Hydrolysis of Oxaziridines. Part 3.[1] Evidence for Both *O*- and *N*-Conjugate Acid Formation with 2,3,3-Triethyloxaziridine

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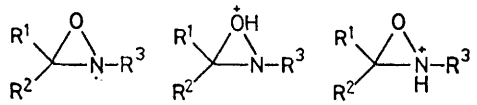
Both the kinetics and the products for the hydrolysis of 2,3,3-triethyloxaziridine in aqueous acid at 25 °C are reported. The reaction is subject to general acid or base catalysis in acetic acid buffers, but in aqueous perchloric acid, the acid catalysis is slight with the rate reaching an unusually sharp maximum in *ca.* 0.9M $HClO_4$ and then decreasing at higher acidities. Comparison with 2-[$\alpha\alpha'$-$^2H_2$]ethyl-3,3-diethyloxaziridine reveals a substantial primary deuterium isotope effect at low acidities (k_0^H/k_0^D *ca.* 2.7) which steadily decreases to become negligible in 6.68M $HClO_4$. The variation in kinetic parameters relates to a change in the reaction products. In *ca.* 1M $HClO_4$ the major products are diethyl ketone and acetaldehyde, but *N*-ethylhydroxylamine is formed at the expense of acetaldehyde as the acidity increases.

The results are analysed and shown to be consistent with a mechanism requiring concurrent protonation of both O and N atoms of the oxaziridine ring. The *O*-conjugate acid intermediate undergoes relatively rapid decomposition to diethyl ketone and acetaldehyde by an *E*-2 process where cleavage of the O–N bond is synchronous with H^+-abstraction from the *N*-ethyl group. The *N*-conjugate acid is much more stable. *N*-Ethylhydroxylamine is formed either by thermal decomposition or by a slow breakdown of the *N*-conjugate acid. Calculations suggest that O and N basicities are very similar and this unusual result is attributed to steric hindrance to solvation of the *N*-conjugate acid.

HYDROLYTIC cleavage of the oxaziridine ring (1) under acidic conditions is generally considered to involve reactive conjugate acid intermediates.[2] This expectation has been confirmed for 2-t-butyloxaziridines (1; R^3 = Bu^t) where both kinetic acidity dependences and



(1) (2) (3)

deuterium solvent isotope effects are consistent with rapid substrate protonation preceding either unimolecular or bimolecular (by H_2O) ring cleavage depending on the R^1 and R^2 substituents.[3] It is also apparent from this study that oxaziridines are sufficiently basic (pK_A +0.13 to −1.81 depending on the R^1 and R^2 substituents) for protonation to be complete in quite dilute acids.

With both O and N atoms in the oxaziridine ring, either (2) or (3) is a possible structure for the conjugate acid intermediate. None of the kinetic studies with 2-t-butyl compounds unambiguously identifies the site of pre-equilibrium protonation. This conclusion applies particularly to recent claims by O'Connor, Fendler, and Fendler.[4] Their proof for a common *O*-conjugate acid intermediate [PhCH=N$^+$(Bu^t)OH] in the hydrolysis of 3-phenyl-2-t-butyloxaziridine (1; R^1 = Ph, R^2 = H, R^3 = Bu^t) and the isomeric nitrone, *N*-(benzylidene)-t-butylamine *N*-oxide, is fallacious because their supposed rates of oxaziridine hydrolysis by u.v. measurements are *ca.* 60 times faster than the loss [3] of active oxygen from the substrate under identical conditions. Further, their proposed *A*-2 mechanism for both reactions is inconsistent with the absence of general acid catalysis in acetic acid buffers. Their findings are explicable by thermal isomerization of the oxaziridine to the nitrone prior to kinetic investigation. Nonetheless, the products obtained from acid-catalysed hydrolyses are generally more consistent with reaction *via* the *O*-conjugate acid.[2] N.m.r. studies of five representative oxaziridines bearing either primary- or secondary-alkyl R^3 substituents, however, suggest that protonation by 20% trifluoroacetic acid in organic solvents produces the *N*-conjugate acid (3).[1] This finding agrees with theoretical calculations showing that N is the more basic atom of oxaziridines in the gaseous state,[5] with experimental studies of their complexation with silver(I) salts,[6] and with general expectations that N is usually more basic than O. Thus oxaziridines appear to resemble other compounds containing both O and N atoms, such as amides, where *N*-protonation is thermodynamically favourable (at least at low acidity) but hydrolysis usually proceeds *via* the less stable *O*-conjugate acid intermediate.[7] Because the mechanism of amide hydrolysis has been the subject of considerable controversy, it is of interest to establish similar behaviour for related compounds. In this context, it is worth noting that amides and oxaziridines are isomeric compounds.

