Mechanism and Solvent Reorganization Accompanying Hydrolyses of Anchimerically Assisted Alkyl Halides in Water[1]

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Abstract: This paper deals with the problem of solvent reorganization, anchimeric assistance, and mechanism for hydrolysis of nine alkyl halides where the neighboring group is –OH, –OMe, or –SMe. By using the temperature coefficient of the enthalpy ($\Delta C_p{}^*$) as a gauge of relative solvent reorganization, we show that the transition state in the hydrolysis of those alkyl halides giving evidence of anchimeric assistance resembles that for an SN1 mechanism. This conclusion was supported in one case by ^{13}C labeling experiments in spite of product analysis seemingly favoring SN2 nucleophilic displacement by the solvent.

While a complete treatment of solvent effects associated with reactions in solution must await the development of a satisfactory theoretical treatment of liquids, this is no reason that all progress in this area must cease until such an ultimate theory exists. Linear free energy correlations are relatively insensitive to solvent effects, while as yet it has not proven practical to separate the contributions to ΔH^* and ΔS^* arising from solvent reorganization. For the particular case of solvolytic reactions occurring in structured solvents, a considerable body of data now exists supporting the conclusion that new and useful insights into the role of solvents in such reactions can be gained from examining the second derivative of the rate with respect to temperature[4,5] and pressure.[6] The interpretation of changes in these parameters is severely limited by a paucity of corresponding initial state data, but sufficient data are available such that useful broad conclusions can be drawn from the accumulating kinetic evidence.

In this paper we report a study of the temperature dependence of the rate of hydrolysis of a number of substituted alkyl halides in some of which anchimeric assistance had been established previously and for others, having the same substituent, where there is no evidence of such effects. We have established[4] that there is a systematic shift of about 20 cal deg^{-1} mol^{-1} to more negative values for the $\Delta C_p{}^*$ characterizing hydrolysis by an SN1 mechanism compared to the normal value for the SN2 hydrolysis. Since anchimeric assistance is sometimes regarded as an internal SN2 displacement, it was of interest to discover in which grouping the $\Delta C_p{}^*$'s of alkyl halides hydrolyzing with anchimeric assistance fall.

Results and Discussion

Rate data[7] for a series of alkyl halides over the conveniently accessible temperature range for hydrolysis in water were fitted by a LMS method to a three constant equation of the form

$$\log k = A/T + B \log T + C \qquad (1)$$

The values of the empirical constants corresponding to eq 1, together with the standard deviations of the derived constants, are given in Table I. From these, the rate corresponding to any intermediate temperature can be calculated to give values within the experimental error. In practice the calculations followed the methods outlined by Clarke and Glew,[8] adapted to the kinetic problem. The corresponding pseudothermodynamic activation parameters, calculated according to this method from the constants of eq 1,[9] together with corresponding errors, are given in Table II.

Relative rate data at 50° are presented in Table III for the substituted alkyl halides and their unsubstituted analogs. From these rate ratios it is apparent that oxygen substituents on β- and γ-carbon atoms retard the hydrolysis rate relative to the parent compound by a factor of 30 and 3, respectively. That the *trans*-2-bromocyclohexanol (**9**) does not hydrolyze faster than cyclohexyl bromide (**8**) is not surprising. The favored conformation for this species is probably the diequatorial one, whereas it is the diaxial conformer in which anchimeric assistance would occur. Thus, only the inductive effect of the hydroxyl group is important. This conclusion differs from that of Roberts[10] for the solvolysis of the corresponding tosylates in alcohol-water mixtures.

By placing methyl groups on the site of the β-hydroxyl function, anchimeric assistance is promoted as evidenced by the relative rate of 2 for 3-bromo-2-methyl-2-butanol (**11**) compared with isopropyl bromide (**10**).[11] These effects are consistent with the general relation between structure and anchimeric assistance summarized by Winstein and Grunwald.[12] Those compounds possess-

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[2] NRC Postdoctorate Fellow, 1960–1961.

[3] NRC Postdoctorate Fellow, 1966–1968.

[4] R. E. Robertson, *Progr. Phys. Org. Chem.*, 4, 213 (1967).

[5] G. Kohnstam, *Advan. Phys. Org. Chem.*, **5**, 121 (1967).

[6] J. B. Hyne, "Hydrogen-Bonded Solvent Systems," Taylor and Francis Ltd., London, 1968, pp 99–113.

[7] The individual rate constants for hydrolysis in H_2O have been deposited with the Depository of Unpublished Data, National Science Library, National Research Council of Canada, Ottawa, Ontario, Canada, from which photocopies are available upon request.

[8] E. C. W. Clarke and D. N. Glew, *Trans. Faraday Soc.*, **62**, 539 (1966).

