Kinetics of Hydrolysis of Aziridines in Moderately Concentrated Mineral Acids. Relationship of φ Parameters to Reaction Mechanism[1]

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Abstract: Rates of hydrolytic ring opening of aziridinium ion (**1a**) and 2-methylaziridinium ion (**1b**) diminish with increasing acid concentration in 1–6 M HClO$_4$. From **1b**, the fraction of 2-amino-1-propanol (**2b**) product decreases from about 65% in 1 M to 48% in 6 M HClO$_4$. 2,2-Dimethylaziridinium ion (**1d**) hydrolyzes faster than **1a** or **1b**. Rates of hydrolysis of **1d** are nearly constant in 1–4 M HClO$_4$ and 1–5 M H$_2$SO$_4$, but increase with further augmentation of acid concentration. The fraction of 2-amino-2-methyl-1-propanol (**2d**) product decreases from about 12% in 1 M acid to amounts too small to determine above 4 M HClO$_4$ or H$_2$SO$_4$. Plots of log k_ψ vs. (H_0 + log [H$^+$]) are reasonably linear, except for hydrolysis of **1d** to 1-amino-2-methyl-2-propanol (**3d**) in HClO$_4$. The slopes (ϕ parameters) appear to be about −0.05 for reactions by the SN1 mechanism and about +0.35 for SN2 reactions, but special activity coefficient effects appear to intervene for **1d** hydrolysis in HClO$_4$.

The rates of acid-catalyzed reactions generally increase with the acid concentration, but the steepness of increase in moderately concentrated mineral acids (usually 1–10 M HCl, HClO$_4$, or H$_2$SO$_4$) is sharply dependent on the identity of the substrate. Also, as was first evident to Hammett in the 1930's,[4] there is some relationship between the steepness of increase and the mechanism of the reaction which occurs.

For the familiar case of a weakly basic substrate (S), it is profitable to consider an acid-catalyzed reaction to comprise two idealized steps. Step 1 is equilibrium

$$S + H^+ \rightleftharpoons SH^+ \tag{1}$$

$$SH^+ (+ H_2O) \rightleftharpoons \ddagger \longrightarrow \text{products} \tag{2}$$
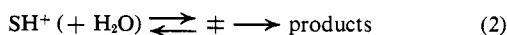
protonation of the substrate. In step 2, the protonated substrate (SH$^+$) reacts, sometimes with water, to form ultimate products, via a transition state ($\ddagger$).

The essential features of the problem are revealed by formulation of rate equations. Let us consider the rate of destruction of total substrate, [S]$_{st}$ = [S] + [SH$^+$]. Phenomenologically

$$-d[S]_{st}/dt = k_\psi[S]_{st} \tag{3}$$

where k_ψ is the pseudo-first-order rate constant. Conceptually, with attention first to reaction step 2

$$-d[S]_{st}/dt = k_r^0[SH^+]\gamma_{SH^+}/\gamma_\ddagger \tag{4}$$

where k_r^0 is the rate constant for step 2 at infinite dilution in water and γ_{SH^+} and $\gamma_\ddagger$ are activity coefficients. Utilizing the equilibrium constant expression for step 1, and substituting for [SH$^+$] in eq 4, we obtain

$$-d[S]_{st}/dt = (k_r^0[S][H^+]/K_{SH^+}) \times$$
$$(\gamma_S\gamma_{H^+}/\gamma_{SH^+})(\gamma_{SH^+}/\gamma_\ddagger) \tag{5}$$

where K_{SH^+} is the thermodynamic dissociation constant of SH$^+$, with infinite dilution in water the reference state.

Equating the right sides of eq 3 and 5, and recognizing that for a weakly basic substrate [S]$_{st}$ is virtually the same as [S], we get

$$k_\psi = (k_r^0[H^+]/K_{SH^+})(\gamma_S\gamma_{H^+}/\gamma_{SH^-})(\gamma_{SH^+}/\gamma_\pm) \tag{6}$$

The dependence of k_ψ on acid concentration is determined by the acid concentration dependence of two activity coefficient ratios, $\gamma_S\gamma_{H^-}/\gamma_{SH^+}$ pertaining to equilibrium step 1 and $\gamma_{SH^+}/\gamma_\pm$ pertaining to reaction step 2.

Thus, the overall medium dependence of rate for a weakly basic substrate is composite, being determined in part by one activity coefficient ratio which, because it concerns an equilibrium, *cannot* be related to reaction mechanism and in part by another ($\gamma_{SH^+}/\gamma_\pm$) which may be related to mechanism. There is abundant evidence that the dependence of both ratios is strongly dependent on the identity of the substrate and/or the character of the reaction which occurs in step 2. Failure fully to appreciate the composite character of the medium dependence of rate, for weakly basic substrates, was a flaw in early hypotheses seeking to relate medium dependence to reaction mechanism.[4,5]

For the purpose of getting valid information as to what part of the total medium dependence of rate is attributable to reaction step 2, two approaches may be used. One is to study independently the medium dependence of equilibrium protonation of the weakly basic substrate under kinetic study, or of another substance of the same functional type whose protonation is likely to be governed by virtually the same activity coefficients, and thus to evaluate independently the variation of $\gamma_S\gamma_{H^-}/\gamma_{SH^+}$ in eq 6. This approach has been utilized in particular by Yates[6] and by Scorrano.[7]

The second approach is to study kinetically reactions of strongly basic substrates which are essentially fully protonated at the lowest acid concentration of interest.