Both the kinetics and products of the acid-catalysed hydrolysis of 2,3,3-triethyloxaziridine (1; R^1 = R^2 = R^3 = Et) are reported. This compound was chosen because the absence of a chiral ring C-atom simplifies the mechanistic interpretation of the results. From earlier studies,[2] 2,3,3-triethyloxaziridine would be expected to give a mixture of diethyl ketone and acetaldehyde when hydrolysed under acidic conditions.

EXPERIMENTAL

2,3,3-Triethyloxaziridine (1; R^1 = R^2 = R^3 = Et) was prepared by peroxidic oxidation of the corresponding imine as previously described.[3] It was purified by vacuum distillation, b.p. 52 °C at 10 Torr (lit.,[2a] 62 °C at 19 Torr), n_D^{20} 1.4222 (lit.,[2a] 1.422 5), active content oxygen 93.6%

(Found: C, 65.3; H, 11.4; N, 10.7. Calc. for $C_7H_{15}NO$: C, 65.1; H, 11.7; N, 10.8%). 2-[αα′-$^2H_2$]Ethyl-3,3-diethyloxaziridine was prepared similarly *via* the imine from [1,1′-$^2H_2$]ethylamine. The deuterium label was introduced by the reaction of nitroethane with NaOD (pH 11) for 18 h. After separation and purification by vacuum distillation, the [1,1′-$^2H_2$]nitroethane was reduced to the corresponding amine with tin–hydrochloric acid at 50 °C. The product was extracted by bubbling nitrogen through the neutralized reaction solution at 60 °C; the nitrogen stream was then dried by passage through a column packed with sodium hydroxide pellets, and the product collected in two liquid-air traps. After purification by further low temperature distillation, an n.m.r. spectrum of the [1,1′-$^2H_2$]ethylamine hydrochloride in trifluoroacetic acid showed no detectable signal for methylene hydrogens. Further details of the experimental procedure are given elsewhere.[8] Despite repeated vacuum distillation, the 2-[αα′-$^2H_2$]ethyl-3,3-diethyloxaziridine could not be obtained entirely free of diethyl ketone impurities: b.p. 40 °C at 8 Torr, M^+ 131, τ(CCl_4) 9.06 (3 H, t), 8.94 (3 H, t), 8.83 (3 H, s), and 8.32 (4 H, q), active oxygen content 75%. Other reagents (*e.g.* $HClO_4$, $MeCO_2H$, and $MeCO_2Na$) were of AnalaR grade.

Both the kinetic procedure and the analysis of carbonyl products (as 2,4 dinitrophenylhydrazone derivatives) were as described previously.[3]

RESULTS AND DISCUSSION

The hydrolysis reactions were examined mainly in aqueous perchloric acid at 25 °C, but the undeuteriated compound was also studied in acetic acid buffers. Good first-order kinetics (rate = k_0 [substrate]) were observed throughout for at least 90% reaction. The results for hydrolysis in aqueous acetic acid buffers at constant pH (4.70) are given in Table 1. The related plot of k_0 *vs.* [HOAc] is linear {rate = (6.6 × 10^{-6} s^{-1} + 3.7 × 10^{-5} l mol^{-1} s^{-1}) [HOAc] [substrate]} so this reaction is subject to general-acid and/or general-base catalysis. One explanation, consistent with both the reaction products (*vide infra*) and the absence of similar catalysis for the hydrolysis of 2-t-butyloxaziridines,[3] is that H^+ abstraction from the 2-ethyl substituent of the neutral substrate or its conjugate acid intermediate is rate-limiting. Confirmation of this explanation was obtained by observing a primary deuterium isotope effect for the hydrolysis in aqueous perchloric acid. These data for 2-[αα′-$^2H_2$]-ethyl-3,3-diethyloxaziridine and the undeuteriated compound are plotted in Figure 1. Both plots have a characteristic shape with a sharp maximum at about the same acidity (*ca.* 0.8M $HClO_4$) after which the reaction rate slowly decreases. Hydrolysis is clearly slower for the dideuteriated substrate, which confirms that α-H^+ abstraction is kinetically important, but to an extent that depends on solvent acidity. The largest isotopic rate ratio (see Table 2) applies to the lowest acidity