[9] $A = -\Delta H_0{}^*/2.303R$, $B = \Delta C_p{}^*/R + 1$, $C = (\Delta S_0{}^* - \Delta C_p{}^*)/2.303R + \log (k/h)$, $\Delta H_T{}^* = \Delta H_\circ{}^* + T\Delta C_p{}^*$, $\Delta S_T{}^* = \Delta S_\circ{}^* + 2.303 \cdot \Delta C_p{}^* \log T$.

[10] D. R. Roberts, *J. Org. Chem.*, **33**, 118 (1968).

[11] If the inductive retarding effect of the OH group is taken into account, the anchimeric acceleration represents a rate enhancement by a factor of 60.

[12] S. Winstein and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 828 (1948).

Table I. Empirical Constants for Eq 1

Compound	$-A$	$-B$	C	$n_{T_2}^{T_1}$[a]	Std dev[b]
2-Bromoethanol	8408.376	17.5428	63.5393	41_{75}^{120}	0.001
2-Chloroethyl methyl sulfide	8916.278	34.6356	113.6598	40_{1}^{19}	0.0009
n-Propyl bromide	8175.930	20.5020	71.6000	40_{70}^{100}	0.003
3-Bromo-1-propanol	8795.810	22.4242	77.7825	43_{65}^{105}	0.001
4-Chloro-1-butanol	7961.362	19.6863	69.5862	42_{50}^{85}	0.001
4-Bromobutyl methyl ether	8195.091	22.2782	77.9086	26_{35}^{60}	0.001
Cyclohexyl bromide	9755.835	28.9229	98.6951	43_{27}^{70}	0.001
trans-2-Bromocyclohexanol	9062.693	20.6080	74.2253	65_{60}^{100}	0.003
3-Bromo-2-methyl-2-butanol	10906.106	37.5280	124.2650	51_{41}^{85}	0.004

[a] n is the number of rate constants used in the calculations, and T_1 and T_2 are the limits of the temperature range used. [b] Std dev is the standard deviation between the calculated and observed log k's.

Table II. Derived Activation Parameters for Hydrolysis in Water[a]

Compound	No.	T, °C	ΔH^*, cal/mol	ΔS^*, eu	ΔC_p^*, cal deg^{-1} mol^{-1}	$k \times 10^5$ sec^{-1} (50°)
		A				
Ethyl bromide[b]	**1**	90	22,390	−11.7	−49	1.09
			60	0.2	4	
2-Bromoethanol	**2**	90	25,090	−10.53	−37	0.0315
			10	0.04	2	
2-Chloroethyl methyl sulfide	**3**	25	19,680	−1.4	−71	14,170.0
			50	0.2	3	
		B				
n-Propyl bromide	**4**	90	21,830	−14.3	−50	0.711
			70	0.2	10	
3-Bromo-1-propanol	**5**	90	23,330	−12.25	−47	0.196
			30	0.07	3	
4-Chloro-1-butanol	**6**	90	21,490	−12.2	−41[c]	3.32
			80	0.2	3	
		60	22,720	−8.70	−41	
			30	0.09	3	
4-Bromobutyl methyl ether	**7**	60	22,080	−5.68	−46	44.1
			20	0.08	2	
		C				
Cyclohexyl bromide	**8**	75	23,920	−3.1	−60	8.44
			50	0.1	2	
trans-2-Bromocyclohexanol	**9**	75	26,500	−1.9	−42	0.293
			30	0.1	5	
Isopropyl bromide[b]	**10**	75	22,870	−5.8	−59	11.0
			50	0.2	2	
3-Bromo-2-methyl-2-butanol	**11**	75	23,240	−3.3	−77	22.0
			80	0.2	5	
		60	24,385	0.09	−77	
			27	0.08	5	
		D				
t-Butyl chloride[d]	**12**	25	22,550	10.1	−83	53,700.0
			70	0.2	5	
2-Chloro-2-methylpropyl methyl ether[d]	**13**	25	25,420	8.38	−62	263.0
			10	0.04	2	

[a] The second line in each entry indicates the corresponding error calculated from a reduction of the data by the method of Clarke and Glew.[8] This error will have a minimal value at the center of the experimental range (note, for example, 4-chloro-1-butanol, above). The temperatures were selected as a compromise to enable a comparison between like compounds rather than selecting a common temperature or the temperature of the best fit. [b] R. L. Heppolette and R. E. Robertson, *Can. J. Chem.*, **44**, 677 (1966). [c] An incorrect value of −23 cal deg^{-1} mol^{-1} was published earlier from preliminary data.[4] Kohnstam quotes this erroneous value.[5] [d] Reference 16.

