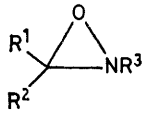
Hydrolysis of Oxaziridines. Part 4.[1] The Effects of Substituents on the Kinetics and Mechanisms of the Acid-catalysed Reactions

By **Anthony R. Butler** and **Joan G. White** (in part), Department of Chemistry, The University, St. Andrews, Fife KY16 9ST
Brian C. Challis * and **Ana M. Lobo**, Department of Chemistry, Imperial College, London SW7 2AY

Hydrolysis rates in aqueous acid up to 7M and at 25 °C are reported for six oxaziridines bearing various *N*-alkyl- and either aryl- or alkyl-*C*-substituents. The major reaction products are also identified. With earlier data, these results show that the extent of acid-catalysis is overwhelmingly determined by the structure of the *N*-alky substituent (tertiary > secondary > primary) irrespective of the hydrolysis pathway, which is influenced by both *N*- and *C*-substituents. The kinetic acidity dependences confirm that some oxaziridines may undergo concurrent protonation at both O and N atoms, with *N*-conjugate acid formation being more extensive for compounds with primary than for those with secondary or tertiary alkyl-*N*-substituents. Generally, the products arise from hydrolysis of the *O*-conjugate acid, but for compounds bearing *C*-aryl substituents hydrolysis of the *N*-conjugate acid is also important. The influence of *N*-alkyl substituents on conjugate acid formation is not related to the usual electronic interactions, but can be rationalised by steric inhibition to solvation of the *N*-conjugate acid. Calculations suggest that the basicities of oxaziridine O and N atoms are closely similar.

EMMONS' [2] original studies and other subsequent work [3] have shown that the ring substituents have an important influence on the pathways by which oxaziridines (1) undergo hydrolysis in acidic solutions. With R^1 or



(1)

	R^1	R^2	R^3
a	Et	Me	Bu^n
b	Pr^i	Me	Pr^n
c	Ph	H	Et
d	*p*-NO_2·C_6H_4	H	Et
e	Et	H	Pr^i
f	*p*-NO_2·C_6H_4	H	Pr^i

R^2 = aryl, a mixture of a carbonyl compound ($R^1R^2C{=}O$) and a substituted hydroxylamine is usually obtained. With R^1 and R^2 = H or alkyl, cleavage of the N–R^3 bond as well as the oxaziridine ring occurs to give NH_3 and a second carbonyl product in addition to $R^1R^2C{=}O$. If the R^3 group is either secondary or tertiary, however, rearrangement accompanies N–R^3 bond cleavage and a primary amine is obtained in place of NH_3. Two general assumptions have been that all these products arise from a transformation of an *O*-conjugate acid intermediate and that most reactions are strongly acid catalysed.

We have shown [4] that both assumptions are probably correct for several 2-t-butyloxaziridines (1; $R^3 = Bu^t$). From the preceding paper, however, it is clear that the second assumption does not apply to 2,3,3-triethyloxaziridine, (1; $R^1 = R^2 = R^3 = Et$), because of concurrent protonation of both O and N atoms. Although the *O*-conjugate acid does undergo relatively rapid decomposition to the expected products (diethyl ketone and acetaldehyde), formation of more stable *N*-conjugate acid is favoured as the solvent acidity increases. The outcome is only mild acid-catalysis with a reduction in rate at acidities beyond 0.9M $HClO_4$ and the formation of *N*-ethylhydroxylamine at the expense of acetaldehyde. Thus substituents on the oxaziridine ring may influence the acid-catalysed hydrolysis reactions by determining both the site of protonation and the subsequent decomposition of the conjugate acid intermediates.

One other interesting result from the preceding paper is that the O and N atoms of 2,3,3-triethyloxaziridine appear to be of similar basicity, in contrast to most other compounds (*cf.* hydroxylamines [5]) where N is considerably more basic than O. This was tentatively attributed to an attenuation of the basicity of the N atom by steric hindrance to solvation. To test this explanation, the acid-catalysed hydrolysis of oxaziridines bearing a wider range of both *C*- and *N*-substituents was examined and the results are reported below. These studies also provide information on the optimum conditions for the synthetic applications of oxaziridine hydrolyses.

