The acid-catalysed decomposition of *N*-nitrotolazoline

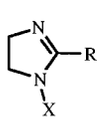
Jim Iley,*[a] Fatima Norberto *[bc] and Paula Sardinha[b]

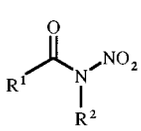
[a] *Chemistry Department, The Open University, Milton Keynes, UK MK7 6AA*
[b] *CECF, Faculdade de Farmácia, Avenida das Forças Armadas, 1600 Lisboa, Portugal*
[c] *Departamento de Química e Bioquímica, Faculdade de Ciências, 1700 Lisboa, Portugal*

Received (in Cambridge) 27th July 1998, Accepted 10th August 1998

Reaction of tolazoline with N_2O_4 yields *N*-nitrotolazoline, the prototypical nitroamidine. *N*-Nitrotolazoline undergoes acid-catalysed hydrolysis of the nitroamidine function to form *N*-(2-hydroxyethyl)phenylacetamide. The observed pseudo-first-order rate constants, k_0, have a non-linear dependence upon acidity, displaying saturation at higher acid concentrations consistent with a mechanism involving equilibrium protonation of *N*-nitrotolazoline prior to subsequent decomposition of the protonated intermediate. Reactions are subject neither to general acid- or base-catalysis nor to catalysis by thiocyanate ion. The solvent deuterium isotope effect for protonation was found to be 0.3, and for decomposition of the protonated intermediate, 1.7. A value of (-100 ± 5) J K^{-1} mol^{-1} was determined for $\Delta S^{\ddagger}$ for the decomposition step. Thus, hydrolysis of the protonated intermediate involves rapid attack of a molecule of water at the amidine carbon atom followed by a slow, intramolecular rearrangement involving proton transfer.

Our interest in the nitrosation of compounds containing the amidine and guanidine functional groups,[1–5] some [*e.g.* clonidine (**1**)] possessing useful therapeutic activity, has led us to turn our attention to tolazoline (IUPAC name for tolazoline is 2-benzyl-4,5-dihydro-1*H*-imidazole), **2**, an α-adrenergic blocking agent used in the treatment of hypertension. Using the standard White methodology (N_2O_4 in CH_2Cl_2)[6] we have found that, in contrast to the analogous phenylimidazolines, **3**, which *nitrosate* using these conditions, tolazoline gives rise to the *N-nitro* derivative **4**. *N*-Nitration under these conditions, while uncommon, has been reported before.[6] *N*-Nitrotolazoline is the prototypical *N*-nitroamidine, and we were therefore interested to study its mechanism of hydrolysis since, on the one hand, it is analogous to *N*-nitroamides **5**[7] and, on the other, to *N*-nitrosoamidines **6**,[5] both of which we have investigated previously. *N*-Nitroamides are susceptible to nucleophilic catalysis in basic medium[7] and require strongly acidic media for acid catalysis.[8] *N*-Nitrosoamidines are susceptible only to acid catalysis, a process that involves two competing pathways, denitrosation and amidine hydrolysis.[5]





1 R = 2,6-$Cl_2C_6H_3NH$ X = H
2 R = $PhCH_2$ X = H
3 R = Ar X = H
4 R = $PhCH_2$ X = NO_2
6 R = Ar X = NO

5

Experimental

NMR chemical shifts are given in ppm.

Synthesis of *N*-nitrotolazoline

A mixture of sodium acetate (30 mmol) and N_2O_4 (15 mmol) in dichloromethane (10 cm^3) was added dropwise to a solution of tolazoline (5 mmol) in dichloromethane (10 cm^3) maintained at −10 °C. Upon completion of the reaction (t.l.c.) the reaction mixture was washed with 10% aqueous sodium hydrogen carbonate, dried, evaporated and the residue purified by preparative chromatography [diethyl ether–light petroleum (40–60 °C) 8:2] to give *N*-nitrotolazoline (**4**) as an oil in 55% yield: λ_{max}/nm 262 (log ε 4.07); ν_{max}/cm^{-1} 1640, 1425, 1275, 1230, 1000, 825, 710; δ_H 3.75 (2H, t, CH_2N=C), 3.98 (2H, t, CH_2NNO_2), 4.35 (2H, s, PhCH_2), 7.39 (5H, m, *Ph*); δ_C 34.3 (PhCH_2), 43.6 (N–CH_2), 52.8 (CH_2NNO_2), 127 (*C*H), 128 (*C*H), 129 (*C*H), 134 (*C*), 159 (N=*C*–N); *m*/*z* (%) 205 ($M^{\cdot+}$) (1), 188 (100), 170 (25), 158 (15), 143 (22), 129 (21), 116 (35), 103 (40), 91 (10). Found: C, 58.9; H, 5.6; N, 20.5. $C_{10}H_{11}N_3O_2$ requires C, 58.5; H, 5.4; N, 20.5%.