ing oxygenated functions in the δ position experience a considerable rate enhancement compared with the unsubstituted analog, which is recognized as nucleophilic displacement by the neighboring group.[12,13]

In contrast to the oxygen compounds, the β-sulfur substituent of **3** enhances the hydrolytic rate by a very large factor (10^5). This has been attributed to formation of an intermediate cyclic sulfonium ion.[14] The greater efficiency of the β-sulfur atom over the β-oxygen atom as an intramolecular catalyst is probably a result of the unbonded sulfur electrons being in 3p orbitals rather than in 2p orbitals. This should tend to make them more polarizable and therefore more readily available to the reaction site. Molecular model studies also suggest that interatomic distances are more favorable for reaction in the case of the sulfur analog.

(13) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 103–156.

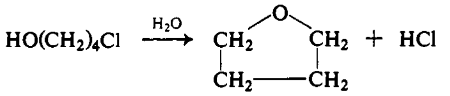
(14) P. D. Bartlett and C. G. Swain, *J. Am. Chem. Soc.*, **71**, 1406 (1949).

Table III. Relative Rates for Hydrolysis at 50° in H_2O

Compound	No.	Relative rate Obsd	Relative rate Corr[a]
Ethyl bromide	**1**	1.00	1.00
2-Bromoethanol	**2**	0.0289	0.0289
2-Chloroethyl methyl sulfide	**3**	13,000.0	191,000.0
n-Propyl bromide	**4**	1.00	1.00
3-Bromo-1-propanol	**5**	0.276	0.276
4-Chloro-1-butanol	**6**	4.67	68.5
4-Bromobutyl methyl ether	**7**	61.9	61.9
Cyclohexyl bromide	**8**	1.00	1.00
trans-2-Bromocyclohexanol	**9**	0.0347	0.0347
Isopropyl bromide	**10**	1.30	1.30
3-Bromo-2-methyl-2-butanol	**11**	2.61	2.61
t-Butyl chloride	**12**	1.00	
2-Chloro-2-methylpropyl methyl ether	**13**	0.00490	

[a] The primary chlorides were corrected to bromides by multiplying the observed relative rate by $k_{MeBr}/k_{MeCl} = 14.7$ at 50°.[4]

The general idea that anchimeric assistance is accompanied by the formation of an ionic intermediate of some degree of stability seems well accepted,[12,14] but a study of the products resulting from hydrolysis of **3**, **6**, and **7** leaves the existence of such intermediates open to question.



6 (2)

$$CH_3O(CH_2)_4Br \longrightarrow CH_3O(CH_2)_4OH + HBr \quad (3)$$

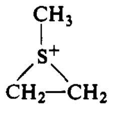
7 **15**

$$CH_3S(CH_2)_2Cl \longrightarrow CH_3S(CH_2)_2OH + HCl \quad (4)$$

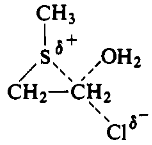
3 **14**

Thus product analyses proved surprising in that only one product was formed in each of the three cases studied to the virtual exclusion of the other expected product(s).[15]

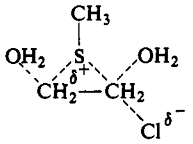
The fact that **3** gives rise to only 2-hydroxyethylmethyl sulfide (**14**) is not conclusive evidence for the existence of the cyclic sulfonium ion intermediate **16A**. On the contrary, involvement of the sulfonium ion would be expected to give rise to methanol and ethylene sulfide in addition to the observed product. However, the strain inherent in the three-membered ring might make ring opening the favored route for hydrolysis. Alternately, it could be argued that were such ring strain significant the cyclic structure would not form in the first place. In support of the nonexistence of such an intermediate, it is known that the rates of sulfonium ion hydrolyses are very slow in water[16-18] compared with the hydrolysis rate of **3**. Therefore it may be concluded that there is no compelling evidence to warrant the assumption of the sulfonium ion, **16A**, as an intermediate in this reaction. The increase in hydrolysis rate, and the product analysis, can be readily explained by invoking a transition state of either type **16B** or **16C**.