TABLE 1

Decomposition of 2,3,3-triethyloxaziridine in aqueous acetic acid buffers at 25 °C; [HOAc] = [NaOAc]; ionic strength = 1 ($NaClO_4$ added)

[HOAc]/M	$10^6k_0/s^{-1}$
0.10	9.5
0.30	16.7
0.50	22.5
0.70	27
1.00	38

TABLE 2

Primary deuterium isotope effect for the decomposition of 2,3,3-triethyloxaziridine in aqueous $HClO_4$ at 25 °C

$[HClO_4]$/M	k_0^H/k_0^D
0.106	2.7
0.738	2.6
2.61	2.1
6.68	1.2

(k_0^H/k_0^D *ca.* 2.7 in 0.106M $HClO_4$) and the ratio decreases to give k_0^H/k_0^D *ca.* 1.2 in 6.68M $HClO_4$.

The change in kinetic parameters with acidity relates to a change in the reaction products. Thus for hydrolysis in *ca.* 1M $HClO_4$, both diethyl ketone and acetaldehyde were identified as products by their 2,4-dinitrophenylhydrazone derivatives. For hydrolysis in 6.68M $HClO_4$, however, only diethyl ketone could be detected by a similar procedure after suitable neutralization of the reaction solution. The products were also examined by n.m.r. spectroscopy by carrying out the reaction in D_2SO_4, and these spectra are shown in Figure 2. Spectrum 1 was obtained 5 min after dissolving 2,3,3-triethyloxaziridine in 3M D_2SO_4 when little hydrolysis had occurred as shown by titration with iodine. This spectrum therefore refers to the protonated substrate which appears to be an *N*-conjugate acid structure by analysis of the chemical shifts relative to the neutral compound.[1] Spectrum 2 refers to hydrolysis in 0.25M D_2SO_4 after *ca.* 10 half-lives: as well as diethyl ketone, signals for acetaldehyde (of reduced amplitude because exchange with the solvent gives CD_3CHO) and a small amount of *N*-ethylhydroxylamine are apparent. Spectrum 3 refers to hydrolysis in 3M D_2SO_4 again after *ca.* 10 half-lives (5 days) where the only detectable signals are those for $(CH_3CD_2)_2CO$ and nitrosoethane. The latter is known to be formed readily by oxidation of *N*-ethyl-

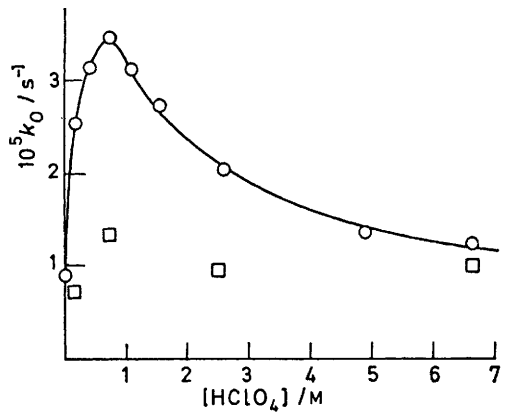


FIGURE 1 Variation of k_0 with $[HClO_4]$; ○ 2,3,3-triethyloxaziridine; □ 2-[αα′-$^2H_2$]ethyl-3,3-diethyloxaziridine; solid line calculated as discussed in text

