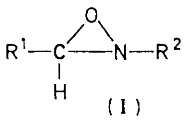
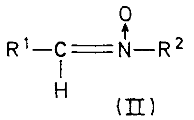
The Acid Catalysed Hydrolysis of *N*-t-Butylbenzaldoxime and 2-t-Butyl-3-phenyloxaziridine

By **Charmian J. O'Connor, Eleanor J. Fendler,** and **Janos H. Fendler,*** Department of Chemistry, Texas A and M University, College Station, Texas 77843

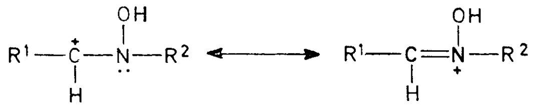
The rates of hydrolysis of *N*-t-butylbenzaldoxime and 2-t-butyl-3-phenyloxaziridine have been measured over a wide range of acidities in HCl, H_2SO_4, and $HClO_4$. Interpretation of the rate data by use of the Bunnett criteria of mechanism, deuterium isotope effects, and Arrhenius parameters are consistent with a bimolecular specific acid catalysed mechanism for hydrolysis of both substrates reacting through the protonated nitrone as a common intermediate.

THE preparation and properties of oxaziridines (I) and nitrones (II) have been reviewed.[1-6] The reactions of


(I)


(II)

simple oxaziridines consist mainly of ring opening, presumably to relieve steric strain, followed by rearrangements or cleavage. In aqueous acid oxaziridines were shown to undergo ring opening and cleavage to form carbonyl compounds and *N*-substituted hydroxylamines,[4,5] *e.g.* 2-t-butyl-3-phenyloxaziridine is hydrolysed in aqueous acid to benzaldehyde and *N*-t-butylhydroxylamine. Hydrolysis of substituted 2-t-butyloxaziridines in aqueous $HClO_4$ has been investigated kinetically.[7] Based on the acidity dependence and on deuterium solvent isotope effects the proposed mechanism involved pre-equilibrium protonation followed by ring opening.[7] From the dependency of rate on acid concentration the role of water could not be established, however, unequivocally. Increasing perchloric acid concentrations increased the rate up to a maximum after which it seemed to level off.[7] We have extended this investigation to wider range of acidities using $HClO_4$, HCl, and H_2SO_4, observed rate maxima, and applied Bunnett's[8] and Bunnett and Olsen's[9] mechanistic criteria to the data. No mechanistic study of the solvolytic reactions of the corresponding nitrone, *N*-t-butylbenzaldoxime, has been reported; however, the products have been shown to be the same as from the oxaziridine in aqueous acid.[5] Consequently the hydrolysis of *N*-t-benzaldoxime has been examined in the same range of acidities since hydrolysis of (I) and (II) could well involve a common intermediate, the protonated nitrone (III).


(III)

Arrhenius parameters have been evaluated for the three acids and the deuterium isotope effect measured in D_2SO_4. The reactions have also been carried out in sodium acetate–acetic acid buffer solutions at constant pH and in sodium hydroxide.

EXPERIMENTAL

Materials.—2-t-Butyl-3-phenyloxaziridine (I; $R^1 = Ph$; $R^2 = Bu^t$) was prepared from the reaction of *N*-benzylidene-t-butylamine with peracetic acid [prepared from acetic anhydride and 90% hydrogen peroxide (FMC Corp.) in methylene chloride with H_2SO_4 as the catalyst] according to a slightly modified procedure of Emmons.[5] *N*-Benzylidene-t-butylamine was prepared by the slow addition (*ca.* 30 min) of benzaldehyde (42·45 g, 0·80 mol) t-butylamine (29·2 g, 0·80 mol) at 0 or 10 °C. The mixture was stirred at room temperature for *ca.* 14 h, KOH pellets were added, the organic and aqueous layers were separated, and the organic layer was dried over KOH pellets at *ca.* 0 °C. The crude product was vacuum distilled from fresh KOH pellets through a 37 cm column packed with glass helices, b.p. 88·5—89·5 °C at 10 Torr (lit.,[5] 90—92° at 11 Torr). The oxidation of benzylidene-t-butylamine with peracetic acid was carried out according to the methods of Emmons with the exception that following the washing of the crude product, it was dried over anhydrous sodium sulphate and the methylene chloride was removed by vacuum rotary evaporation at <25 °C.