EXPERIMENTAL

Procedures for the synthesis of substrates, the identification of products and the measurement of reaction rates are described in the preceding paper. The physical properties of each substrate are summarised in Table 1; their structures were also confirmed by n.m.r. and i.r. spectroscopy.

RESULTS AND DISCUSSION

The hydrolyses of compounds (1a—f) were examined mainly in aqueous perchloric acid at 25 °C, but compound (1a) was also studied in sulphuric acid and [$^2H_2$]sulphuric acid. Generally, good first-order kinetics (rate = k_0 [substrate]) were observed for at least 90% reaction. All the substrates gave a small but significant spontaneous reaction (*i.e.* hydrolysis in pure H_2O) and in analysing the kinetic acidity dependencies this contribution has been substracted from the observed k_0. The resulting rate constant is denoted k_ψ. The variation of k_0 with solvent acidity for each oxaziridine is listed in Table 2. With the exception of (1c), those compounds [*i.e.* (1a—d)] bearing a primary alkyl 2-substituent exhibit a low degree of acid catalysis and for (1a) and (1b), which also

TABLE 1

Properties of the oxaziridines (1a—f)

Compound	C (%) Calc.	C (%) Found	H (%) Calc.	H (%) Found	N (%) Calc.	N (%) Found	B.p. (T/°C) (P/Torr)	Active oxygen (%)	n_D (T/°C)
(1a)	67.1	67.0	11.9	11.9	9.1	9.4	52 (7)	94.6	1.4267 (20)
(1b)	67.1	66.7	11.9	11.7	9.8	9.2	70 (22)	94.1	1.4222 (20)
(1c)	*a*						73 (1.7)	97.0	1.5202 (22.5)
(1d)	(see ref. 2)						42—43 [b]	100	
(1e)	62.6	62.5	11.4	11.3	12.2	12.1	50 (20)	96	1.4149 (25)
(1f)	57.7	57.6	5.8	5.6	13.4	13.6	40 [b]	94	

[a] This compound was very unstable. N.m.r. and i.r. spectra were consistent with the assigned structure but both showed traces of benzaldehyde that could not be removed by distillation. [b] M.p.

TABLE 2

Hydrolysis of oxaziridines in aqueous acid at 25 °C (k_0 in s^{-1})

(1a)

$[HClO_4]$/M	10^5k_0
0	1.72
0.15	4.77
0.37	6.53
0.73	6.97
1.49	5.50
2.60	3.93
5.86	1.90
7.34	1.62

(1a)

$[H_2SO_4]$/M	10^5k_0
0	1.72
0.36	7.60
0.75	9.28
1.00	8.80
1.52	8.61
2.50	6.62
3.55	5.36
5.05	4.17
6.03	3.10
6.53	2.85

(1a)

$[D_2SO_4]$/M	10^5k_0
0	1.28
0.44	6.13
0.76	6.11
1.05	5.93
1.83	5.08
2.86	4.10
3.78	3.43

(1b)

$[HClO_4]$/M	10^5k_0
0	1.07
0.72	8.25
1.00	7.69
1.54	6.90
2.66	4.47
3.95	2.53
5.11	2.05
6.13	1.65

(1c)

$[HClO_4]$/M	10^5k_0
0	1.83
0.106	2.66
0.738	15.0
1.54	45.0
2.61	100
4.62	470

(1d)

$[HClO_4]$/M	10^5k_0
0.106	1.67
0.738	1.83
1.54	2.67
2.61	4.50
4.62	5.83
6.67	5.0

(1e)

$[HClO_4]$/M	10^5k_0
0	0.325
0.106	0.70
0.738	3.28
1.01	4.67
1.25	5.67
1.54	6.77
2.67	8.75
4.62	8.60
6.67	6.80

(1f)