16A

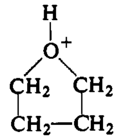


16B



16C

Tetrahydrofuran (THF) was the sole product formed in the hydrolysis of **6** and is the product to be expected when the anchimeric assistance of the hydroxyl group proceeds to complete oxygen–methylene bond formation. The absence of a *primary* deuterium isotope effect when the reaction is conducted in D_2O ($k_{D_2O}/k_{H_2O} = 0.848$ at 50°, see also ref 19a and b) indicates that the O—H bond is not undergoing rupture during the activation process. It is therefore improbable that the intermediate **17** has formed at the transition state.[20]



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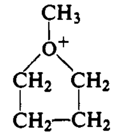
For a like reason methanol and THF are not formed in the hydrolysis of **7** as would be expected if **18** were an intermediate. It is therefore doubtful that this ion plays a role in this particular hydrolysis. Further evidence that



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(15) These results are from studies of homogeneous mixtures—less than 0.02 *M* in the alkyl halide. Studies in heterogeneous mixtures showed that tetrahydrofuran and methanol were products from 4-bromobutyl methyl ether and that 2-chloroethylmethyl sulfide gave only a sulfonium ion $(-(CH_3)S^+CH_2CH_2-)_x$ with the average value of *x* about 3.5.

(16) K. T. Leffek, R. E. Robertson, and S. E. Sugamori, *J. Am. Chem. Soc.*, **87**, 2097 (1965).

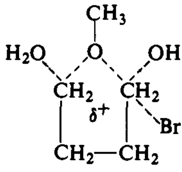
(17) A. L. Jacobson and J. B. Hyne, *ibid.*, **82**, 2418 (1960).

(18) J. B. Hyne, *Can. J. Chem.*, **39**, 1207 (1961).

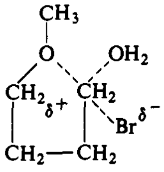
(19) (a) P. M. Laughton and R. E. Robertson, *ibid.*, **39**, 2155 (1961); (b) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Am. Chem. Soc.*, **87**, 1553 (1965).

(20) V. J. Shiner and C. A. Bunton, *ibid.*, **83**, 3207 (1961).

such an ionic intermediate is unnecessary is found in the fact that methyl–oxygen cleavage is important in the solvolyses of *o*-methoxyneophyl, 3-*o*-anisyl-1-propyl, and 3-*o*-anisyl-3-methyl-1-butyl *p*-toluenesulfonates[21] where five- and six-membered cyclic ethers are formed. Thus, if **18** were involved in the hydrolysis of **7**, the five-membered cyclic ether, THF, should be formed. However, the product analysis does not indicate whether a symmetrical transition state, such as **19**, or an unsymmetrical one, such as **20**, is favored.



19



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In order to determine whether the methoxyl group of **7** undergoes migration during hydrolysis, 4-bromobutyl-4-^{13}C methyl ether (**7**-^{13}C) was hydrolyzed and the isolated product analyzed by mass spectroscopy. The ion of greatest abundance obtained from **7** had an *m/e* of 45, while *m/e* 58 was the second most abundant; **7**-^{13}C, containing 53.3% ^{13}C in the 4 position, also showed these two peaks with no significant increase in the amount of either *m/e* 46 or *m/e* 59. Thus, these ions must be $CH_3OCH_2^+$ and $CH_3OCH{=}CH_2^+$, respectively, from the ethereal end of the molecule. Furthermore, scrambling of the ^{13}C in the product does not occur in the mass spectrometer since the synthesized labeled alcohol, 4-hydroxybutyl-4-^{13}C methyl ether (**14**-^{13}C), did not show intense peaks at *m/e* 46 and 59.

The alcohol isolated from the hydrolysis of the labeled bromide, **7**-^{13}C, gave relative abundances of I_{45}/I_{46} = 2.75, 2.77 and I_{58}/I_{59} = 2.34, 2.35. In order to calculate the fraction of rearrangement which occurred during hydrolysis, eq 5 was used where X_M and X_{M+1} are

$$\frac{I_M}{I_{M+1}} = \frac{X_M(1 - N_{M+1}) + X_{M+1}(1 - N_{M+2})(1 - r)}{X_{M+1}r(1 - N_{M+2}) + X_M N_{M+1} + X_{M+1}N_{M+2}(1 - r)} \quad (5)$$

the mole fractions of unlabeled and labeled alcohol, respectively, N_{M+1} and N_{M+2} are corrections for the natural abundance of ^{13}C in the unlabeled and labeled species, respectively, and *r* is the fraction of rearrangement occurring during the hydrolysis. The terms in the numerator represent the contributions from the ions obtained from the unlabeled alcohol and the labeled alcohol which has not rearranged, respectively. Those terms in the denominator represent the contributions from the ion obtained from the rearranged, labeled alcohol, the natural abundance contribution from the unlabeled alcohol, and the natural abundance contribution from the labeled but unrearranged alcohol, respectively. The minor contributions due to the natural abundance of ^{2}H and ^{17}O were not considered specifically in developing this equation, but the manner in which it was employed did account for this factor. Any isotope effect on ionization in the mass spectrometer was also neglected. Assuming[22] that $X_M + X_{M+1} = 1$ and that $N_{M+2} = N_{M+1}$, eq 5 gives rise, on rearranging, to eq 6.