Product analysis

The acid-catalysed hydrolysis reactions were carried out in mixed acetonitrile–water 50% (v/v) solutions at room temperature. Upon completion of the reaction (t.l.c.), the solution was neutralised (aqueous 10% sodium hydrogen carbonate) and extracted with dichloromethane. The organic extracts were dried, evaporated and the residue subjected to chromatography (chloroform–methanol 9:1) to yield a product identified as *N*-(2-hydroxyethyl)phenylacetamide (**7**): ν_{max}/cm^{-1} 3248 (N–H), 1626 (C=O); δ_H 3.38 (2H, t, NCH_2), 3.58 (2H, s, PhCH_2), 3.62 (2H, t, CH_2O), 6.25 (1H, br, N*H*), 7.25 (5H, m, *Ph*); *m*/*z* (%) 179 ($M^{\cdot+}$) (8), 161 (20), 149 (10), 136 (30), 118 (10), 91 (100).

Kinetic studies

Kinetic runs were initiated by injecting a small aliquot (20 μl) of a dioxane solution of *N*-nitrotolazoline (1.75×10^{-2} mol dm^{-3}) into a thermostatted cell containing 3 cm^3 of the solution under study. Ionic strength was kept constant (0.5 M) by addition of $NaClO_4$. Reactions were monitored by UV spectrophotometry following the disappearance of substrate at λ 270 nm. Reactions were first-order with respect to [substrate] and the observed pseudo-first-order rate constants k_0 were obtained from plots $\ln(A_t - A_\infty)$ *versus* time, where A_t and A_∞ are the absorbances at time *t* and infinity, respectively. Values of k_0 were reproducible to within ±5%.

Results and discussion

For solubility reasons, the hydrolysis of *N*-nitrotolazoline was studied using 50% aqueous acetonitrile solutions. Hydrolysis

Table 1 Pseudo-first-order rate constants, k_0, for hydrolysis of **4** in 50% MeCN–H_2O buffers at 25.4 °C

Buffer	Buffer ratio	[Buffer]/10^{-2} mol dm^{-3}	k_0/10^{-4} s^{-1}
Monochloroacetate	0.86	1.07	87.5
		1.61	87.4
		2.15	87.3
		2.69	87.7
	3.8	0.42	38.2
		0.63	37.7
		0.84	41.0
		1.05	37.6
Acetate	0.45	1.37	1.70
		2.06	1.83
		2.69	1.70
		3.53	2.07
	4.8	0.34	0.235
		0.52	0.25
		0.69	0.263
		0.86	0.263

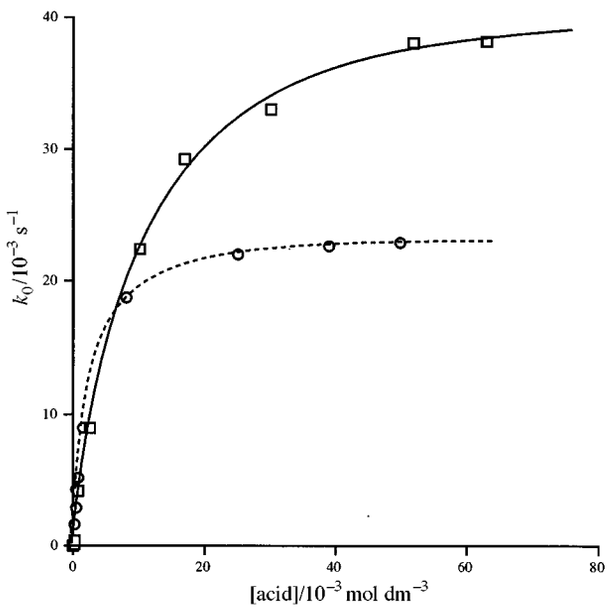


Fig. 1 Influence of acidity upon k_0 for the acid-catalysed hydrolysis of *N*-nitrotolazoline: □, in 50% MeCN–H_2O (v/v); ○, in 50% MeCN–D_2O (v/v).

was observed only in acidic media, and the reaction profiles showed the decomposition to be first-order in [*N*-nitrotolazoline]. The influence of acidity on the reaction was studied in perchloric acid and buffer solutions (acetate, formate and monochloroacetate) in both H_2O and D_2O. Decomposition in buffer solutions is not subject to catalysis by the buffer material (Table 1). A plot of the observed first-order rate constants, k_0, *versus* [H^+] clearly reveals a non-linear dependence upon acidity (Fig. 1). We take the form of this curve to imply that the reaction involves equilibrium protonation of *N*-nitrotolazoline followed by decomposition of the protonated intermediate, as described by eqn. (1). From the steady-state assumption, k_0 can be described by eqn. (2), which simplifies to eqn. (3).

$$S + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SH^+ \overset{k_2}{\rightleftharpoons} \text{Products} \quad (1)$$

$$k_0 = k_2[H^+]/\{k_{-1}/k_1 + k_2/k_1 + [H^+]\} \quad (2)$$

$$k_0 = k_2[H^+]/\{K_m + [H^+]\} \quad (3)$$

For $[H^+] < K_m$, $k_0 \approx k_2[H^+]/K_m$, while for $[H^+] > K_m$, $k_0 \approx k_2$. Fitting the experimental data to eqn. (3) gives rise to the k_2 and K_m values contained in Table 2.

