Organic and Biological Chemistry

The Role of Neighboring Groups in Replacement Reactions. XXVII.[1] 5-Methoxyl Participation in Some Solvolysis Reactions[2]

Evan L. Allred and S. Winstein

Contribution No. 2053 from the Department of Chemistry, University of California, Los Angeles, California 90024, and the Department of Chemistry, University of Utah, Salt Lake City, Utah. *Received February 25, 1967*

Abstract: MeO-5 participation in the solvolysis of δ-methoxyalkyl *p*-bromobenzenesulfonates has been scrutinized to provide information regarding the factors affecting ring closure and the reactivity of the resulting intermediates. Rates of solvolysis of 4-methoxy-1-pentyl (IP) and 5-methoxy-2-pentyl (IS) *p*-bromobenzenesulfonates show that an α- or δ-methyl group is rate enhancing by a factor of *ca.* 6 in acetic acid and ethanol. These results are discussed in terms of k_c, k_s, and k_Δ. The effect of both α- and δ-methyl groups is approximately additive for *threo*-5-methoxy-2-hexyl *p*-bromobenzenesulfonate. However, the *erythro* isomer is slower than the *threo* by a factor of 2.4. The difference can be ascribed most plausibly to steric retardation. This suggests that the O-methyl and δ-methyl groups prefer to be in a *trans* orientation. Both IP and IS give identical ratios of $CH_3OCH(CH_3)(CH_2)_2CH_2OS$ and $CH_3OCH_2(CH_2)_2CH(CH_3)OS$ as solvolysis products (60:40 for EtOH and 40:60 for AcOH). A trace of 2-methyltetrahydrofuran was detected in ethanolysis. These results collectively have been taken as evidence for the formation of O-methyl-2-methyltetrahydrofuranium ion which undergoes nucleophilic attack at the methyl and primary and secondary C–O carbon atoms. The change in product ratio on going from ethanol to acetic acid may be looked upon as the consequence of a shift to a less nucleophilic solvent.

Earlier, in a preliminary communication, we summarized some of our observations regarding methoxyl participation in solvolytic substitution reactions.[1b] These showed that participation is substantial for the MeO-5 and MeO-6 cases. Since the first report we have completed a more extensive investigation of the MeO-5 participation mechanism. The investigation of this system was of special interest to us because of the importance of the results in several directions. Such a study has a bearing on the phenomenon of neighboring group participation and furnishes information regarding the factors which control ring closure and the reactivity of any resulting intermediate. In another aspect, it represents a structural extreme among possible RX substrates in solvolysis and provides an important calibration point for our understanding of ion pairs and dissociated ions in solvolysis.[3]

This paper reports the portions of our study concerned with a broad survey of the MeO-5 mechanism in solvolysis, and particularly with the structural factors which influence participation and subsequent product formation. In subsequent papers we will describe ion pair phenomena connected with MeO-5 participation in acetolysis and the observation that participation accompanies lithium aluminum hydride reduction in ether.

(1) (a) Part XXVI: C. B. Anderson, E. C. Friedrich, and S. Winstein, *Tetrahedron Letters*, No. 29, 2037 (1963); (b) part XXV: S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, 3, 1, (1958); some of the material of the present manuscript has been presented previously at the symposium on "Dynamic Stereochemistry," Manchester, England, March 31, 1954: see *Chem. Ind.* (London), 562, 569 (1954); and S. Winstein, *Experientia Suppl.*, 2, 137 (1955); (c) part XXIV: R. M. Roberts, J. Corse, R. Boschan, D. Seymour, and S. Winstein, *J. Am. Chem. Soc.*, 80, 1247 (1958).

(2) This research supported by the National Science Foundation.

(3) S. Winstein, *et al.*: (a) *Chem. Ind.* (London), 664 (1954); (b) *J. Am. Chem. Soc.*, 78, 328 (1956); (c) *ibid.*, 80, 169 (1958); (d) *ibid.*, 86, 2072 (1964); (e) *ibid.*, 86, 2720 (1964); (f) Special Publication No. 19, The Chemical Society, London, 1965, p 109.

Results

Substrate Systems and Rates of Solvolysis. The required methyl-substituted methoxybutanols and the corresponding *p*-bromobenzenesulfonates were readily available through well-known synthetic routes. In the case of the 5-methoxy-2-hexyl system, the study was made with the pure *erythro* isomer and with a mixture of *threo* and *erythro* isomers. Pure *dl-erythro*-5-methoxy-2-hexanol was made *via* the action of methyl iodide on the monosodium salt of *meso*-2,5-hexanediol. The diastereomeric mixture of 5-methoxy-2-hexanols was prepared from acetaldehyde and the Grignard reagent of 1-chloro-2-methoxybutane. Kinetic results from the acetolysis of the mixed *p*-bromobenzenesulfonates indicated an *erythro*:*threo* ratio of *ca.* 0.8.