$[HClO_4]$/M	10^5k_0
0	1.03
0.79	0.97
0.94	1.03
1.54	1.42
2.66	3.20
3.67	6.98
5.11	18.7
6.13	24.2
6.65	23.7

have alkyl 3-substituents, there is a sharp rate maximum at *ca.* 0.9M acid similar to that reported in the preceding paper for 2,3,3-triethyloxaziridine. For compounds (1e) and (1f) with a secondary alkyl 2-substituent the acid catalysis is stronger and the rate maxima occur at higher acidities (*ca.* 4M). The trend towards increased catalysis with branching of the 2-alkyl substituent is readily apparent in the Figure which compares a plot of k_ψ *versus* $[HClO_4]$ for (1e) with data for 2,3,3-triethyloxaziridine [1] and for 3-ethyl-2-t-butyloxaziridine.[4] In contrast, the results in Table 2 show that [with the exception of (1c)] the structure of the 3-substituent has only a small effect on the reaction kinetics. Thus data for (1e) and (1f) and for 3-*p*-nitrophenyl-2-t-butyloxaziridine [4] give similar plots to those described by the Figure.

In addition to their kinetic influences, 2- and 3-substituents are known [2,3] to have a profound effect on the hydrolysis pathway. In the present instance, this was confirmed by identification of the carbonyl products as 2,4-dinitrophenylhydrazone derivatives (Table 3). For substrates (1a) and (1b), the two carbonyl products in each case are consistent with Emmons' [2] mechanism (Scheme 1) and the preceding paper where an *O*-conjugate acid intermediate decomposes with synchronous N–O bond fission and H^+ abstraction from the 2-substituent. The two carbonyl products obtained with (1e), however, show that Me migration occurs in preference to H^+ abstraction, so this compound behaves like the 2-t-butyloxaziridines studied previously. Finally, the formation of only *p*-nitrobenzaldehyde from (1d) and (1f),

TABLE 3

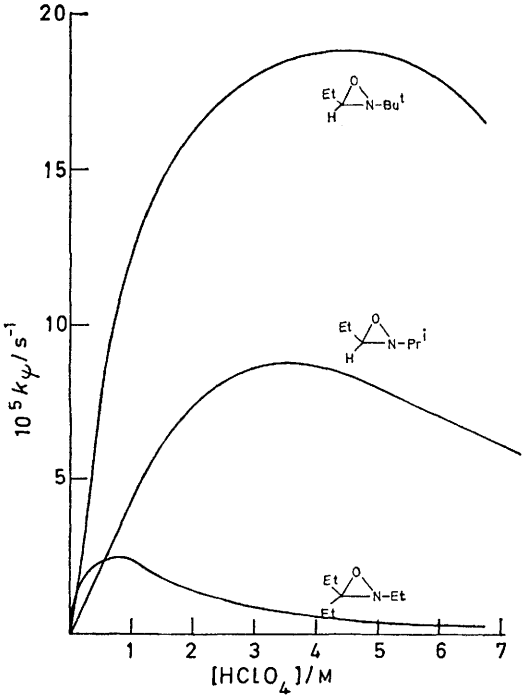
Products of oxaziridine hydrolysis

Compound	Carbonyl products [a]
(1a)	EtMeCO and Pr^nCHO
(1b)	Pr^iMeCO and EtCHO
(1c)	PhCHO
(1d)	*p*-$NO_2C_6H_4CHO$
(1e)	Pr^nCHO and MeCHO
(1f)	*p*-$NO_2C_6H_4CHO$

[a] Identified as their 2,4-dinitrophenylhydrazone derivatives.

and only benzaldehyde from (1c), can be explained (again after Emmons [2]) by C–O bond cleavage of an *O*-conjugate acid intermediate (Scheme 2). This pathway would be favourable as it involves an incipient aryl carbonium ion. For compounds (1c) and (1d), the n.m.r. spectra for reaction in deuteriated solvents showed the concurrent formation of *N*-ethylhydroxylamine and for compound (1e) the formation of methylamine.