(4) (a) L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.*, **61**, 2791 (1939); (b) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940, pp 267–277.
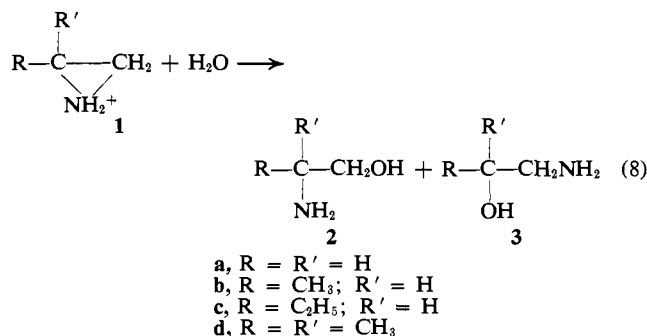(5) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4968 (1961).
(6) K. Yates, *Accounts Chem. Res.*, **4**, 136 (1971).
(7) G. Scorrano, *Accounts Chem. Res.*, **6**, 132 (1973).

In this case $[S]_{st}$ is virtually equal to $[SH^+]$, and from eq 3 and 4 one obtains

$$k_\psi = k_r{}^0\gamma_{SH^+}/\gamma_\pm \qquad (7)$$

It is the second approach that is applied in the present work, with attention to the hydrolytic ring opening of aziridine (1a) and its 2-methyl (1b) and 2,2-dimethyl (1d) derivatives.

$$
\begin{array}{ccc}
 & R' & R' \\
 & | & | \\
R\text{—}C\text{—}CH_2OH & + & R\text{—}C\text{—}CH_2NH_2 \quad (8) \\
 & | & | \\
 & NH_2 & OH \\
 & 2 & 3
\end{array}
$$

a, R = R' = H
b, R = CH₃; R' = H
c, R = C₂H₅; R' = H
d, R = R' = CH₃

The acid-catalyzed hydrolysis of aziridine and its 2-alkyl and 2,2-dialkyl derivatives was earlier studied by Buist and Lucas[8] and by Earley, et al.[9] On the basis of good evidence, they agreed that the aziridinium ions (1), not the aziridines, suffer the actual hydrolysis, that water opens the ring of 1a by S_N2 displacement on carbon, and that the greater part of the hydrolysis of 2,2-dimethylaziridinium ion (1d) occurs via S_N1 heterolysis of the bond between nitrogen and the tertiary carbon atom.[10] However, about 19% of the hydrolysis product from 1d was reported[9] to be 2-amino-2-methyl-1-propanol (2d), unlikely to result from an S_N1 reaction.

The two groups of workers were less emphatic in their views regarding hydrolysis of 2-alkylaziridinium ions. They assigned the S_N2 mechanism to scission at primary carbon, but considered the reaction at secondary carbon to be partially if not totally S_N1.

The present investigation comprises both kinetic and product studies. The rates of hydrolysis of 1a, 1b, and 1d have been measured in aqueous $HClO_4$ solutions to ca. 6 M, and for 1d also in aqueous H_2SO_4 to 7 M. For 1a, the temperature dependence of hydrolysis rates has been measured in 1, 4, and 6 M $HClO_4$. For 1a and 1d, the solvent isotope effect on hydrolysis rates has been determined by comparing rates in 1 M D_2SO_4 (in D_2O) with those in 1 M H_2SO_4 (in H_2O). Finally, product compositions (2 vs. 3) have been determined for hydrolysis of 1b in 0.7–6.1 M $HClO_4$ and for hydrolysis of 1d in both $HClO_4$ and H_2SO_4 up to 4 M.

Experimental Section

Materials. Aziridine, obtained from the Borden Chemical Co., was twice distilled prior to use, bp 56° (lit.[8] 55° (744 mm)). 2-Methylaziridine, obtained from K&K Laboratories, Inc., was twice distilled prior to use, bp 65° (lit.[9,11] 63–64). 2,2-Dimethylaziridine, prepared from commercial 2-methyl-2-amino-1-propanol according to the directions of Cairns,[12] was dried over sodium and twice distilled prior to use, bp 71° (lit.[8] 70.3° (741 mm)). 1-Amino-2-propanol (3b), commercial, was distilled prior to use, bp 161° (lit.[13] 160–161°). 2-Amino-1-propanol (2b), prepared by Raney

nickel reduction of 2-nitro-1-propanol formed from the condensation of formaldehyde with nitroethane according to the directions of Vanderbilt and Hass,[14] was distilled prior to use, bp 110° (30 mm) (lit.[15] 76–78° (15 mm)).

N-(2,4-Dinitrophenyl)-1-amino-2-propanol. 1-Amino-2-propanol (100 mg) was added to 5 ml of methanol containing 250 mg of 2,4-dinitrofluorobenzene. After 1 hr at room temperature, the methanol solution was added to 50 ml of water and the product (290 mg; 90%) was collected by filtration. After repeated crystallization from ethanol–water, the melting point was constant at 97°.
Anal. Calcd for $C_9H_{11}N_3O_5$: C, 44.81; H, 4.56. Found:[16] C, 44.65; H, 4.51.

N-(2,4-Dinitrophenyl)-2-amino-1-propanol prepared in the same manner appeared as an oil rather than a solid. This oil was taken up in chloroform and purified by chromatography on alumina. Attempted crystallization from a variety of solvents gave oils which solidified on long standing. The melting point, 88–93° (lit.[17] 96°), could neither be raised nor sharpened.