N-t-Butylbenzaldoxime (nitrone) (II; $R^1 = Ph$, $R^2 = Bu^t$) was prepared in quantitative yield by the thermal isomerization[4,5] of 2-t-butyl-3-phenyloxaziridine. After refluxing the oxaziridine (8·8 g) for 91 h in acetonitrile (100 ml), freshly distilled from P_2O_5, and removal of the solvent by vacuum rotary evaporation, a viscous light yellow oil was obtained which crystallized, m.p. 73—74°, on the addition of dry light petroleum (Skellysolv B). Recrystallization from dry light petroleum gave prisms which melted very sharply at *ca.* 73·5—73·8° (lit.,[5] m.p. 75—76°).

The purity of 2-t-butyl-3-phenyloxaziridine and *N*-t-butylbenzaldoxime was verified by the ^1H n.m.r. spectra of *ca.* 2M solutions in $(CD_3)_2SO$ determined on a Varian Associates T60 spectrometer at sweep widths of 500 Hz and 34 ± 1 °C with tetramethylsilane as internal reference: (I; $R^1 = Ph$; $R^2 = Bu^t$) δ 1·12 (s, Me_3C), 4·92 (s, CH), and 7·43 (m, ArH); (II; $R^1 = Ph$; $R^2 = Bu^t$) δ 1·52 (s, Me_3C), 7·83 (s, CH), and 7·38 (three lines, A_2B_3, ArH-3, -4,

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[1] J. F. Dupin, *Bull. Soc. chim. France*, 1967, 3085.

[2] K. Shinzawa and I. Tanaka, *J. Phys. Chem.*, 1964, **68**, 1205.

[3] W. Rundel in 'Methoden der Organischen Chemie,' ed. J. Houben, Georg Thieme Verlag, Stuttgart, 1968, Band X, Teil 4, p. 465.

[4] W. D. Emmons in 'Heterocyclic Compounds with Three- and Four-membered Rings, Part I,' ed. A. Weissberger, Interscience, New York, 1964, p. 624 and references cited therein.

[5] W. D. Emmons, *J. Amer. Chem. Soc.*, 1957, **79**, 5739.

[6] G. R. Delpierre and M. Lamchen, *Quart. Rev.*, 1965, **19**, 329.

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

[8] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956, 4968, 4973, 4978.

[9] J. F. Bunnett and F. Olsen, *Canad. J. Chem.*, 1966, **44**, 1917.

and -5) and 8·36 (four lines, A_2B_3, ArH-2 and -6). The upfield shift of the methine proton resonance frequency of the oxaziridine (I; $R^1 = Ph$; $R^2 = Bu^t$) relative to that of the nitrone (II; $R^1 = Ph$; $R^2 = Bu^t$) ($\Delta\delta$ 2·91) as well as that of the t-butyl protons ($\Delta\delta$ 0·40) is in accord with the structure of the oxaziridine ring.

Concentrated (A.C.S. reagent grade) HCl, $HClO_4$, and H_2SO_4 (Matheson Scientific) were diluted with twice distilled water and were standardized with 1·00 or 0·100M-NaOH (BDH) using lacmoid as the indicator. Sodium acetate and acetic acid were reagent grade. The pH of the sodium acetate–acetic acid buffers at 25·0 °C were adjusted and monitored using a Radiometer PHM-26 expanded scale pH meter. Solutions of D_2SO_4 were made by diluting concentrated D_2SO_4 (Diaprep; 99·5%) with D_2O (Diaprep; 99·8%).