Table 2 Values of k_2 and K_m for the acid-catalysed hydrolysis of **4** in H_2O and D_2O

T/K	k_2/10^{-2} s^{-1}	K_m/10^{-2} mol dm^{-3}
288.8	1.90	0.578
293.6	2.71	0.570
298.6	4.42	0.931
	2.57[a]	3.10[a]
302.8	6.37	0.829

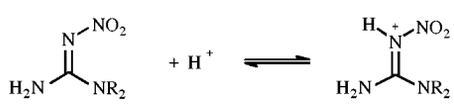
[a] In D_2O.

Table 3 Influence of [SCN^-] upon k_0 for the acid-catalysed hydrolysis of **4** in 0.04 M $HClO_4$ solutions

[KSCN]/10^{-3} mol dm^{-3}	k_0/10^{-2} s^{-1}
0	2.68
1	2.78
2	2.69
4	2.76
5	2.83

Reaction in D_2O solutions gives similar results (Fig. 1), but it is obvious from the comparative shapes of the two curves that K_m and k_2 display different solvent kinetic deuterium isotope effects (SKIEs). From the data in Table 2, the SKIE for k_2 is 1.7, and 0.3 for K_m. The latter is indeed consistent with pre-equilibrium protonation of substrate.

If we assume that the protonation step, k_1, is rapid compared to decomposition of the protonated intermediate, k_2, then $k_2/k_1 \rightarrow 0$ and $K_m \approx K_a$, the acid dissociation constant of *N*-nitrotolazoline. Thus, the kinetically derived pK_a for this compound in 50% H_2O–CH_3CN is 2.03, which, as we have found that the experimentally determined pH in 50% H_2O–CH_3CN is consistently 1.03 ± 0.03 units higher than in pure water,† corresponds to an aqueous pK_a of *ca.* 1. This represents a reduction of some 9–10 pK_a units from tolazoline itself (pK_a 10.6 at 20 °C[9]) and is consistent with the presence of the powerfully electron-withdrawing NO_2 group conjugated to the non-bonding electron pair of the amidine nitrogen. Even larger reductions in pK_a have been observed for guanidines (pK_a *ca.* 13.5)[10] and their *N*-nitro derivatives (pK_a *ca.* −1)[11] where the *N*-NO_2 group resides on the imino nitrogen atom involved in protonation (Scheme 1) and for anilines (pK_a *ca.* 5)[10] and *N*-nitroanilines, where protonation is incomplete in 7 M $HClO_4$.[12]

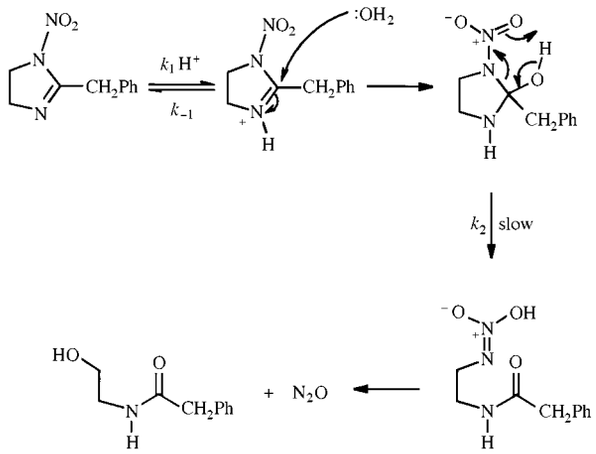


Scheme 1

Thiocyanate ion is a powerful nucleophilic catalyst for the denitrosation of nitrosoamidines and nitrosoamines,[13] whereas *N*-nitroamides are not subject to nucleophile-catalysed denitration.[8] For *N*-nitrotolazoline, the data in Table 3 demonstrate that the acid-catalysed hydrolysis reaction is not promoted by added NCS^-. Moreover, in none of these reactions was the product of denitration, tolazoline, observed.