$$r = \frac{1 - N_{M+1}\left(1 + \frac{I_M}{I_{M+1}}\right)}{X_{M+1}\left[1 - N_{M+1} + \frac{I_M}{I_{M+1}}(1 - 2N_{M+1})\right]} \quad (6)$$

In order to eliminate any error due to ions having *m/e* 45, 46, 58, or 59 other than the ions of interest, N_{M+1} was taken to be I_{M+1}/I_M as observed for the unlabeled alcohol. These figures were I_{46}/I_{45} = 0.02508 and I_{59}/I_{58} = 0.05336. The former is very near the ^{13}C natural abundance for a two-carbon atom species, but the latter indicates a significant amount of an ion with *m/e* 59 which could be either $CH_3OCH_2CH_2^+$ or $CH_2CH_2CH_2OH^+$. Either of these ions resulting from the labeled alcohol could contain the ^{13}C label, and a correction should be applied to the calculation. However, such a correction would probably be negligible and was omitted in this work.

Using the relative intensity of *m/e* 45 and 46, 47.3 ± 0.2% rearrangement was calculated, whereas the relative intensity of *m/e* 58 and 59 indicated 50.7 ± 0.1% rearrangement. The average, 49 ± 4%, is probably within the experimental error. In any case, it appears that scrambling is complete as a result of the hydrolysis of **7**-^{13}C and half of the label is found in each of the 1 and 4 positions.

Hence we conclude that at some stage a symmetrical transition state such as **19** is involved which can collapse to form either oxygen–methylene bond. Apparently the bromide ion is sufficiently removed in the transition state so as not to protect the reaction site from attack by a water molecule. If such protection were important, the amount of methoxyl migration would be expected to be in excess of 50%, the exact amount being dependent upon the distance between the carbon and bromine atoms.

More generally we conclude that for hydrolysis in water an ionic intermediate is not a necessary concomitant of anchimeric assistance. Similarly Brown and Kim, in a study of aryl participation,[23] concluded that their results were not compatible with the formation of symmetrically bridged arylonium intermediates.

The inductive effect of a β-OH (-OMe) (Table II) leads to an increase in ΔH^* of about 2.6–2.8 kcal where the substituent is on a primary carbon atom (*cf.* **2**, **9**, **13**) adjacent to the reaction site, and about half this value where a second carbon atom intervenes (**5**). Where the substituted carbon atom is tertiary (**11**), the increase in ΔH^* is much reduced. But in this example there is the complication of anchimeric assistance since the rate is higher for **11** than for **10** in spite of the inductive effect of the -OH group.

Differences in solvent reorganization should also contribute to ΔH^* and ΔS^* if only in a compensatory manner,[24] but to date the clue has yet to be found for making ΔS^* a useful parameter for such a purpose. By way of contrast, ΔC_p^{*4} (and ΔC_v^{*6}) has been shown to be a useful indicator of solvent reorganization at least for structured solvents.

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[21] S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).

[22] This is not strictly correct since $X_{M+2} \neq 0$ due to the natural abundance of ^{13}C in the unlabeled positions of the tagged ion.

[23] H. C. Brown and C. J. Kim, *J. Am. Chem. Soc.*, **90**, 2082 (1968).

[24] D. G. Ives and P. D. Marsden, *J. Chem. Soc.*, 649 (1965).

The value of ΔC_p^* for the hydrolysis of primary halides has a rather wide range (-39 to -62 cal deg^{-1} mol^{-1}), but the normal values for chlorides and bromides are about -47 ± 5 cal deg^{-1} mol^{-1}. This is attributable to solvent disruption during the activation process. Thus the less negative value of ΔC_p^* found for 2-bromoethanol (-37 cal deg^{-1} mol^{-1}) compared to that for **1** can be safely attributed to some small effect of the –OH group on the initial-state solvation shell in the vicinity of –Br. That it is an effect on the initial-state solvation shell adjacent to the –Br is supported by the "normal" value of $\Delta C_p^* = -47$ cal deg^{-1} mol^{-1} for 3-bromopropanol-1, where the OH is removed from the Br. In each of these examples anchimeric assistance is absent and the mechanism is SN2.