Kinetic Procedures. Hydrolysis rate determinations on 1a and 1b and some of those on 1d were made by measuring the disappearance of aziridine with time by the thiosulfate titration method of Earley, et al.[9] At measured times, 5-ml aliquots of the reaction solution (100 ml of standardized 1–6 M perchloric acid containing 1.0–1.5 ml of the aziridine) were withdrawn by pipet and discharged into 100-ml volumetric flasks containing 25 ml of standard 0.05 N aqueous sodium thiosulfate and 35 mequiv of potassium acetate. A precipitate of $KClO_4$ appeared. The flasks were diluted to the mark and allowed to stand at 30° in a constant-temperature bath for 23 hr. They were then titrated with standard iodine solution (0.05 N) to the iodine or starch end point. The procedure was shown to give an accurate assay for aziridine content for each of the compounds studied by application to solutions of concentration known by previous standardization against standard hydrochloric acid solution. Clean pseudo-first-order kinetics were observed throughout. Rate constants from rate determinations on 1a in aqueous $HClO_4$ are presented in Table I, and on 1b in Table II.

Table I. Rates of Hydrolysis of Aziridine in Perchloric Acid Solutions

Temp, °C	$[HClO_4]$,[a] M	$k_\psi \times 10^7$, sec⁻¹ [b]
29.5	0.96	12.85
29.5	0.97	12.78
29.5	1.96	10.85
29.5	1.97	10.85
29.5	2.97	8.87, 8.96, 9.07[c]
29.5	3.00	8.56
29.5	3.97	6.69, 6.90
29.5	4.02	6.34
29.5	4.98	4.82, 5.04
29.5	5.04	4.60
29.5	5.50	3.73, 4.34
29.5	5.98	3.36, 4.26
29.5	6.05	2.76
49.4	0.96	162.2
49.4	3.97	90.1
49.4	5.98	44.6
67.8	0.96	1311
67.8	3.97	709
67.8	5.98	365

[a] $HClO_4$ concentrations are corrected for the amount used in protonation of aziridine. [b] Duplicate entries represent duplicate runs. [c] Run by periodate titration method.

The periodate titration method of Buist and Lucas[8] was used to follow one 1a hydrolysis run; the rate constant obtained did not differ significantly from two others under the same conditions by the thiosulfate titration method. It is noteworthy that the one

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(15) J. Attenburrow, J. Elks, B. A. Hems, and K. N. Speyer, *J. Chem. Soc.*, 510 (1949).
(16) Analysis by Micro-Tech Laboratories, Skokie, Ill.
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Table II. Rates and Products of Hydrolysis of 2-Methylaziridine in Perchloric Acid Solutions at 29.5°

[HClO₄],[a] M	$k_\psi \times 10^7$, sec⁻¹	Products, %[b] 2b	3b
0.70	13.2	62	38
0.98	12.4	66	34
1.46	11.8		
1.56		66	34
2.01	10.1	58	42
3.04	7.98	57	43
4.07	6.07	47	53
5.08		43	57
5.10	4.28		
5.57	3.54	49	51
6.12	3.09	48	52

[a] HClO₄ concentrations are corrected for the amount used in protonation of 2-methylaziridine. [b] Percentages of total amino alcohols formed are listed.

Table III. Rates and Products of Hydrolysis of 2,2-Dimethylaziridine in Perchloric and Sulfuric Acid Solutions at 29.5°

Acid (HX)	[HX],[a] M	Method[b]	$k_\psi \times 10^7$, sec⁻¹	Products, % 2d	3d
HClO₄	0.52	Nmr	68.4	13.5	86.5
	0.96	Nmr	73.3	10.3	89.7
	0.96	Tit.	68.6		
	1.53	Nmr	63.9	9.9	90.1
	1.96	Tit.	67.3		
	2.05	Nmr	69.6	7.3	92.7
	2.49	Nmr	63.5	6.5	93.5
	2.87	Nmr	66.0	5.4	94.6
	2.97	Tit.	65.9		
	3.97	Tit.	69.1		
	3.98	Nmr	74.8	<4	>96
	4.98	Tit.	82.8		
	5.05	Nmr	90.3	c	d
	5.98	Tit.	127.5		
	6.04	Nmr	151	c	d
	6.54[e]	Nmr	162	c	d
H₂SO₄	1.05	Nmr	75.1	11.4	88.6
	1.48	Nmr	76.0	8.4	91.6
	1.78	Nmr	77.2	8.9	91.1
	2.50	Nmr	74.4	7.5	92.5
	2.98	Nmr	77.7	5.1	94.9
	3.96	Nmr	71.9	5.4	94.6
	5.02	Nmr	76.8	c	d
	6.96[e]	Nmr	88.5	c	d

[a] HClO₄ and H₂SO₄ concentrations corrected for the amount used in protonation of 2,2-dimethylaziridine. [b] Thiosulfate titration or nmr; see Experimental Section. [c] Too little to determine. [d] Nearly 100%. [e] On assumption of no volume change on mixing of 6.90 M HClO₄ or 7.38 M H₂SO₄ with 2,2-dimethylaziridine.

Table IV. Rates of Hydrolysis of Aziridine and 2,2-Dimethylaziridine in H₂SO₄ and D₂SO₄ at 29.5°

Solvent[a]	$k_\psi \times 10^7$, sec⁻¹
Aziridine	
0.95 M D₂SO₄ in D₂O	10.90
0.95 M H₂SO₄ in H₂O	14.97
2,2-Dimethylaziridine	
0.95 M D₂SO₄ in D₂O	63.0
0.95 M H₂SO₄ in H₂O	77.7

[a] Acid concentrations corrected for the amounts used in protonation of aziridine or 2,2-dimethylaziridine.

method determines unreacted aziridine, the other amino alcohol product.