Ionization Spectra.—The changes in the spectra of *N*-t-butylbenzaldoxime and 2-t-butyl-3-phenyloxaziridine in aqueous and acid solutions were measured on a Cary 14 spectrophotometer.

Kinetic Measurements.—Rates of hydrolysis were measured spectrophotometrically on a Beckman Kintrac VII recording spectrophotometer at 287 nm. Reactions were initiated by injecting small volumes (*ca.* 5 μl) of aqueous solutions of the substrates to thermostatted acid, buffer, or alkali solutions. Whenever feasible the reactions were allowed to run for 8—10 half-lives and good first-order plots were obtained up to 90% reaction giving rate constants with an error of ±2%. For the slower runs, Guggenheim plots[10] were used and the accuracy of the obtained values is ±5%. The temperature of the thermostatted baths and the cell compartment was maintained within ±0·05°, as monitored by N.B.S. thermometers.

RESULTS AND DISCUSSION

U.v. Spectra.—Emmons[4] reports the spectra of *N*-t-butylbenzaldoxime, $\lambda_{max.}$ 295 nm (ε 16,700 l mol^{-1} cm^{-1}), and 2-t-butyl-3-phenyloxaziridine, $\lambda_{max.}$ 249 nm (ε 930 l mol^{-1} cm^{-1}), in ethanol. In water we found a broad band at $\lambda_{max.}$ 287 nm (ε 20,500 l mol^{-1} cm^{-1}) for the nitrone and for the oxaziridine sharp peaks at 252, 262·5, and 269 nm and a broad band at 285 nm (ε 1410, 1420, 1315, 1200, and 1113 l mol^{-1} cm^{-1}, respectively). In 8·4M-$HClO_4$ the broad peak for the nitrone shifts to 273 nm (ε 27,200 l mol^{-1} cm^{-1}) and the fine structure present in the neutral aqueous spectrum for the oxaziridine disappears and is replaced by a broad band with $\lambda_{max.}$ 257 nm (ε 1205 l mol^{-1} cm^{-1}). An aqueous solution of benzaldehyde has an absorption maximum[11] at 249·5 nm (ε 11,400 l mol^{-1} cm^{-1}).

All hydrolyses were followed under pseudo-first-order kinetic conditions by monitoring the consumption of reactant at 287 nm. At this wavelength large decreases in optical density were observed under all conditions for both substrates, even though we were often using the side of the absorption band and not the maximum.

Rate Constants of Hydrolysis.—Table 1 summarizes the results obtained for the rate constants, k_ψ, of hydrolysis of *N*-t-butylbenzaldoxime in HCl, $HClO_4$, and H_2SO_4, in sodium acetate–acetic acid buffer at pH 4·05, and in NaOH at 24·2 °C. Rate constants in low $HClO_4$ concentrations are in good agreement with those determined previously.[7] Data for the hydrolysis of 2-t-butyl-3-phenyloxaziridine are presented in Table 2.

TABLE 1

Rate constants for hydrolysis of *N*-t-butylbenzaldoxime[a] at 24·2 °C

HCl

[HCl]/M	10^5k_ψ/s^{-1}	pH	10^5k_ψ/s^{-1}
10·0	3·61	2·00	34·2
8·56	10·2	2·10	30·6
7·55	20·3	2·25	21·6
6·52	44·7	2·52	11·8
5·58	89·0	3·05	3·92
4·58	142		
3·58	280		
2·60	473		
1·67	767		
1·15	978		
0·575	857		
0·200	482		
0·150	371		
0·095	302		
0·078	256		
0·059	192		
0·030	101		

$HClO_4$		H_2SO_4	
[$HClO_4$]/M	10^5k_ψ/s^{-1}	[H_2SO_4]/M	10^5k_ψ/s^{-1}
7·55	1·13	7·08	0·729
6·75	2·29	6·35	1·97
5·90	6·10	5·55	5·76
4·56	28·0	4·75	20·5
3·30	65·8	4·20	45·2
2·30	135	3·25	124
1·55	330	2·90*	119
0·900	597	2·38	294
0·405	632	1·65	514
0·160	451	0·805	830
0·0800	271	0·375	840
0·008	31·3	0·168	506
		0·0800	349
		0·0695*	412
		0·0600	276
		0·006	38·3

Sodium acetate–acetic acid buffer at pH 4·05		NaOH	
[Buffer]/M	10^5k_ψ/s^{-1}	[NaOH]/M	10^5k_ψ/s^{-1}
0·100	0·545	1·00	1·29
0·0200	0·545	0·100	~0·15

[a] [Substrate] = 2—5 × 10^{-5}M.
* D_2SO_4.