From Table II it will be apparent that those compounds which appear to be accelerated in hydrolysis by anchimeric assistance (*cf.* **3**, **6**, **7**, **11**) show widely different values of ΔC_p^*. These differences can be understood if reasonable allowance is made for the possible effect the substituent may have on the stability of the adjacent solvation shell. This reasoning has already been used to account for the systematic difference between the value for ΔC_p^* for alkyl sulfonates and alkyl halides[25] and for the parallel case illustrated by **12** and **13**.[16]

The enhancement of the rate of hydrolysis by a factor of about 2×10^5 on the substitution of the 2-methylmercapto group in ethyl bromide provides an unambiguous example of anchimeric assistance, with a reduction of 5 kcal in ΔH^* (assuming a linear extrapolation from 90 to 25°). For the purpose of this paper the most interesting differences are those in ΔC_p^*. Ethyl bromide and 2-bromoethanol gave values of ΔC_p^* characteristic of an SN2 mechanism (*i.e.*, reflecting a critical breakdown of water structure about the quasi-anion), the presence of the –OH group in the latter modifying the initial-state solvent shell resulting in a less negative ΔC_p^* as noted above. There is no evidence of anchimeric assistance in **2** as there is in **3**. Since the methylmercapto group has negligible hydrogen-bonding properties compared to water, the solvation will approximate to that of an alkyl group of comparable size. The implication of the more negative ΔC_p^* value for **3** is that while anchimeric assistance for the methylmercapto group possibly forms an intermediate sulfonium ion, this interaction alone does not lead to products, as is the case with the SN2 hydrolysis of ethyl bromide. Rather the anchimerically assisted reaction requires solvent reorganization associated with an SN1 mechanism at the transition state. In this respect it is misleading to regard such reactions as "internal" SN2 displacements, particularly in the case of **3** and **7**.

In the second group (Table III) relative rate data for hydrolysis supports the conclusion[26] that both **6** and **7** are anchimerically assisted. The corresponding ΔC_p^* values, however, appear to be "normal" for solvolysis by an SN2 mechanism in contrast to the result found for **3** above. The presence of an –OH (or –OMe) will, in the absence of steric effects (**11**), have the effect of reducing the stability of the adjacent initial-state solvation shell (*cf.* **12**, **13**); hence the value of ΔC_p^* found for such reactants will be more positive. We note that this is just the opposite conclusion to the explanation proposed by Heine and coworkers[26] to account for the more positive ΔS^* found for the hydrolysis of **6** compared to the value of ΔS^* for the chloro analogs of **1** and **5**. This is merely another example of the current uncertainty attending interpretation of changes in ΔS^*.

The –OH group in **5** will have a similar effect on the initial-state solvent shell to that of **6** but there is no evidence of anchimeric assistance in the hydrolysis of the former; hence that part of the solvent shell is not involved in the activation process.

In the third grouping (**8–11**) the halogen is being displaced from a secondary carbon atom and the hydrogen-bonding substituent is either secondary (**9**) or tertiary (**11**). The qualitative effect on ΔC_p^* of these modifications is readily fitted into the developing hypothesis.

The "normal" value of ΔC_p^* for the hydrolysis of secondary alkyl halides is about -60 cal deg^{-1} mol^{-1}. Whether this reflects an extended solvent disordering about the forming anion or a reduction in the requirements for nucleophilic interaction or (an equivalent statement) a gradual transition from the SN1 to the SN2 mechanisms is not clear. Whatever the proper interpretation, the presence of the –OH substituent in **9** leads to a positive shift in ΔC_p^* compared to the value for **8**. There is no evidence of anchimeric assistance in **9** (Table III); hence it is reasonable to assume that here again, as in **2**, the –OH is favorably situated to reduce the stability of the initial-state solvent shell. If this is so, we would not expect this effect to be as significant in the value of ΔC_p^* for the corresponding *cis* compound.

3-Bromo-2-methyl-2-butanol provides a further combination of variables in which displacement occurs at a secondary carbon atom with some anchimeric assistance, the activity of the –OH group being promoted by the steric interactions of the two adjacent methyl groups.[12] But the steric effects also tend to interfere with the interaction of the –OH group and the adjacent solvent shell. Thus, there is no disruption of the initial-state solvent shell, and hence ΔC_p^* reflects the normal requirement of a more extensive solvent breakdown in the activation process as is characteristic of the SN1 mechanism.

From the results in Table II, it appears that the effect of an unshielded β-OH (or –OMe) on ΔC_p^* for hydrolysis is to make the coefficient more positive by 17 ± 7 cal deg^{-1} mol^{-1} (average of ΔC_p^* for **2**, **9**, **13**). Where the –OH is more remote (**5**) the effect on ΔC_p^* is negligible, in the absence of anchimeric assistance. It is presumed that the positive shift in ΔC_p^* where found is a direct result of initial-state interaction and hence independent of mechanism. Thus if ΔC_p^* values of **6** and **7** are corrected by this amount, values of -58 ± 10 and -63 ± 9 cal deg^{-1} mol^{-1}, respectively, are obtained. These values approach the corresponding values of ΔC_p^* for **3** and **11**, and thus are symptomatic of the solvent reorganization normal for an SN1 mechanism. Granted this conclusion, the lack of correspondence between the transition state and the products in these cases is not surprising and the need for some definite ionic intermediate is probably superfluous.