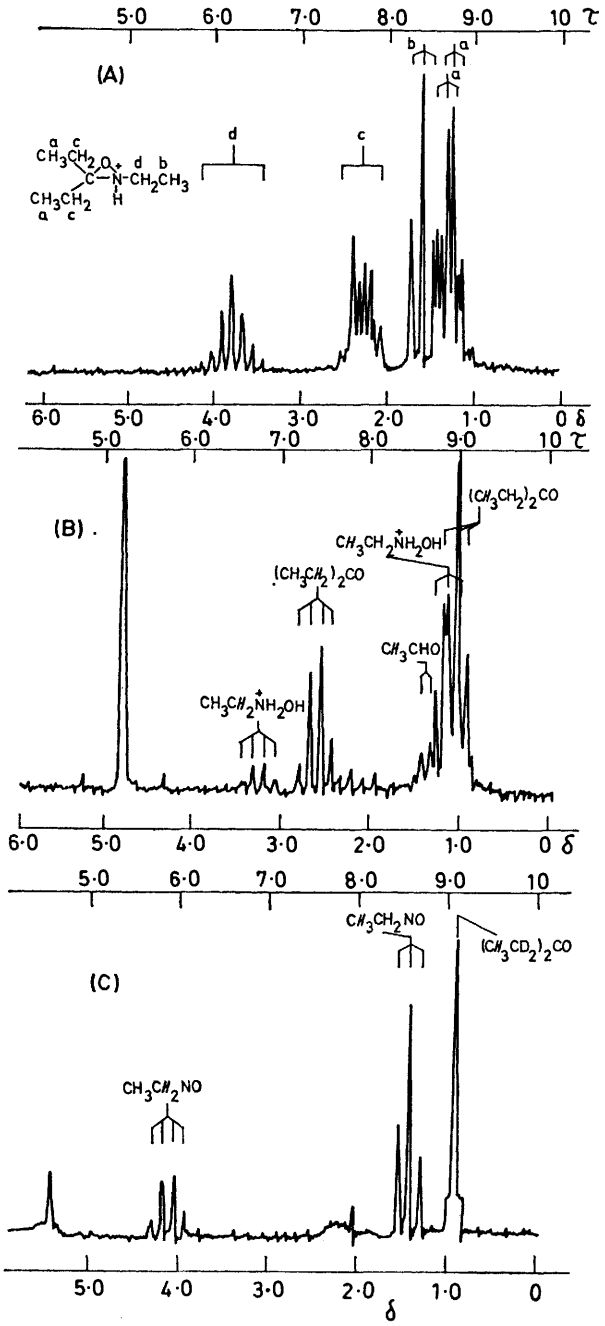
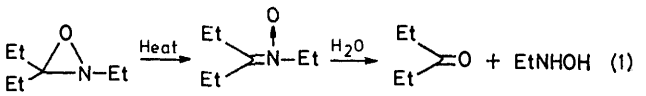


FIGURE 2 N.m.r. spectra of 2,3,3-triethyloxaziridine in D_2SO_4 solutions: (A) after 5 min, 3M D_2SO_4; (B) after 10 half-lives, 0.25M D_2SO_4; (C) after 10 half-lives, 3M D_2SO_4

hydroxylamine.[9] The reaction products at low acidity (diethyl ketone and acetaldehyde) are those expected from earlier related studies.[2] At high acidity *N*-ethylhydroxylamine appears to be formed at the expense of acetaldehyde. The alteration in reaction products together with the diminution of the primary deuterium isotope effect suggest that the mechanism of hydrolysis changes with increasing acidity.

The sharp maximum in the k_0 acidity profile (see Figure 1) is uncharacteristic of either complete formation of a reactive intermediate or a change in the rate-limiting step. Its appearance is consistent, however, with rapid hydrolysis *via* an *O*-conjugate acid intermediate (4) with extensive concurrent *N*-protonation [to give (5)] that is relatively unproductive as far as hydrolysis is concerned. This last assumption seems reasonable because the value of k_0 at the highest acidity examined is very similar to that obtained from decomposition in pure water. This 'spontaneous reaction' is attributed to thermal isomerization of the oxaziridine to the corresponding nitrone [equation (1)]. It