Most of the rate determinations on **1d** hydrolysis were performed with analysis by proton magnetic resonance, using a 60 MHz Jeolco Minimar spectrometer. Reaction solutions were prepared by placing in a volumetric flask (10 or 25 ml) measured volumes of 6.90 M HClO₄ or 7.38 M H₂SO₄ (standardized by titration), adding distilled water to fill the flasks about ⅔ full, weighing, cooling with ice, adding 2,2-dimethylaziridine rapidly with shaking, reweighing to determine the amount of the aziridine added, adding distilled water to the mark, and shaking thoroughly. Small samples (ca. 1 ml) were withdrawn at measured times and examined in the nmr spectrometer. When partial hydrolysis had occurred, the nmr spectra of the reaction solutions showed two methyl resonances: a singlet for unreacted **1d**, and another singlet ca. 12 Hz upfield due to the conjugate acids of **2d** and **3d**. The latter were not resolved in these strongly acidic solutions. Photocopies of the nmr spectra were made on uniform paper and the relative areas of the two methyl peaks were determined by the cut-and-weigh technique. Plots of ln [(wt of **1d** peak plus wt of products peak)/(wt of **1d** peak)] vs. time were linear, and their slopes were taken as k_ψ.

Rate constants for **1d** hydrolysis, by both the nmr and thiosulfate titration techniques, are listed in Table III.

Solvent Isotope Effect. Deuteriosulfuric acid, 2 M, was prepared by distilling sulfur trioxide (Baker and Adamson Sulfan B) into >99.7% deuterium oxide. This acid was standardized and an amount was added to a 10-ml volumetric flask such that, after dilution to the mark, [D₂SO₄] would be 1 M. Aziridine or 2,2-dimethyl-aziridine (0.2 ml) was added, and the flask was diluted to the mark with D₂O and it was placed in the thermostat; the thiosulfate titration technique was used as described above, except that 1-ml aliquots were taken and the potassium acetate, Na₂S₂O₃, and I₂ were all diluted fivefold. A similar reaction solution in ordinary H₂SO₄ was treated in an identical manner. Data are presented in Table IV.

Analysis of Products from 2-Methylaziridine. Preliminary investigations showed the following. 1-Amino-2-propanol (**3b**) reacted nearly quantitatively with 2,4-dinitrofluorobenzene in aqueous methanol while 2-amino-1-propanol (**2b**) with the same reagent gave lower and variable yields. The N-dinitrophenyl derivatives of these amino alcohols could be separated well from impurities by chromatography on alumina but could not be well separated from one another. Once pure, each compound could be recovered quantitatively from alumina. The dinitrophenyl derivative of 2-amino-1-propanol had a modest band in the infrared at 11.55 μ which was absent in the derivative of 1-amino-2-propanol. (A methylene chloride solution containing about 3% of the compound was examined in 1-mm matched cells) Less definite differences also appeared at 9.98 and 10.45 μ. Both amino alcohols could be accurately determined by the periodate titration of Buist and Lucas.[8] The rates of reaction of the two with periodate were about the same.

With attention to the above findings, an analytical scheme was devised and used to establish product ratios at various HClO₄ concentrations. The total amino alcohol concentration for each sample (2-methylaziridine in perchloric acid after 8 months at reaction temperature) was determined by titrating an aliquot with sodium periodate as described by Buist and Lucas, the periodate solution having been standardized against a 1:1 mixture of **2b** and **3b**. The

concentration of **3b** was determined for each sample by isolation and infrared analysis of the products of reaction of an aliquot with dinitrofluorobenzene, as follows. A 10-ml aliquot was discharged into a separatory funnel and titrated with 50% aqueous sodium hydroxide to the pink phenolphthalein end point. The color was discharged by addition of 0.5 g of NaHCO₃ and 10 ml of methanol containing 500 mg of 2,4-dinitrofluorobenzene was added. After 2 days at room temperature, 20 ml of water was added and the solutions were extracted five times with 5-ml portions of chloroform. The combined extracts were placed on 20 ml of alumina and eluted with 85 ml of chloroform to remove contaminants. The mixed N-dinitrophenyl derivatives were then obtained free of other materials by eluting with 35 ml of a 3:1 chloroform-methanol solution. The solvent was removed under vacuum, the residue was weighed, and sufficient methylene chloride was added to give a 3% solution. The amount of N-(2,4-dinitrophenyl)-1-amino-2-propanol isolated was determined by infrared analysis at 11.55 μ. The amount of **3b** in the original solution was calculated assuming 90% isolation and detection, since pure samples behaved thus. The amount of **2b** was calculated as the difference between the total amino alcohol and the **3b** contents. Application of the technique to mixtures of known composition under similar conditions gave results accurate to about ±5%.

The percentages of **2b** and **3b** formed at several HClO₄ concentrations are given in Table II.

Analysis of Products from 2,2-Dimethylaziridine. After reactions had reached at least 90% completion, aliquots were removed,

chilled with ice, and basified by addition of concentrated aqueous NaOH until the pH exceeded 14. Under these conditions, the methyl protons of **2d** absorb *ca.* 8 Hz upfield from those of **3d**. This was verified by addition of authentic **2d** to one sample. The relative amounts of **2d** and **3d** were determined from the areas under these two nmr peaks by the cut-and-weigh technique described above.

For runs at the lowest and highest concentrations of both $HClO_4$ and H_2SO_4 investigated, material balance was verified by use of an integration standard. For 0.52 M $HClO_4$, the standard was aniline present in the reaction mixture from the start of the reaction. For the others, it was an external standard, a capillary tube containing methanol, water, and a few drops of H_2SO_4. The capillary tube was inserted into the nmr tube containing the reaction mixture, and the spectra of both solutions were obtained together in a single scan. The peak area ratios, (imine + products)/standard, were independent of time in all cases.

The percentages of **2d** and **3d** formed at several concentrations of $HClO_4$ and H_2SO_4 are given in Table III.

Temperatures. Thermostat temperatures were verified with reference to thermometers calibrated by the National Bureau of Standards.