Experimental Section

Kinetic Method. The conductimetric method used for determining the hydrolytic rates was similar to that used previously.[4]

Mass Spectra. Mass spectra were obtained using a Hitachi-

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Perkin-Elmer Model RMU-6D mass spectrometer. We are indebted to Mr. R. Pilon for obtaining these spectra.

Vapor Phase Chromatography. Preparative vpc was conducted on an Aerograph Autoprep Model A-700 instrument. The glass column measured 10 mm × 3 m and was packed with 20% neopentylgylcol sebacate on Chromosorb W. Analytical vpc was conducted on an F & M Model 700 instrument using the following columns: A, 6 mm × 3 m glass packed with Porapak Q; B, 6 mm × 2 m copper packed with 10% tetraethylene glycol dimethyl ether on Chromosorb W; and C, 3 mm × 3 m glass packed with 10% neopentylglycol sebacate on Chromosorb W.

Product Analysis of 4-Chloro-1-butanol (6) Hydrolysis. Two sealed ampoules containing aqueous solutions of **6** (0.05–0.4 *M*) were placed in each of two thermostats at temperatures of 45.5 and 86°, respectively, where they were kept for a period of ten half-lives. The vials were removed from the thermostats and refrigerated, and 25-μl aliquots were analyzed by vpc (column A, temperature 187°, He flow 58 cc/min). A set of standard aqueous solutions of THF and tetramethylene glycol, the two expected products, was used to determine quantitatively the amount of product formed. The concentrations used were such that 2-μl injections gave peak areas of a convenient size for planimeter integration. The peak area of water was used as an internal standard, and the ratio of peak area of solute to that of water was plotted against concentration. It was found that at 86°, 69–73% of the theoretical amount of THF was formed while only 1.5% of the theoretical amount of tetramethylene glycol could be detected. We were unable to account for the loss of material. At 45.5° the amount of THF formed was 95–100% of theory, and no glycol could be detected. Since it was shown in control experiments that 2% of tetramethylene glycol could be detected, it can be concluded that between 45.5 and 86° the only significant product is THF resulting from intramolecular displacement of the chloride ion.

Product Analysis of 4-Bromobutyl Methyl Ether (7) Hydrolysis. Two reaction mixtures of **7** (0.006–0.008 *M*) in water were placed in each of two thermostats at 23 and 91°, respectively, for a period greater than ten half-lives. The vials were then refrigerated and 25-μl aliquots were analyzed.

Use of column A (temperature 258°, He flow 50 cc/min) revealed that **15** was formed in 85–100% yield at room temperature and in 70–80% yield at 91°. At a column temperature of 177° no THF could be detected for any of the mixtures.

Column B (temperature 47°, He flow 50 cc/min) was used in an effort to detect any methanol that may have formed. None was found. It is to be noted that the elution time for methanol under these conditions was 5 min whereas the water appeared at 8 min and took a considerable time to elute. In order to speed up the analysis, the He flow was increased at 8 min to 400 cc/min for 2 min, and then reduced to 50 cc/min. Only 5 min was required to restabilize the instrument for the next sample.

Product Analysis of 2-Chloroethyl Methyl Sulfide (3) Hydrolysis. Water, 100 ml, was vigorously stirred in each of two flasks at room temperature (*ca.* 23°), and 20 μl of **3** was injected into each flask and allowed to react for 15 half-lives. Another 20 μl was injected and allowed to react for a similar period. This was repeated for a total of 80 μl of material (*ca.* 0.009 *M*). This procedure was used in order to ensure that the solubility limit was not reached.[27]

Addition of chloroplatinic acid to aliquots of the two reaction mixtures did not produce any precipitate indicating that if any sulfonium ion was formed as an intermediate it did not accumulate. The reaction mixtures were analyzed for chloride and hydrogen ions by the Volhard method and titration with sodium hydroxide to a phenolphthalein end point, respectively. It was found that the ratio of hydrogen ion concentration to chloride ion concentration was 0.80 ± 0.01 and 0.78 ± 0.03, respectively. Vpc of 50-μl aliquots on column B (temperature 47°, He flow 55 cc/min) showed the absence of methanol and ethylene sulfide. Therefore, if the cyclic sulfonium ion, **16**, is an intermediate it would have to decompose solely by attack of water at an ethylene carbon atom, whereas statistically 30% of the sulfonium should decompose by attack at the methyl carbon atom.

Vpc of 25-μl aliquots on column A (temperature 193°, He flow 57 cc/min) showed that **14** is formed to the extent of 84 ± 6%.