The Figure gives plots of $\log_{10} k_\psi$ against pH (for $C_{H^+} < 1$M) and against $-H_0$ (for $C_{H^+} > 1$M) for (a) the oxaziridine and (b) the nitrone. All the profiles exhibit a rate maximum similar to those exhibited for the hydrolysis of moderately basic substrates, *e.g.* amides,[12–14] esters,[15] ureas,[16] and dipeptides.[17] Moreover, as we have

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[10] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

[11] H. H. Jaffe and M. Orchin, 'Theory and Application of Ultraviolet Spectroscopy,' Wiley, New York, 1962, p. 257.

[12] C. J. O'Connor, *Quart. Rev.*, 1970, **24**, 553.

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[14] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1973, 220.

[15] K. Yates, *Accounts Chem. Res.*, 1971, **4**, 136.

[16] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1973, 1457.

[17] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1973, 685.

found previously,[13-20] both the magnitude and the position of the rate maximum is dependent on the nature of the mineral acid used as the catalysing medium.

TABLE 2

Rate constants for hydrolysis of 2-t-butyl-3-phenyloxaziridine [a] at 24·2 °C

HCl			
[HCl]/M	10^5k_ψ/s^{-1}	pH	10^5k_ψ/s^{-1}
9·73	5·26	2·00	36·8
8·52	12·9	2·10	32·3
7·60	25·1	2·52	11·9
6·55	45·7	3·05	2·99
5·57	89·0		
4·50	169		
3·68	238		
2·82	403		
1·80	917		
1·67	1060		
1·15	987		
0·920	896		
0·550	748		
0·200	552		
0·150	428		
0·078	309		
0·059	203		
0·030	112		

$HClO_4$		H_2SO_4	
[$HClO_4$]/M	10^5k_ψ/s^{-1}	[H_2SO_4]/M	10^5k_ψ/s^{-1}
7·55	1·03	7·08	0·447
6·75	2·24	6·35	1·45
5·90	5·52	5·55	4·81
4·56	23·6	4·75	18·1
3·30	68·3	4·20	46·3
2·30	163	3·25	116
1·55	345	2·90*	118
0·900	684	2·38	257
0·405	706	1·65	496
0·160	461	0·805	942
0·080	283	0·375	883
0·008	31·7	0·168	568
		0·080	358
		0·0695*	417
		0·060	275
		0·006	37·7

Sodium acetate–acetic buffer at pH 4·05		NaOH	
[Buffer]/M	10^5k_ψ/s^{-1}	[NaOH]/M	10^5k_ψ/s^{-1}
0·100	0·528	1·00	1·34
0·0200	0·512	0·100	~0·10