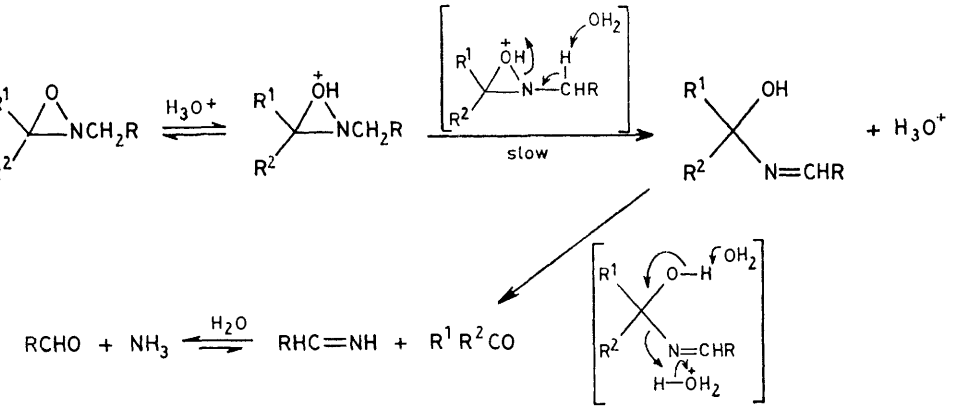
Acidity Dependences and Reaction Mechanisms.—Both the position and magnitudes of the rate maxima are unusually dependent on the nature of the 2-alkyl substituent. It is unlikely that transformations sub-



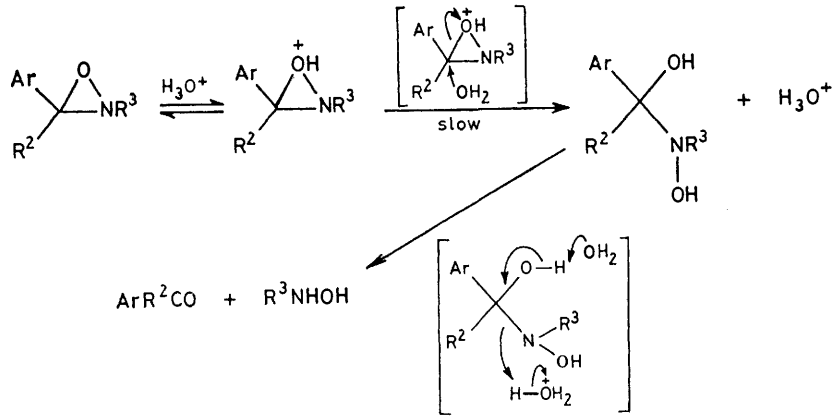
Effect of *N*-alkyl substituents on the extent of acid catalysis for the hydrolysis of alkyloxaziridines

sequent to the initial ring cleavage are important in this respect because the reactions were followed by measuring the oxidation of I^- to I_2 by unchanged substrate. This conclusion presumes that the oxaziridine ring is not reformed on quenching the reaction prior to iodometric titration, which can be justified by the good kinetic plots obtained. Further, independent checks showed that nitrones [$R^1R^2C{=}N(R^3) \longrightarrow O$] do not isomerise to oxaziridines when exposed to the kinetic assay. It is also unlikely that the different directions for ring cleavage and subsequent group migrations indicated by the product analyses exert a major influence on the acidity dependences. For example, the data in the Figure would require that Me migration (for 2-t-butyl- and 2-isopropyl-3-ethyloxaziridine) is both much faster and more strongly acid-catalysed than H^+-abstraction (for 2,3,3-triethyloxaziridine) for reactions involving common N–O bond fission. Further, the hydrolysis of 2-t-butyl compounds is more strongly acid-catalysed irrespective of C–O or N–O bond fission. Thus a more plausible explanation is that 2-alkyl substituents exert a strong influence on the concentration of the reactive intermediate, which is an *O*-conjugate acid for most reactions. Specifically, the *O*-conjugate acid concentration at any given acidity must be substantially larger for compounds bearing 2-t-butyl substituents irrespective of other structural differences.