Data Correlations. For plots of log k_ψ *vs.* $(H_0 + \log [H^+])$, H_0 values of Yates and Wai[18] were used for $HClO_4$ and of Johnson, Katritzky, and Shapiro[19] at 25° for H_2SO_4, and [H+] was taken to equal the molar concentration of mineral acid.[20] For plots of log k_ψ *vs.* log a_w, values of log a_w interpolated from those listed by Bunnett[21] were employed.

Results

The kinetic data in Table I show that the rate of hydrolysis of the aziridinium ion (**1a**) diminishes steadily as the $HClO_4$ concentration increases from 1 to 6 M. The isotope effect data in Table IV demonstrate that hydrolysis is somewhat slower in deuterated aqueous acids than in systems of normal isotopic composition.

At three acid concentrations, the hydrolysis rate was determined at three temperatures, as reported in Table I. Activation parameters, reckoned from the measured k_ψ values,[22] are presented in Table V. They show very

Table V. Activation Parameters for **1a** Hydrolysis

[HClO4], M	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
1.0	24.1	−5.8
4.0	24.2	−6.9
6.0	24.4	−7.5

little change of either $\Delta H^{\pm}$ or $\Delta S^{\pm}$ with $HClO_4$ concentration.

The overall rate of hydrolysis of the 2-methylaziridinium ion (**1b**) closely resembles that of **1a**. Data in Tables I and II show that both the absolute rate constants and the pattern of variation with $HClO_4$ concentration are nearly the same for the two substrates. There is some change in the relative amounts of **2b** and **3b** produced, in the sense that the fraction of **3b** increases with acid concentration, but the change is modest.

In $HClO_4$ solutions, the overall rate of hydrolysis of the 2,2-dimethylaziridinium ion (**1d**) is considerably greater than of **1a** or **1b**; see Table III. It remains

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nearly constant between 0.5 and 4 M $HClO_4$, but then rises rather sharply with further increase in acid concentration. The pattern in H_2SO_4 is similar, except that the initial plateau extends to 5 M H_2SO_4 and the final rise is less steep. In both systems, the hydrolysis product is about 12% **2d** in rather dilute acid, and the fraction of this product diminishes steadily so that it can scarcely be detected at acid concentrations above 4 M.

Comparison with Other Measurements. From the data of Earley, *et al.*,[9] for aziridine hydrolysis in *ca.* 0.7 M $HClO_4$, we interpolate 11.8 × 10^{-7} sec^{-1} as the rate constant at 29.5°. Extrapolation of our data at 29.5° to 0.7 M gives 13.0 × 10^{-7} sec^{-1}. For hydrolysis of 2,2-dimethylaziridine in 0.7 M $HClO_4$ at 29.5°, 7.3 × 10^{-6} sec^{-1} is interpolated from their data and 7.0 × 10^{-6} sec^{-1} from ours. In both cases the agreement is fairly good.

Buist and Lucas[8] reported hydrolysis of **1b** in 0.04 M $HClO_4$ at 65° to be *ca.* 10% faster than of **1a**. We find **1a** to hydrolyze about 3% faster than **1b** in 1.0 M $HClO_4$ at 29.5°. The slight disagreement is no cause for concern.

The products of **1c** hydrolysis in dilute $HClO_4$ were estimated[9] to be about 75% 2-amino-1-butanol (**2c**) and 25% 1-amino-2-butanol (**3c**). Our finding that **1b** affords, in 0.7 M $HClO_4$, 62% of **2b** and 38% of **3b** is in reasonable agreement with that estimate; the structural relationship of **1b** to **1c** is obviously close.

Earley, *et al.*,[9] used two methods to estimate the percentages of **2d** and **3d** formed on hydrolysis of **1d** in dilute $HClO_4$ solutions. By fractional distillation and refractive index measurement, they estimated the product mixture to comprise 15% of **2d** and 85% of **3d**. From potentiometric titration, they estimated 23% of **2d** and 77% of **3d**. Our determination by nmr that 13.5% of **2d** and 86.5% of **3d** are formed in 0.52 M $HClO_4$ is quite close to theirs by the fractional distillation method of analysis.

Discussion

Methods for Correlation of Data. It would be unrewarding to plot log k_ψ for a strongly basic substrate against H_0 or other acidity function, as is sometimes done for reactions of weakly basic substrates. The rationale for such plots is that the extent of protonation of a weakly basic substrate is in some fashion related to H_0, but **1a**, **1b**, and **1d** are already fully protonated in 0.5 M mineral acid.

For many reactions of strongly basic substrates, plots of log k_ψ against $(H_0 + \log [H^+])$, where H_0 is the Hammett acidity function,[4b,18,19] are linear.[23] Equation 9 is obeyed. The slope constitutes a parameter, ϕ,

$$\log k_\psi = \phi(H_0 + \log [H^+]) + \text{constant} \qquad (9)$$

which characterizes the kinetic response of the reaction to changing acid concentration.

It follows from the definition of the Hammett acidity function,[4b] $H_0 \equiv -\log (a_{H^+}\gamma_B/\gamma_{BH^+})$, that $(H_0 + \log [H^+])$ equals log $(\gamma_{BH^+}/\gamma_B\gamma_{H^+})$. Comparison with the logarithmic form of eq 7 shows that ϕ, the proportionality constant in eq 9, is therefore also a proportionality constant between the logarithms of activity coefficient ratios as they vary with mineral acid concentration.[23]

(23) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1917 (1966).

