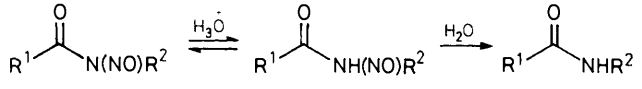
The denitrosation of nitrosoamidines is analogous to the denitrosation of *N*-methyl-*N*-nitrosoaniline and related compounds. Nitrosoamines also require rapid equilibrium protonation prior to nucleophilic denitrosation by H_2O, Cl^-, SCN^-, *etc.*[13] Nitrosoamidines undergo reaction much more readily,

Table 4. Observed rate constants, k_{obs}, and activation parameters $\Delta H^‡$ and $\Delta S^‡$ for k'_{NO} and k'_A for the decomposition of (**9**) in 0.35 mol dm^{-3} H^+. $\mu = 1$ mol dm^{-3}.

T/K	$k_{obs}/10^{-3}$ s^{-1}	$k'_A/10^{-3}$ s^{-1}	$k'_{NO}/10^{-3}$ s^{-1}	$\Delta H^‡_{NO}$/kJ mol^{-1}	$\Delta H^‡_A$/kJ mol^{-1}	$\Delta S^‡_{NO}$/J K^{-1} mol^{-1}	$\Delta S^‡_A$/J K^{-1} mol^{-1}
285.6	1.37	0.89	0.48	74 (±5)	74 (±5)	−48 (±12)	−43 (±12)
297.2	3.8	2.39	1.41				
305	9.5	5.98	3.52				
313.5	30.0	19.8	10.2				
323	54.0	34.0	20.0				

however, and this probably relates to the ease of protonation at the imino nitrogen atom as compared with the protonation of the amino nitrogen atom of nitrosoamines. The range of reactivity observed for substituted nitrosoimidazolines, *ca.* 5, is similar to that for the *N*-nitrosoanilines.[13]

The concurrent decomposition of *N*-nitrosoimidazolines *via* denitrosation and amidine hydrolysis is reminiscent of the acid-catalysed decomposition of *N*-nitrosoamides (**16**). These compounds also undergo concurrent denitrosation and amide hydrolysis.[10,17] However, there are profound differences between the behaviour of *N*-nitrosoamides and *N*-nitrosoamidines. For example, denitrosation of (**16**; R^1 = Me, R^2 = Bu) exhibits a normal solvent isotope effect of *ca.* 1.9, is general acid catalysed and does not involve nucleophilic catalysis by Cl^-.[10] The reaction thus involves slow proton transfer to form the *N*-conjugate acid (**17**), followed by denitrosation by a molecule of water (Scheme 5).

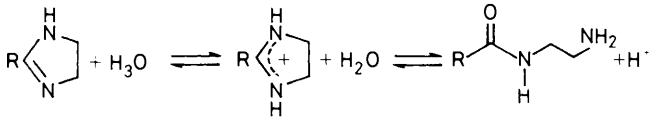


(**16**) (**17**)

Scheme 5.

Since the difference in pK_a between amidines and amides is *ca.* 13,* it is not surprising that nitrosoamidines involve rapid pre-equilibrium protonation whereas nitrosoamides undergo rate-determining protonation.

It is of interest to compare the hydrolysis of *N*-nitrosoimidazoline with that of the parent imidazoline (**1**). In acidic solutions, such imidazolines exist as their conjugate acids, and hydrolysis to the *N*-acylethylenediamine is reversible, the equilibrium strongly favouring the imidazolinium ion (**18**) (Scheme 6).[18] Little hydrolysis is thus observed.



(**18**)

Scheme 6.

In neutral solutions imidazolines are stable, and significant hydrolysis is observed only at high pH. The kinetic profile indicates that, even in alkaline solutions, the reaction proceeds *via* nucleophilic attack by OH^- on the imidazolinium ion.[18] For nitrosoimidazolines, the presence of the nitroso group must lower the basicity to the extent that the amount of protonated substrate is so small in neutral or alkaline solutions that attack by H_2O or OH^- is not observed. This implies that nitrosoimidazolines themselves are not sufficiently electrophilic to undergo attack by OH^-. Conversely, in acidic solutions formation of the protonated nitrosoimidazoline enables water to act as a nucleophile.

As for the ability of nitrosoimidazolines to generate incipient alkylating agents, it is clear that under approximately gastric conditions (pH 1 HCl) only *ca.* 50% of the decomposition of the nitrosoimidazoline will proceed *via* amidine hydrolysis to form an alkyl diazonium ion. More importantly, however, intramolecular trapping of this diazonium ion appears to be particularly efficient, and we could not detect any products arising from attack by H_2O or Cl^- on this ion. It is unlikely, therefore, that nitrosoimidazolines will alkylate nucleic acids or protein. The acyclic nitrosoamidine (**6**) however generates diazomethane,[6] a known toxic, powerful alkylating agent.

* For example, the pK_a of benzamidine is 11.6 and that of benzamide −1.5.

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