Evidence in the preceding paper suggests that 2,3,3-triethyloxaziridine undergoes concurrent protonation of both O and N atoms with hydrolysis proceeding prefer-



SCHEME 1 Acid-catalysed hydrolysis of 2-(primary alkyl)oxaziridines



SCHEME 2 Acid-catalysed hydrolysis of 3-aryloxaziridines

entially *via* the *O*-conjugate acid. This produces an unusual acidity dependence with a sharp rate maximum at relatively low acidity similar to that observed for compounds (1a) and (1b). Accordingly, the kinetic data for (1a) and (1b) have been analysed in terms of equation (1) where k_ψ = difference between k_0 in acid and in pure water, k = first-order rate coefficient for decomposition of the *O*-conjugate acid, and K_1 and K_2 are the equilibrium constants for *O*- and *N*-conjugate acid formation, respectively. Assumptions made in the derivation of equation (1) are discussed in the preceding paper. Best

$$k_\psi = kh_0/(K_1 + h_0 + K_1h_0'''/K_2) \qquad (1)$$

values of k, K_1, and K_2 were obtained from each set of data, as before, by transforming equation (1) into a linear expression and solving by computerised least-squares analysis. The values obtained for the constants are given in Table 4 where they are seen to be self-consistent

TABLE 4

Rate and acid dissociation constants for the hydrolysis of oxaziridines in aqueous $HClO_4$ at 25 °C

Compound	$10^5k/s^{-1}$	K_1 [a]	K_2 [b]	Ref.
(1; $R^1 = R^2 = R^3 =$ Et)	7.5	0.47	0.47	*d*
(1a)	15	0.265	0.28	*e*
	(15.5) [c]	(0.32) [c]	(0.52) [c]	
(1b)	17.5	0.455	0.64	*e*
(1e)	10.4	2.82		*e*
(1; R^1 = Me, R^2 = H, $R^3 = Bu^t$)	18.2	0.74		*f*
(1; R^1 = Et, R^2 = H, $R^3 = Bu^t$)	19.2	0.81		*f*
(1; $R^1 = Pr^i$, R^2 = H, $R^3 = Bu^t$)	15.5	2.28		*f*
(1d)	6.7		68	*e*
(1f)	27.8	164		*e*
(1; $R^1 = p$-NO_2·C_6H_4, R^2 = H, $R^3 = Bu^t$)	71.7	64		*f*

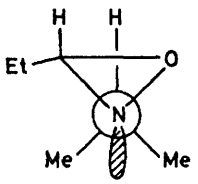
[a] Based on the h_0 scale of acidity. [b] Based on the h'''_0 scale of acidity. [c] Figures in parentheses refer to aqueous H_2SO_4. [d] Preceding paper. [e] This paper. [f] Ref. 4.

and in reasonable agreement with related data for other oxaziridines. It is stressed, however, that the numerical analysis is more dependent on the K_1/K_2 ratio than the actual values of K_1 and K_2. The constants for compound (1a) in aqueous perchloric acid agree well with those for aqueous sulphuric acid which establishes that the acid anion is not an influential factor. Compound (1a) was also examined in aqueous [$^2H_2$]sulphuric acid (Table 2) principally to determine the kinetic solvent isotope effect. The kinetic acidity dependence in both acids is similar with a sharp rate maximum at *ca.* 0.8M, but throughout (both before and after the rate maximum) the rate is faster in H_2SO_4 than in D_2SO_4. The value of $k_\psi^{H_2O}/k_\psi^{D_2O}$ varies slightly from *ca.* 1.5 in 0.5M acid to 1.7 in 3M acid. This is consistent* with compound (1a) being extensively protonated throughout this range of acidity as indicated by the values of K_1 and K_2 in Table 4. As in the preceding paper, the agreement between experimental values of k_ψ and those calculated *via* equation (1) from the constants in Table 4 is excellent for both compounds (1a) and (1b). The fact that the unusual kinetic acidity dependences for these compounds can be reproduced by equation (1) is some proof of the mechanistic explanation. No other mechanism considered can do this including those where the reduction in water activity (a_{H_2O}) with increasing acidity was taken into account. In particular, it was not possible to fit the experimental data to reaction schemes involving only a single conjugate acid with rate reductions at acidities >0.9M being attributed to the decrease of a_{H_2O}. Plots of either log (k_ψ/h_0) or log ($k_\psi/[H^+]$) *versus* log a_{H_2O} were very sharply curved rather than linear as required by the alternative schemes.