Table VI. Rate Correlations

Reaction	Acid	Temp, °C	Horizontal coordinate	Slope[a] (ϕ or w)	Intercept	Statistical parameters[b]		
						σ_y	σ_{sl}	r
1a → 2a	HClO₄	29.5	(H_0 + log [H⁺])	0.33	−5.78	0.035	0.014	0.986
			Log a_w	1.81		0.044	0.09	0.978
		49.4	(H_0 + log [H⁺])	0.31	−4.69	0.007	0.005	0.9998
			Log a_w	1.76		0.041	0.18	0.995
		67.8	(H_0 + log [H⁺])	0.31	−3.78	0.001	0.001	0.9999
			Log a_w	1.76		0.049	0.22	0.992
1b → 2b	HClO₄	29.5	(H_0 + log [H⁺])	0.42	−5.98	0.048	0.024	0.989
			Log a_w	2.39		0.078	0.22	0.971
1b → 3b	HClO₄	29.5	(H_0 + log [H⁺])	0.23	−6.27	0.039	0.019	0.977
			Log a_w	1.35		0.033	0.09	0.983
1d → 2d	HClO₄	29.5	(H_0 + log [H⁺])	0.69	−5.90	0.024	0.045	0.987
			Log a_w	5.92		0.022	0.35	0.990
1d → 3d	HClO₄	29.5	(H_0 + log [H⁺])	−0.20	−5.21[c]	0.057	0.021	0.930
			Log a_w	−1.11		0.041	0.08	0.964
1d → 2d	H₂SO₄	29.5	(H_0 + log [H⁺])	0.38	−5.99	0.051	0.067	0.942
			Log a_w	2.75		0.063	0.63	0.909
1d → 3d	H₂SO₄	29.5	(H_0 + log [H⁺])	−0.05	−5.17[d]	0.023	0.012	0.860
			Log a_w	−0.26		0.019	0.05	0.900

[a] Slope is ϕ vs. (H_0 + log [H⁺]), or w vs. log a_w. [b] σ_y is standard deviation of points, in the y direction, from the least-squares line; σ_{sl} is standard deviation of the slope; r is correlation coefficient. [c] From points through 2.97 M HClO₄ only. [d] From points through 5.02 M H₂SO₄ only.
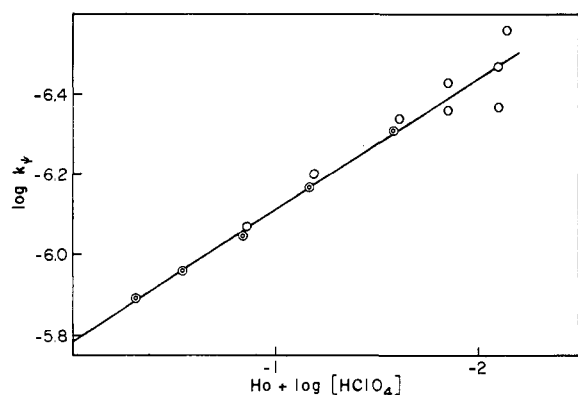

Figure 1. Plot of log k_ψ for **1a** hydrolysis in HClO₄ against (H_0 + log [H⁺]). Bulls eyes represent duplicate determinations. The linear regression line is drawn.

The medium dependence of reaction rates can alternatively be expressed by the w parameter, which for strongly basic substrates is the slope of the linear or approximately linear plot of log k_ψ vs. log a_w, where a_w is the activity of water.[21] If appropriate assumptions are made about the medium dependence of the activity coefficients for *hydrated* SH⁺ and transition state,[24] the w value may be taken as an indication of the average number of water molecules difference of hydration between the two states.[25]

Rate Correlations. For all the sets of data in Tables I–III, we have correlated log k_ψ both with (H_0 + log [H⁺]) and with log a_w. The results of linear regression analysis are summarized in Table VI. Three selected correlations are also plotted, in Figures 1–3.

The overall k_ψ values for **1b** and **1d** hydrolysis were dissected into components representing formation of each of the isomeric amino alcohol products, in proportion to the yields of those products. The dissected rather than the overall rate constants are correlated in those cases.

Most of the correlations are good rather than superb,

(24) The activity coefficients for hydrated species are different from those for formal species, which are the type usually employed.[25]

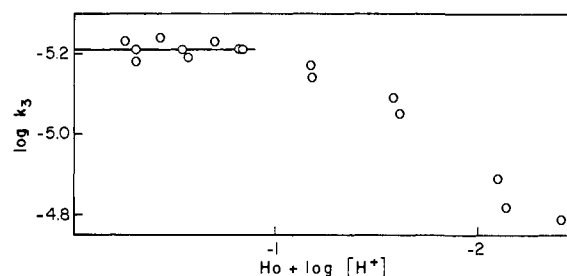(25) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4973 (1961).

Figure 2. Plot of log k_ψ for the **1d** → **3d** reaction in HClO₄ vs. (H_0 + log [H⁺]). The linear regression line through the left nine points is drawn.
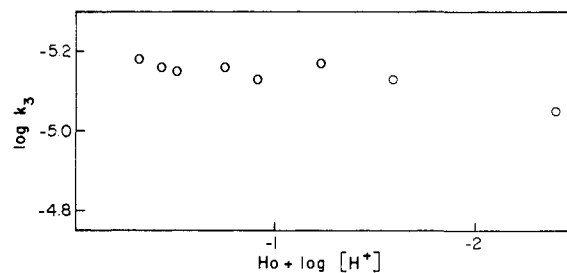

Figure 3. Plot of log k_ψ for the **1d** → **3d** reaction in H₂SO₄ vs. (H_0 + log [H⁺]).

because of scatter of experimental points. Scatter is evident in Figure 1, in which log k_ψ for hydrolysis of **1a** in HClO₄ solutions at 29.5° is plotted against (H_0 + log [H⁺]). The rate constants for formation of **2b** and **3b** from **1b**, and of **2d** and **3d** from **1d**, depend not only on overall k_ψ values but also on the product analysis at each acid concentration, which is a further source of experimental variability. However, the only plot against (H_0 + log [H⁺]) which shows any regular curvature is that for hydrolysis of **1d** to **3d** in HClO₄ solutions (Figure 2).