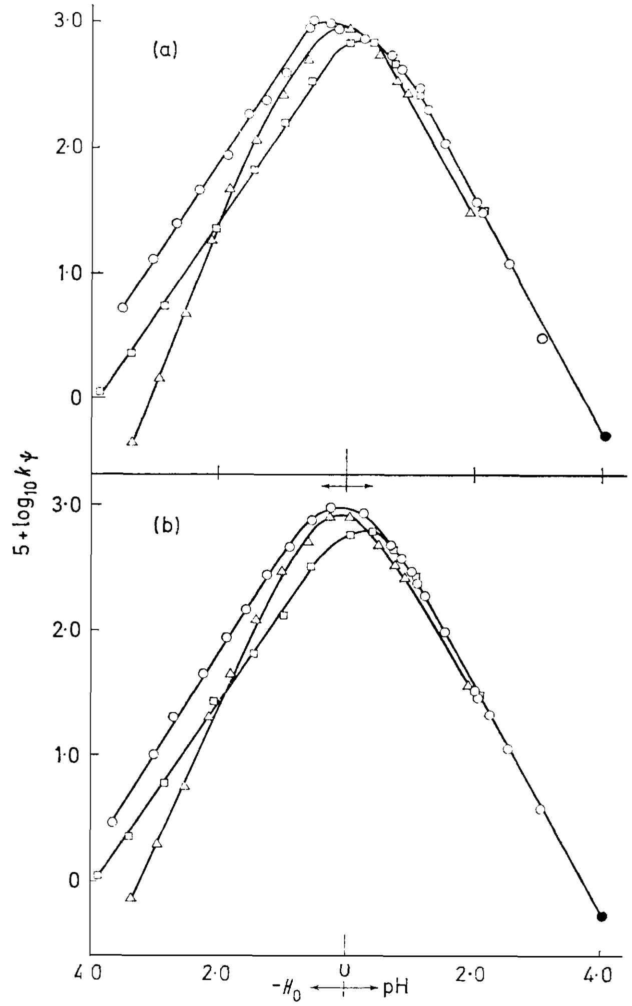
[a] [Substrate] = 1—8 × 10^{-4}M.
* D_2SO_4.

For the nitrone the position of the maximum shifts to lower acidity in the order HCl $\simeq$ H_2SO_4 < $HClO_4$ and for the oxaziridine the order is HCl < H_2SO_4 < $HClO_4$. For both substrates the magnitude of $k_{\psi_{\text{max.}}}$ decreases in the order HCl > H_2SO_4 > $HClO_4$. In the pH region the profiles for HCl and $HClO_4$ are superimposeable and slightly greater than that for H_2SO_4. At higher acidities the profiles for HCl and $HClO_4$ are nearly parallel but that for H_2SO_4 decreases more rapidly with increasing values of $-H_0$.

Data measured in two concentrations of sodium acetate–acetic acid buffer at pH 4·05 are identical, corroborating the conclusion of Butler and Challis[7] that the reaction is catalysed specifically by hydrogen ions, and not by general acids.

Base catalysed hydrolysis exists but is much slower than the acid catalysed reaction.

The immediate changes in u.v. spectra exhibited by the substrates on addition of mineral acids are consistent with a rapid protonation equilibrium, S + H^+ $\rightleftharpoons$ SH^+, to form the conjugate acids. In order to interpret the rate data, one must first correct the observed values of k_ψ for the amount of protonated substrate. Spectrophotometric methods are widely applicable for determination of the ionization ratio, $I = C_{SH^+}/C_S$, of moderately basic substrates.[21] For N-t-butylbenzaldoxime and 2-t-butyl-3-phenyloxaziridine however, the rate of the



Rate constants (a) for hydrolysis of 2-t-butyl-3-phenyloxaziridine and (b) for N-t-butylbenzaldoxime at 24·2 °C as a function of acidity in HCl (○), $HClO_4$ (□), H_2SO_4 (△), and NaOAc–HOAc buffer (●)

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[18] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1972, 2378.

[19] C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, 1965, **30**, 1365.

[20] C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, 1966, **31**, 2307.

[21] C. K. Rochester, 'Acidity Functions,' Academic Press, New York, 1970, p. 113.

hydrolysis reaction ($t_{\frac{1}{2}} \simeq 1$ min) at the maximum in the profile at 24·2 °C made it impossible to measure the zero time absorption of the substrates. However, allowing for medium effects in the absorption spectra, the substrates appeared to be essentially fully protonated in solutions of $C_{H^+} > 2$M in all three acids.