For compound (1e) which bears an isopropyl 2-substituent, both the kinetic acidity dependence (Figure) and reaction products (Table 3) have stronger resemblance to those obtained for 3-ethyl-2-t-butyloxaziridine [4] than for 2,3,3-triethyloxaziridine.[1] In particular, the sharp rate maximum at relatively low acidity characteristic of compounds with primary alkyl-2-substituents is lacking and decomposition involves Me migration to the heterocyclic N rather than H^+ abstraction from the 2-isopropyl substituent. Significantly, the kinetic data for compound (1e) are best fitted by equation (2), where k_ψ, k, and K_1 have the same significance as in equation (1). Equation (2), however, which correlates satisfactorily the data for 2-t-butyloxaziridines,

$$k = k_\psi\{K_1/h_0 + 1\} \qquad (2)$$

requires predominant substrate protonation at only *one* site, thought to be the O atom in the case of 2-t-butyloxaziridines.[4] Values of k and K_1 obtained for compound (1e) from a reciprocal plot (*i.e.* $1/k_\psi$ *versus* $1/h_0$ as discussed further in ref. 4) are also listed in Table 4. Both constants agree sensibly with earlier data, *i.e.* the basicity of compound (1e) is of the same order as that of other alkyloxaziridines, but its rate of decomposition is slower than that of 2-ethyl-3-t-butyloxaziridine because the resultant carbonium ion intermediate is secondary rather than tertiary. The preference for decomposition by Me migration to the N atom rather than by H^+ abstraction from the 2-isopropyl substituent suggests that rotation about the exocyclic C–N bond is restricted. A conformation (2) where the isopropyl-H is *syn* to the



(2)

heterocyclic O atom is sterically favoured in the neutral substrate and should be even more so in the *O*-conjugate acid.

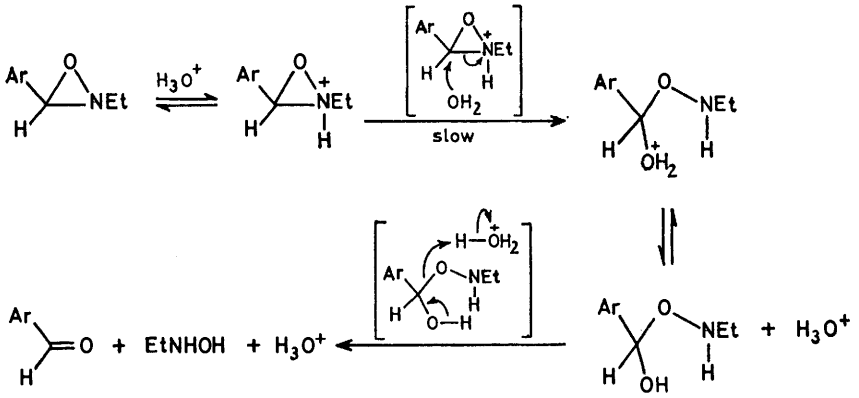
The influence of 2-alkyl substituents on the kinetic

* Enhanced pre-equilibrium protonation in D_2O relative to H_2O is not kinetically significant if the substrate is extensively protonated. Thus the isotopic rate ratio reflects only the difference in solvolytic ability of the two solvents.