To determine whether the cyclic sulfonium forms as an intermediate, it was thought that hydrolysis of 2 μl of the chlorosulfide in 5 ml of 1 *M* H_2PtCl_6 (*ca.* 0.005 *M*) would trap the ion. However, it was found that trimethyl sulfonium chloride is soluble to at least 0.006 *M* in this solution, and not all of the chlorosulfide would be in the sulfonium configuration simultaneously.

When the chlorosulfide was hydrolyzed in a heterogeneous system (0.08 mol/l. of mixture), a precipitate was observed on addition of chloroplatinic acid. This was presumably due to hydrolysis at the interface giving rise to dimeric or polymeric sulfonium ions.

Product Analysis of 4-Bromobutyl-4-^{13}C Methyl Ether (7-^{13}C) Hydrolysis. 7-^{13}C (5.0 μl) was mixed with 5.0 ml of water at 97°, and the solution was left in the 97° thermostat for 10 min (*ca.* 30 half-lives) after which it was cooled in an ice–water bath. Anhydrous K_2CO_3 (5.5 g) was added and the mixture extracted five times with 1 ml of CH_2Cl_2. The combined extracts were dried over anhydrous K_2CO_3. The liquid was decanted and the solution concentrated by heating on a water bath at 50°. The concentrated solution was cooled to −20° and the solvent removed under vacuum. CH_2Cl_2 (5 μl) was added to the residue, and the alcohol collected by vpc on column C (temperature 95°C, He flow 18 cc/min). The trapped alcohol was analyzed by its mass spectrum.

2-Bromoethanol (2). A commercial sample was redistilled (bp 51–52° (14 mm)) and kept under refrigeration during the investigation.

2-Chloroethyl Methyl Sulfide (3). The Columbia Organic Chemicals material was purified by vpc on the Aerograph instrument (temperature 97°, He flow 300 cc/min).

***n*-Propyl Bromide (4).** A commercial reagent grade sample was redistilled and gave constants in good agreement with the literature values.

3-Bromo-1-propanol (5). A commercial sample was redistilled (bp 65° (10 mm)) and kept under refrigeration during the investigation.

4-Chloro-1-butanol (6). The Eastman Yellow Label material was purified by vpc on the Aerograph instrument (temperature 97°, He flow 300 cc/min). It was found that when the injection block temperature was higher than 100° significant decomposition occurred during the purification.

4-Bromobutyl Methyl Ether (7). This material was prepared by the method of Karrer and Schmid[28] by Mr. W. J. Meath of Carleton University, Ottawa, Ontario, Canada: bp 44–45° (20 mm); n^{25}D 1.4479, d_{25}^{25} 1.280. The product was purified by vpc on the Aerograph instrument (temperature 80°, He flow 150 cc/min).

Cyclohexyl Bromide (8). A commercial sample was redistilled and gave constants in good agreement with the literature values.

***trans*-2-Bromocyclohexanol (9).** A pure sample of this material was kindly supplied by Dr. R. A. B. Bannard of the Defence Research Laboratories, Ottawa, Ontario, Canada.

3-Bromo-2-methyl-2-butanol (11). This was prepared by the method of Winstein and Ingraham:[29] yield 59.3%, bp 45.0–45.5° (12 mm) (lit.[25] bp 48–51° (10 mm)).

4-Hydroxybutyl Methyl Ether (14). This material was prepared by the method of Smith and Sprung:[30] yield 49.0%, bp 171–175° (759 mm) (lit.[31] bp 171° (745 mm)). A sample was purified by vpc, using column C (temperature 95°, He flow 18 cc/min), for mass spectral analysis.

2-Hydroxyethyl Methyl Sulfide (15). This material was prepared by the method of Kirner:[32] yield 71.3%, bp 84–85° (18 mm) (lit.[28] bp 69° (20 mm)).[28]

Anal. Calcd for C_3H_8OS: C, 39.10; H, 8.75; S, 34.79. Found: C, 39.73; H, 8.69; S, 34.53.

4-Hydroxybutyl-4-^{13}C Methyl Ether (14-^{13}C). This material was prepared by Dr. L. Leitch of these laboratories. A sample was purified by vpc, using column C (temperature 95°, He flow 18 cc/min), for mass spectral analysis.

4-Bromobutyl-4-^{13}C Methyl Ether (7-^{13}C). This material was prepared by Dr. L. Leitch of these laboratories. The material was purified by vpc, using column C (temperature 95°, He flow 18 cc/min).

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[27] The solubility limit was taken as equal to that of mustard gas, 0.0275 *M*: E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. II, Chemical Publishing Co., New York, N.Y., 1960, p 253.

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