TABLE 3

Analysis of rate data for hydrolysis of *N*-t-butylbenzaldoxime and 2-t-butyl-3-phenyloxaziridine at 24·2 °C by use of Bunnett *w* and Bunnett–Olsen linear free energy relationships

	(I; R^1 = Ph, R^2 = Bu^t)		(II; R^1 = Ph, R^2 = Bu^t)	
Acid	w	ϕ	w	ϕ
HCl	3·80	0·80	3·80	0·96
$HClO_4$	3·78	0·84	3·40	0·88
H_2SO_4	6·21	1·49	5·70	1·44

TABLE 4

Rate constants for hydrolysis of *N*-t-butylbenzaldoxime and 2-t-butyl-3-phenyloxaziridine at elevated temperatures

	$10^4k_4/s^{-1}$					
Acid	36·8 °C (I; R^1 = Ph, R^2 = Bu^t)	48·8 °C (I; R^1 = Ph, R^2 = Bu^t)	59·7 °C (I; R^1 = Ph, R^2 = Bu^t)	36·8 °C (II; R^1 = Ph, R^2 = Bu^t)	47·1 °C (II; R^1 = Ph, R^2 = Bu^t)	58·2 °C (II; R^1 = Ph, R^2 = $Bu^{t\prime}$)
0·078M-HCl	85·0	243	648	82·4	189	471
4·58M-HCl	57·8	163	380	55·5	138	347
0·080M-$HClO_4$	87·6	245	638	82·7	189	483
4·56M-$HClO_4$	7·50	21·2	50·7	7·37	18·9	46·0
0·060M-H_2SO_4	87·3	204	594	76·2	173	430
4·20M-H_2SO_4	14·3	39·8	99·0	14·7	36·9	100

TABLE 5

Arrhenius parameters for acid catalysed hydrolysis of *N*-t-butylbenzaldoxime and 2-t-butyl-3-phenyloxaziridine

	$\Delta H^‡$/kJ mol^{-1}		$\Delta S^‡$/J mol^{-1} K^{-1}	
Acid	(I; R^1 = Ph, R^2 = Bu^t)	(II; R^1 = Ph, R^2 = Bu^t	(I, R^1 = Ph, R^2 = Bu^t)	(II; R^1 = Ph, R^2 = Bu^t)
0·078M-HCl	63·2	66·3	−23·4	−19·1
4·58M-HCl	69·4	72·5	−3·1	0·75
0·080M-$HClO_4$	63·2	65·3	−41·3	−1·5
4·56M-$HClO_4$	68·3	63·7	−29·5	−43·1
0·060M-H_2SO_4	63·2	59·1	−24·3	−37·6
4·20M-H_2SO_4	62·3	70·5	−29·5	−14·9

We have therefore analysed the data at high acidities using existing rate correlation expressions applicable to hydrolysis of a fully protonated substrate. Plots of the Zucker–Hammett *A*-2 relationship,[21] $\log_{10} k_\psi$ against $\log_{10} C_{H^+}$, were curved; plots of the Bunnett *w* criterion,[8] $\log_{10} k_\psi$ against $\log_{10} a_w$, were nearly linear; while those of the Bunnett–Olsen linear free energy relationship,[9] $\log_{10} k_\psi$ against $(H_0 + \log_{10} C_{H^+})$, were good straight lines. Values of the *w* and ϕ parameters obtained are summarized in Table 3.

The values of *w* lie outside the range 1·2—3·3 said to be characteristic of water acting as a nucleophile in the rate-determining step.[8] Moreover values of ϕ are all >0·58, and thus also fall in the region indicative of water acting as a proton transfer agent.[9] Bearing in mind the magnitude of the Arrhenius parameters (*vide infra*) and in view of the fact that the reactions are not general acid catalysed, such a mechanism seems very unlikely. We have previously found values of ϕ, for hydrolysis of amides,[13,14,21] which lie outside Bunnett and Olsen's original classification and have suggested [22] that limits on values of *w* and ϕ may have to be revised for application to each particular class of substrates.