Inasmuch as the vertical coordinate is the same in plots against (H_0 + log [H⁺]) as against log a_w, the comparative quality of fit by the two methods of correlation is best judged by comparison of σ_y parameters,

which are tabulated in Table VI. These show that for most reactions, a better correlation is obtained with (H_0 + log [H$^+$]) than with log a_w, in agreement with earlier observations. Some of the plots against log a_w show obvious curvature whereas their counterparts against (H_0 + log [H$^+$]) are straight.

Let us now consider the constant in eq 9. As the acid becomes more and more dilute, H_0 approaches −log [H$^+$] and at infinite dilution they are equal.[4b] Therefore the constant is log k_r^0; see eq 7. Substituting into eq 9

$$\log k_\psi = \phi(H_0 + \log [\text{H}^+]) + \log k_r^0 \qquad (10)$$

The intercepts in such plots, which are listed in Table VI, are therefore log k_r^0, the rate constants for hydrolysis of the relevant *aziridinium ions* at infinite dilution in water. Because plots against log a_w are less straight, they are less satisfactory for extrapolation to infinite dilution and the intercepts therefore are not listed.

For the two plots in Figures 2 and 3, intercepts were reckoned by linear regression analysis applied only to points in the initial flat portions of the plots. The statistical parameters for analysis of the short set of data for 0.52–2.97 M HClO$_4$ are instructive. The correlation coefficient (r) is 0.023, suggesting a horrible correlation, but the σ_y of 0.021 shows that the quality of fit to a straight line is much better than when linear regression analysis is applied to data covering the whole range of 0.52–6.54 M, for which σ_y is 0.057. However, r for the latter is 0.930, as listed in Table VI. The explanation lies in the fact that the slope (ϕ) for the short set is only 0.002. The correlation coefficient was developed by social scientists as an index of whether two variables are correlated, and the social scientist would conclude in the case of the short set that there is no correlation. The natural scientist, in contrast, sees it as a fair correlation with essentially zero slope. The natural scientist is thus better informed, in comparing two methods of correlation involving the same vertical coordinate, by σ_y than by r.

The intercepts in Table VI for the **1d** → **2d** reaction in HClO$_4$ and H$_2$SO$_4$ should be the same, namely, k_r^0 (see eq 10). Likewise, the intercepts for the **1d** → **3d** reaction should be identical. Statistical analysis reveals, for each comparison, that the actual discrepancy only slightly exceeds the sum of the standard deviations of the two intercepts. The discrepancies are thus within experimental error.

Interpretation of Correlations. Our interest is to assess the extent to which medium dependence of rate, that is, of the activity coefficient ratio in eq 7, is related to reaction mechanism and what part stems from other factors. For this purpose, we shall consider the experimentally determined medium dependence, as represented by the ϕ parameter, with respect to the prevailing reaction mechanism as indicated by independent criteria.

Following earlier workers,[8,9] as discussed above, we acknowledge hydrolytic cleavage of the C–N bond to occur by the SN2 mechanism at primary carbon (in **1a** and at the terminal carbon atoms of **1b** and **1d**) and by the SN1 mechanism at the tertiary carbon atom of **1d**. Though we do not wish to concern ourselves with the finer details of these mechanisms, we do note that once the bond in **1d** between nitrogen and tertiary carbon

has parted it is unlikely to re-form rapidly in comparison with events that consummate hydrolysis. Ring strain would cause the carbon and nitrogen atoms to spring apart once the bond had broken, and the nature of the medium is such as to ensure rapid protonation of the amino group of the resulting carbonium ion.

As for the mechanism of scission of the bond between nitrogen and secondary carbon in **1b**, we shall for the moment take no position. The mechanism of nucleophilic substitution at secondary aliphatic carbon is controversial.

If there were a simple, direct relationship of ϕ value to mechanism, the ϕ values for the SN2 processes (**1a** → **2a**, **1b** → **2b**, and **1d** → **2d**) would be equal, except as affected by experimental error. However, they are not equal; in HClO$_4$ at 29.5°, they are +0.33, +0.42, and +0.69, respectively. This is a wide spread. We must conclude either that the ϕ value has no close intrinsic relationship to reaction mechanism or that in the present case effects of other origin also substantially affect the activity coefficient ratio in eq 7.

It is noteworthy that the ϕ value for conversion of **1d** to **2d** in H$_2$SO$_4$ (+0.38) lies between those for the **1a** → **2a** and **1b** → **2b** reactions in HClO$_4$. These three ϕ values, for hydrolyses by the SN2 mechanism, fall within a relatively narrow spread of 0.09. Attention should therefore perhaps be focused on the difference in ϕ values for the **1d** → **2d** transformation between HClO$_4$ and H$_2$SO$_4$.

The plot of log k_ψ vs. (H_0 + log [H$^+$]) for hydrolytic scission of **1d** at tertiary carbon in HClO$_4$ (Figure 2) is markedly curved; the slope is zero at low acid concentrations and about −0.36 above 4 M HClO$_4$. Curvature in such plots can arise from a change in reaction mechanism,[6,23] but in the present case it is difficult to conceive of a further mechanism that could supersede SN1 at the higher HClO$_4$ concentrations. Also, if there were a change of mechanism, similar curvature should appear in the corresponding plot for H$_2$SO$_4$, but that plot (Figure 3) is almost straight. We seem forced to conclude that the curvature in Figure 2 stems from activity coefficient effects not related to reaction mechanism.