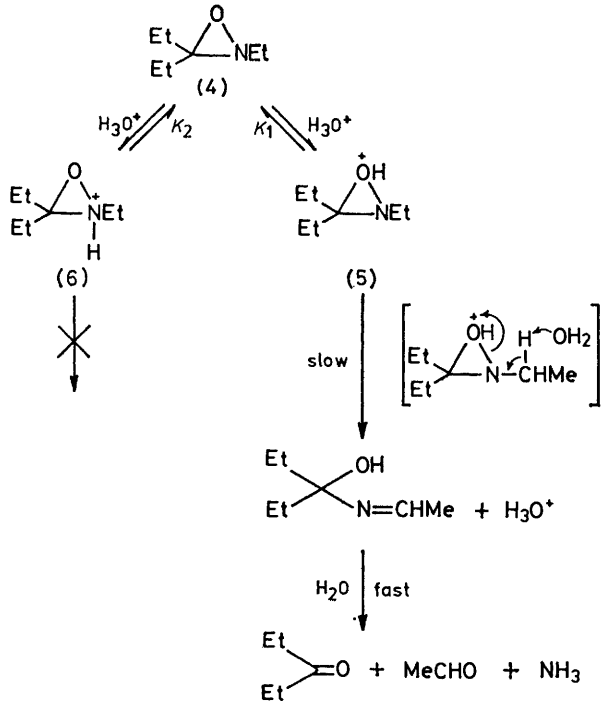


seems unlikely that the protonation of both O and N atoms would follow the same acidity function. From studies of the acid-catalysed hydrolysis of epoxides by Pritchard and Long,[10] *O*-protonation is known to follow the Hammett acidity function (h_0) and we have observed a similar dependency for the hydrolysis of some 2-t-butyloxaziridines.[3] There appears to be no corresponding study of aziridines at high acidity to suggest which acidity function is applicable to *N*-protonation. A reasonable choice, however, is that determined with tertiary amine indicators (h_0''') and since the oxaziridine N is tertiary the choice is not arbitrary. Significantly, h_0''' increases much more rapidly with increasing acidity than h_0, being of similar magnitude in 0.75M $HClO_4$ but *ca.* 10 times larger in 5M $HClO_4$.[11] This difference accounts qualitatively for the depressed rate of hydrolysis at high acidity if the *N*-conjugate acid (5) is relatively unreactive. The situation is then described by the Scheme, to which equation (2) applies where $K_1 = [(4)]h_0/[(5)]$, $K_2 = [(4)]h_0'''/[(6)]$, k = decomposition rate of the *O*-conjugate acid (5), and k_ψ = difference between k_0 in acid and in pure H_2O ('spontaneous reaction'). By substituting the known values of k_ψ, h_0, and h_0''', equation (2) may be

$$k_\psi = kh_0/(K_1 + h_0 + K_1h_0'''/K_2) \qquad (2)$$

solved. To obtain the best values of k, K_1, and K_2, equation (2) was transformed into a linear expression and solved by computerized least-squares analysis. For 2,3,3-triethyloxaziridine, $k = 7.5 \times 10^{-5}$ s^{-1}, $K_1 = 0.47$ mol l^{-1}, and $K_2 = 0.47$ mol l^{-1}. Agreement between experimental values of k_0 and those calculated from the above constants is excellent as shown in Figure 1, and this constitutes some verification of the Scheme. The calculated plot is relatively insensitive to both the numerical values of K_1 and K_2 and the addition of a small decomposition rate for the *N*-conjugate acid, and its shape is determined largely by the K_1/K_2 ratio. Thus no great store can be set by the absolute values of K_1 and K_2 but both K_1 and the rate coefficient (k) show sensible agreement with equivalent constants obtained previously for 2-t-butyloxaziridines.[3]

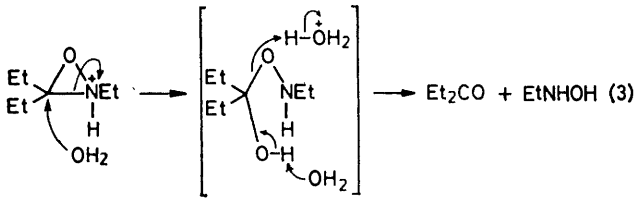
Our mechanistic conclusions for the hydrolysis under acidic conditions are summarized by the Scheme where the 2,3,3-triethyloxaziridine is considered to undergo both *O*- and *N*-conjugate acid formation [(4) and (5) respectively]. Following Emmons' [2a] original suggestion, the diethyl ketone and acetaldehyde products are best rationalized as arising from a reaction of the *O*-conjugate acid species. This intermediate must be formed in a rapid pre-equilibrium step. The primary deuterium isotope effect implies that α-H^+ abstraction from the *O*-conjugate acid is concerted with N–O bond cleavage so the rate-limiting step is an *E*-2 process as shown. Jeanniot and his colleagues [12] have reached a similar conclusion from the products obtained from the