Deuterium Isotope Effect.—The solvent deuterium kinetic isotope effect, $k_{H_2O}/k_{D_2O} = 1·61$ and 1·46 at 2·90M-sulphuric acid and $k_{H_2O}/k_{D_2O} = 0·77$ and 0·74 at 0·0695M-sulphuric acid, for the nitrone and oxaziridine respectively, are, as expected, less than unity at low acidities where the substrate is largely unprotonated and become greater than unity when the substrate is extensively protonated, as reported previously.[7] These observations are consistent with an *A*-2 mechanism for hydrolysis of a modrrately basic substrate,[23,24] and are similar to the effects observed during hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide.[13]

Temperature Effects.—Rate constants for hydrolysis of *N*-t-butylbenzaldoxime and 2-t-butyl-3-phenyloxaziridine at an acidity above and below the position of the rate maximum in HCl, $HClO_4$, and H_2SO_4 at elevated temperatures are given in Table 4.

Values for the enthalpies and entropies of activation are in Table 5. The enthalpies of activation are not greatly dependent on the medium and are consistent with a bimolecular mechanism of hydrolysis. Entropies of activation fall between the limits of 4·2 to 42 and −63 to −126 J mol^{-1} K^{-1} which broadly define unimolecular (*A*-1) and bimolecular (*A*-2) reactions respectively.[25]

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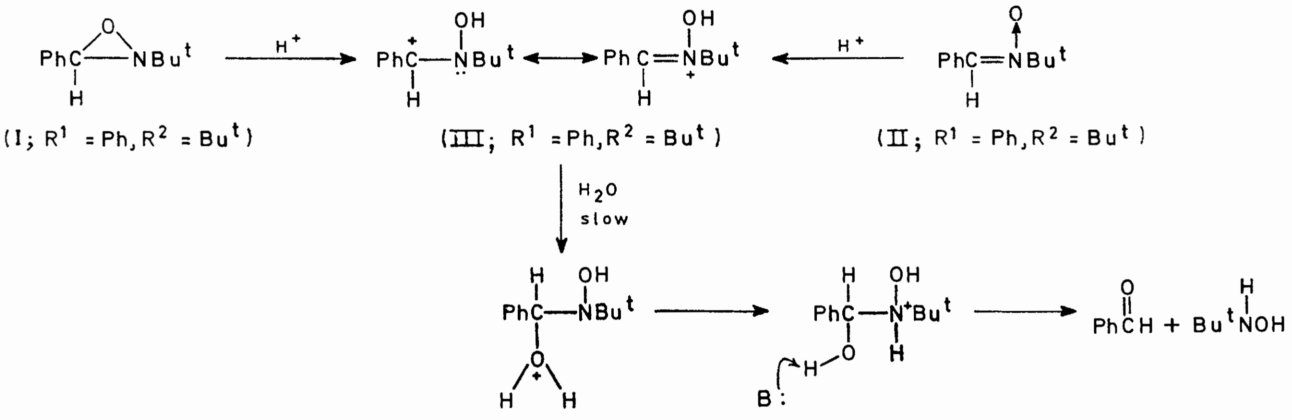
Mechanism.—If the protonated nitrone is the intermediate in both reactions (see Scheme), its formation from either nitrone or oxaziridine should have no effect on its subsequent behaviour under identical conditions.



SCHEME

Tables 1 and 2 and the Figure show that the rate data for hydrolysis of the nitrone are almost identical to that for hydrolysis of the oxaziridine under all conditions of acidity at 24·2 °C. This evidence confirms that the 'salt' of both the oxaziridine and nitrone has the same kinetics on addition to water and forms products at a rate greater than that of unprotonated oxaziridine or nitrone. The decreasing rate at high acidities is due to decreasing water activity in the acid media and is well explained by the Bunnett and Bunnett–Olsen criteria of mechanism.

The evidence we have presented is consistent with the mechanism outlined in the Scheme, *i.e.* a rapid protonation pre-equilibrium of nitrone and oxaziridine to form a common intermediate followed by slow nucleophilic attack by water and rapid decomposition to benzaldehyde and t-butylhydroxylamine.

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