We may then inquire whether the exceptionally high ϕ value for the **1d** → **2d** conversion in HClO$_4$ solutions also represents an activity coefficient effect unrelated to mechanism.

Differences between HClO$_4$ and H$_2$SO$_4$, as they affect kinetic response to changing acid concentration, have been noted many times before. For some reactions, the kinetic response (as judged by the ϕ value or other appropriate parameter) is nearly the same in the two acids,[26] but in others it is remarkably different.[27] Moreover, although plots of log k_ψ + H_0 (for weakly basic substrates) or log k_ψ (for strongly basic substrates) vs. (H_0 + log [H$^+$]) are usually straight, instances of curvature for HClO$_4$ have been encoun-

(26) C. A. Bunton, S. J. Farber, A. J. G. Milbank, C. J. O'Connor, and T. A. Turney, *J. Chem. Soc., Perkin Trans. 2*, 1869 (1972); D. Landini, G. Modena, U. Quintily, and G. Scorrano, *J. Chem. Soc. B*, 2041 (1971); J. W. Barnett and C. J. O'Connor, *J. Chem. Soc., Perkin Trans. 2*, 220 (1973); C. J. Hyland and C. J. O'Connor, *ibid.*, 233 (1973).

(27) (a) C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 1258 (1968); (b) C. A. Bunton and E. Humeres, *J. Org. Chem.*, **34**, 572 (1969); (c) A. J. Kresge, S. G. Mylonakis, and L. E. Hakka, *J. Amer. Chem. Soc.*, **94**, 4197 (1972).

tered.[28,29] There are also some irregularities in LFER correlation of equilibrium protonation in $HClO_4$, in contrast to the prevailing regular behavior in H_2SO_4.[20]

Bunton, Crabtree, and Robinson[27a] pointed out that A-1 reactions tend to go faster in $HClO_4$ than in H_2SO_4 but that A-2 reactions tend to be faster in H_2SO_4. They attributed this behavior in part to a propensity of perchlorate ion, a large ion of low charge density, to associate preferentially with carbonium ions, actual or partially formed in a transition state. They also consider that transition states with little or no carbonium ion character but with good sites for (donor) hydrogen bonding with the medium will be favored in mineral acids having anions of higher charge density (e.g., HSO_4^- or Cl^-).

Kresge, et al.,[27c] on the other hand, think that hydrogen isotope exchange in 1,3-dimethoxybenzene is faster in H_2SO_4 than in $HClO_4$ because there is a component of general acid catalysis by bisulfate ion; perchlorate ion could not be a general acid. However, they did not extend their hypothesis to reactions of other classes of substrates.

Our data for 1d hydrolysis (Table III) indicate that formation of 2d is faster, at higher acid concentrations, in H_2SO_4 than in $HClO_4$, and that formation of 3d is faster in $HClO_4$. Qualitatively, these inequalities are in accord with the generalization of Bunton, Crabtree, and Robinson.[27a]

There is thus reason to suspect that the curvature in Figure 2 and the exceptionally high ϕ value for the 1d → 2d transformation in $HClO_4$ are the consequence of unusual activity coefficient effects. If for that reason the ϕ values for 1d hydrolysis in $HClO_4$ are disregarded, the remaining ϕ values in Table VI may be taken to indicate that in this system the SN1 mechanism is associated with a ϕ value of about -0.05 and the SN2 with a ϕ of about $+0.35$. There is also a suggestion that H_2SO_4 is a better medium than $HClO_4$ for study of acid concentration effects on rate, if they are to be taken as an indication of mechanism.

(28) C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, **30**, 1365 (1965).
(29) C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, **91**, 6072 (1969).

With these tentative conclusions in mind, let us now look at the 1b → 3b conversion. The ϕ value (in $HClO_4$) lies closer to that associated with the SN2 than with the SN1 mechanism. This suggests that the mechanism is basically SN2. If the C–O bond is less formed at the transition state than for reaction at primary carbon, less hydration of the attacking water molecule may be expected, and therefore a lower ϕ value.[25] There might also be some steric interference with solvation.

Temperature Effects. For hydrolysis of 1a, log k_ψ was correlated with $(H_0 + \log [H^+])$ or log a_w at 49.4 and at 67.8°, as well as at 29.5°; see Table VI. Data for the horizontal coordinates are all for ca. 25°. The correlations at the higher temperatures are somewhat better than at 29.5°, and the slope parameters are nearly the same.

As for the activation parameters (Table V), $\Delta H^\pm$ is nearly the same at 1, 4, and 6 M $HClO_4$. There is, however, a moderate trend in the apparent entropy of activation. We say "apparent" because the value of $\Delta S^\pm$ depends on the absolute magnitude of the rate constants from which it is calculated.[22] Inasmuch as water is a reactant in 1a hydrolysis and the activity of water decreases as the acid concentration increases, it would be better to calculate $\Delta S^\pm$ from corrected rate constants, k_ψ', where $k_\psi' = k_\psi/a_w^m$, m being the order of the reaction in water. However, because m is not known with certainty and may change with acid concentration, we do not list corrected $\Delta S^\pm$ values. Some trial computations indicate that the corrected $\Delta S^\pm$ values would show a lesser decrease with augmenting acid concentration, or even a modest increase.

At least part of the negative entropy of activation represents immobilization of water molecules bound into the transition state. The entropy of freezing of water is -5.26 gibbs/mol. Therefore, if the w value of ca. 1.8 for 1a hydrolysis (Table VI) is taken literally as the kinetic order in water, the contribution of water immobilization to entropy of activation may be estimated as $(1.8)(-5.26)$ or -9.5 gibbs/mol. This is somewhat more negative than the measured $\Delta S^\pm$ values.