acidity dependences for 3-*p*-nitrophenyloxaziridines [compounds (1d) and (1f) in Table 2 and the 2-t-butyl compound studied earlier] is superficially similar (*i.e.* tert. > sec. > prim.) to that observed for 3-alkyloxaziridines. Because both sets of compounds hydrolyse by different pathways, it is difficult to explain this similarity in terms other than pre-equilibrium protonation phenomena. Closer scrutiny, however, reveals subtle behavioural differences between 3-aryl- and 3-alkyl-oxaziridines that require additional mechanistic interpretation. For example, the rate maximum for 2-ethyl-3-*p*-nitrophenyloxaziridine (1d) is broad and occurs at much higher acidity than those of corresponding alkyloxaziridines. The difference is not entirely explained by the lower basicity of compound (1d) and the data correlate better with equation (2) than equation (1). Further, hydrolysis of 2-ethyl-3-phenyloxaziridine (1c) is very rapid, despite expectations of extensive *N*-conjugate acid formation as with other 2-ethyl compounds. These plots are also listed in Table 4. The differences of *ca.* 3 in both k and K_1 for compound (1f) and 3-*p*-nitrophenyl-2-t-butyloxaziridine probably reflect the reliability of the numerical analyses, but qualitatively they can also be accounted for by concurrent *O*- and *N*-protonation of compound (1f).

Conclusions.—The extent to which strong acids catalyse the hydrolysis of oxaziridines is unusually dependent on the structure of the *N*-alkyl substituent. The very mild catalysis observed for 2,3,3-triethyloxaziridine is confirmed for several other compounds with primary alkyl *N*-substituents which suggests that their decomposition is much better effected under alkaline conditions.[2,7] Acid-catalysed hydrolysis is more efficacious for oxaziridines with branched-chain alkyl-*N*-substituents, but extensive protonation of the substrate results in the fastest reactions occurring at an optimum, rather than the highest, acidity.

The kinetic acidity dependences relate more closely to



SCHEME 3

observations suggest that the hydrolysis of 3-aryloxaziridines can also proceed *via* the *N*-conjugate acid (Scheme 3) but at a slower rate * than *via* the *O*-conjugate acid (Scheme 2). Significantly, both pathways involve solvolysis of the same carbonium ion centre (unlike the alternative reaction pathways for 3-alkyloxaziridines) and in neutral compounds C–N bonds are actually weaker than C–O bonds. Accordingly, the kinetic data for compound (1d) have been analysed in terms of equation (3) and equation (2), respectively. Equation (4) differs from equation (2) only in the

$$k = k_\psi(K_2/h_0''' + 1) \qquad (3)$$

assumption that *N*-conjugate acid formation follows the h_0''' acidity function [6] but k refers to the decomposition of the *N*-conjugate acid: k_ψ and K_2 have the same significance as in equation (1). Values of k and either K_1 and K_2 derived from the corresponding reciprocal

* Comparison of the data for 3-*p*-nitrophenyloxaziridines requires this conclusion. It is not necessarily vitiated by the observation that (1c) hydrolyses at about the same rate as 3-phenyl-2-t-butyloxaziridine because k_0 depends on both the extent of protonation (pK_1 and pK_2) and the rate of ring cleavage (k_ψ). These constants could not be determined for 3-phenyloxaziridines because their hydrolyses become too fast at high acidities.

different concentrations of the *O*- and *N*-conjugate acid intermediates than to subsequent transformations. A satisfactory rationale is that *N*-conjugate acid formation is more extensive for oxaziridines bearing primary- than secondary- or tertiary-alkyl-*N*-substituents. This difference is clearly not related to the usual electronic interactions and probably arises from steric inhibition to solvation of the *N*-conjugate acid. This factor is thought to be important for the basicity of both primary and secondary amines [8] and a related phenomenon (namely the reduction of a_{H_2O} with increasing acidity) may explain the relative basicities of O and N atoms in both amides [9] and hydroxamic acids.[10] There is less evidence that bulky substituents inhibit the solvation of tertiary amines [8] (including very limited data for aziridines [11]), but the juxtaposition of O and N atoms in oxaziridines may impart atypical behaviour. Also the O and N basicities in oxaziridines appear to be finely balanced and, therefore, particularly sensitive to small destabilising factors.

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