SCHEME Acid-catalysed decomposition of 2,3,3-triethyloxaziridine

base-catalysed decomposition of a steroidal oxaziridine. Concurrent formation of an *N*-conjugate acid, whose relative stability increases with solvent acidity, is necessary to explain kinetics and products, and the n.m.r. spectrum of the substrate in D_2SO_4. Comparable α-H^+ abstraction from this entity is not feasible, hence the diminution in rate, primary deuterium isotope effect, and yield of acetaldehyde with increasing acidity. The *N*-conjugate acid is considered to be unreactive. *N*-Ethylhydroxylamine probably arises from isomerization of the substrate to the corresponding nitrone [equation (1)], although very slow decomposition of the *N*-conjugate acid with C–N bond fission [equation (3)] cannot be excluded.

The ratio of acid dissociation constants (K_1/K_2) suggests that the O and N atoms of 2,3,3-triethyloxaziridine are of equal basicity, which is a major change from the normal relative basicities of these two atoms. This



cannot result from mutual electronic interactions arising from their juxtaposition, because the N atom is considerably more basic than O in hydroxylamines.[13] The probable explanation, examined in more detail in the following paper, is that steric congestion makes solvation of the *N*-conjugate acid more difficult than that of the *O*-conjugate acid. This explanation also accounts for the different acidity function dependences of the two species which results in preferential *N*-conjugate acid formation at the higher solvent acidities.

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REFERENCES

[1] Part 2, B. C. Challis and A. M. Lobo, *J. Heterocyclic Chem.*, 1977, **14**, 1393.

[2] (*a*) W. D. Emmons, *J. Amer. Chem. Soc.*, 1957, **79**, 5739; (*b*) For reviews see, M. Lamchen, 'Mechanisms of Molecular Rearrangements,' vol. 1, ed. B. S. Thyagarajan, Interscience, New York, 1968, p. 1; D. S. Maitland, in 'Saturated Heterocyclic Chemistry,' ed. M. F. Ansell, Specialist Periodical Reports, The Chemical Society, London, 1975, vol. 3, p. 87; D. S. Maitland, 'Saturated Heterocyclic Chemistry,' eds. M. F. Ansell and G. Pattenden, Specialist Periodical Reports, The Chemical Society, London, 1977, vol. 4, p. 81.

[3] A. R. Butler and B. C. Challis, *J. Chem. Soc.* (*B*), 1971, 778.

[4] C. J. O'Connor, E. J. Fendler, and J. H. Fendler, *J.C.S. Perkin II*, 1973, 1744.

[5] R. Bonaccorsi, E. Serocio, and J. Thomasi, *Theor. Chim. Acta*, 1971, **21**, 17; C. Ghio and J. Thomasi, *ibid.*, 1973, **30**, 151.

[6] L. R. Crist, G. J. Jordan, and J. A. Hashmall, *J. Amer. Chem. Soc.*, 1974, **96**, 4927.

[7] For summaries, see A. Williams, *J. Amer. Chem. Soc.*, 1976, **98**, 5645; C. J. Giffney and C. J. O'Connor, *J.C.S. Perkin II*, 1975, 706.

[8] A. M. Lobo, Ph.D. Thesis, London, 1971.

[9] See P. A. S. Smith, 'Open Chain Nitrogen Compounds, Vol. 2,' Benjamin, New York, 1966, p. 12.

[10] J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1956, **78**, 2667; for review see C. H. Rochester, 'Acidity Functions,' Academic Press, London, 1970, p. 138.

[11] K. Yates, H. Wai, G. Welch, and R. A. McClelland, *J. Amer. Chem. Soc.*, 1973, **95**, 418.

[12] J. P. Jeanniot, X. Luschini, P. Milliet, and J. Parello, *Tetrahedron*, 1971, **27**, 401.

[13] M. N. Hughes and G. Stedman, *J. Chem. Soc.*, 1963, 2824.