The variation of k_2 with temperature (Table 2) enabled values for $\Delta H^‡$ and $\Delta S^‡$ for the decomposition step to be calculated as (61 ± 0.5) kJ mol^{-1} and (−100 ± 5) J K^{-1} mol^{-1}, respectively. The $\Delta S^‡$ value is very similar to those determined for the acid-catalysed hydrolyses of esters,[14] and is consistent with an associative mechanism. Thus, the mechanism for the acid-

† For example, the following are the pH values of aqueous solutions together with the corresponding values in 50% H_2O–CH_3CN in parentheses: 2.07 (3.07), 2.48 (3.55), 3.57 (4.64), 3.95 (4.97).



Scheme 2 Mechanism of the acid-catalysed hydrolysis of *N*-nitrotolazoline.

catalysed hydrolysis of *N*-nitrotolazoline that is most consistent with the data is shown in Scheme 2. Pre-equilibrium protonation of the substrate is followed by attack of water at the amidine carbon atom. The solvent kinetic isotope effect on k_2 implies that a proton transfer is rate limiting. One possibility for the proton transfer step is general base-catalysis of the water attack at the amidine carbon atom by another water molecule. However, we think this unlikely due to the absence of general acid- or base-catalysis by any of the buffer species. We therefore propose that the slow proton transfer is associated with a subsequent intramolecular decomposition.

Comparison of the data for *N*-nitrotolazoline with those of *N*-nitro- and *N*-nitroso-amides, -amidines and -guanidines reveals the following. Like the analogous *N*-nitroamides,[8] but unlike *N*-nitroguanidines[15] and *N*-nitroso-amides,[16,17] -amidines[2] and -guanidines,[4] *N*-nitrotolazoline is subject to an acid-catalysed hydrolysis reaction *via* exclusive hydrolysis of the amidine function rather than *via* the alternative, and sometimes competitive, denitration/denitrosation pathway. Like *N*-nitroamides, but unlike *N*-nitrosoamidines, acid-catalysed hydrolysis of the *N*-nitroamidine function is not subject to nucleophilic catalysis. Unlike *N*-nitroamides, however, the *N*-nitroamidine function does not undergo a buffer-catalysed hydrolysis reaction. Nevertheless, our results make it clear that the *N*-nitroamidine group behaves more like an *N*-nitroamide than an *N*-nitroguanidine or *N*-nitrosoamidine.

Acknowledgements

P. S. thanks the *Junta Nacional de Investigação Científica e Tecnológica* (Portugal) for financial support.

References

1 J. R. Leis, J. A. Moreira, F. Norberto, J. Iley and L. García-Rio, *J. Chem. Soc.*, *Perkin Trans. 2*, 1998, 655.
2 J. R. Leis, F. Norberto, J. A. Moreira and J. Iley, *J. Chem. Res.* (*S*), 1997, 88.
3 F. Norberto, J. A. Moreira, E. Rosa, J. Iley, J. R. Leis and E. Peña, *J. Chem. Soc.*, *Perkin Trans. 2*, 1993, 1561.
4 J. Iley, F. Norberto, E. Rosa, V. Cardoso and C. Rocha, *J. Chem. Soc.*, *Perkin Trans. 2*, 1993, 591.
5 J. Iley, F. Norberto and E. Rosa, *J. Chem. Soc.*, *Perkin Trans. 2*, 1989, 1471.
6 E. H. White and W. R. Feldman, *J. Am. Chem. Soc.*, 1957, **79**, 5832.
7 B. Challis, E. Rosa, F. Norberto and J. Iley, *J. Chem. Soc.*, *Perkin Trans. 2*, 1989, 1823.
8 B. Challis, E. Rosa, F. Norberto and J. Iley, *J. Chem. Soc.*, *Perkin Trans. 2*, 1990, 179.
9 *Martindale: The Extra Pharmacopoeia*, ed. J. E. F. Reynolds, The Royal Pharmaceutical Society, London, 29th edn., 1989.
10 W. P. Jencks and J. Regenstein, 'Ionization constants of acids and bases', in *Handbook of Chemistry and Molecular Biology*, ed. G. D. Fasman, CRC Press, Cleveland, OH, 3rd edn., 1976, vol. 1, p. 305.
11 T. G. Bonner and J. C. Lockhart, *J. Chem. Soc.*, 1958, 3858.
12 D. V. Banthorpe, E. D. Hughes and D. L. H. Williams, *J. Chem. Soc.*, 1964, 5349.
13 I. D. Biggs and D. L. H. Williams, *J. Chem. Soc.*, *Perkin Trans. 2*, 1975, 107.
14 N. S. Isaacs, *Physical Organic Chemistry*, Longman, Harlow, 1987, p. 469.
15 T. G. Bonner and J. C. Lockhart, *J. Chem. Soc.*, 1958, 3852.
16 C. N. Berry and B. C. Challis, *J. Chem. Soc.*, *Perkin Trans. 2*, 1974, 1638.
17 B. C. Challis and S. P. Jones, *J. Chem. Soc.*, *Perkin Trans. 2*, 1975, 153.

Paper 8/05854G