Pertinent kinetic data are summarized in Table I for the various methyl-substituted methoxybutyl *p*-bromobenzenesulfonates. This table also lists the values of the thermodynamic quantities of activation, $\Delta H^{\pm}$ and $\Delta S^{\pm}$. The observed solvolysis kinetics were first order within an experimental error of less than ±2% except in acetolysis of the diastereomeric mixture of 5-methoxy-2-hexyl *p*-bromobenzenesulfonates. In this case, the integrated titrimetric rate constants calculated from eq 1 drifted downward during a run in a manner typical of two materials reacting at slightly different rates. Comparison of these results with the lower, but extremely steady first-order rate constant of *erythro*-5-methoxy-2-hexyl *p*-bromobenzenesulfonate made it apparent that the downward drift was caused by a difference in the reaction rates of the two dia-

$$kt = \ln [a/(a - x)] \quad (1)$$

Table I. Summary of Solvolysis Rates

Compound	Solvent	Temp, °C	ROBs concn, 10^2M	k, sec^{-1}	$\Delta H^{\pm}$, kcal/mole	$\Delta S^{\pm}$, eu
$CH_3OCH(CH_3)(CH_2)_2CH_2OBs$ (IP)	AcOH	25.20	3.19	$(1.71 \pm 0.02) \times 10^{-5}$		
	AcOH	50.00	3.25	$(2.87 \pm 0.06) \times 10^{-4}$	20.8	−10.9
	EtOH	25.20	3.36	$(3.87 \pm 0.02) \times 10^{-5}$		
$CH_3OCH_2(CH_2)_2CH(OBs)CH_3$ (IS)	AcOH	25.20	3.37	$(1.72 \pm 0.02) \times 10^{-5}$		
	AcOH	50.03	3.25	$(3.02 \pm 0.02) \times 10^{-4}$	21.1	−9.4
	EtOH	25.20	3.30	$(3.67 \pm 0.04) \times 10^{-5}$		
$CH_3OCH(CH_3)(CH_2)_2CH(OBs)CH_3$						
dl-erythro	AcOH	25.20	3.23	$(3.93 \pm 0.02) \times 10^{-5}$		
	AcOH	50.00	3.09	$(6.77 \pm 0.07) \times 10^{-4}$	21.0	−8.2
dl-threo[a]	AcOH	25.20	3.15	$(9.47 \pm 0.05) \times 10^{-5}$		

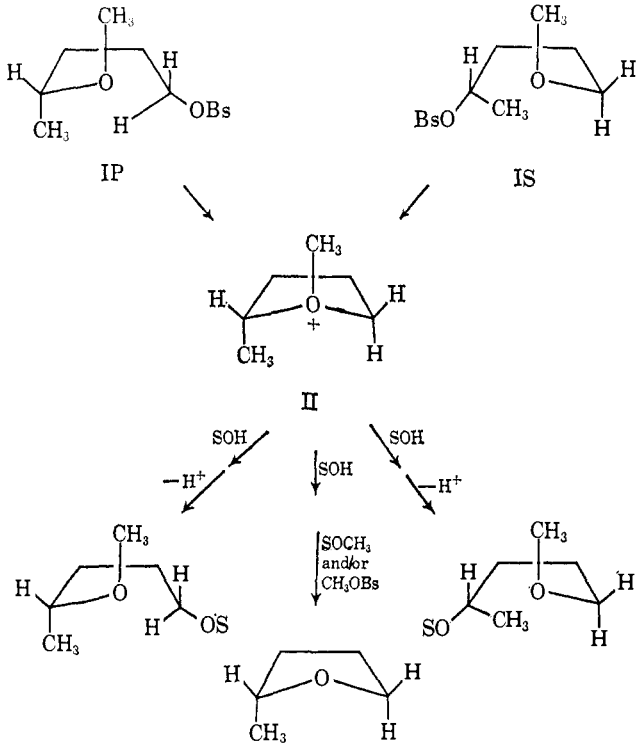
[a] Rate constant calculated by eq 2.

stereomers. Using eq 2, which is derived in the Experimental Section, and the known rate constant of the *erythro* isomer, it is possible to obtain the rate constant of the *threo* constituent. In this equation, x and y

$$k_x t = -\ln \{(z/x_0) - [(z_0/x_0) - 1]e^{-k_y t}\} \qquad (2)$$

refer to the amounts of the *threo* and *erythro* isomers, respectively, while z is the total amount $(x + y)$, all at time t. The initial quantities are denoted as x_0, y_0, and z_0, respectively. The rate constant for *threo*-5-methoxy-2-hexyl *p*-bromobenzenesulfonate was calculated using a best value of x_0 obtained by carrying out successive approximations until k_x remained constant throughout a kinetic run. Average deviation for nine points covering the range 20–85% reaction was ±0.5%. The results indicate that the *threo* isomer solvolyzes faster by a factor of 2.4.

It was somewhat surprising to find that 4-methoxy-1-pentyl *p*-bromobenzenesulfonate (IP) and 5-methoxy-2-pentyl *p*-bromobenzenesulfonate (IS) have identical rate constants for acetolysis at 25° and differ by only 5% for ethanolysis. This raised the question whether the bromobenzenesulfonate samples used were indeed different compounds. However, examination of the usual properties revealed that the samples designated IP and IS were different. Unequivocal evidence that the bromobenzenesulfonate samples were different, pure, and of the indicated structure came from the observation that during acetolysis the two materials rearrange into each other and actual rates of isomerization can be measured. A detailed account of these results is presented in a subsequent paper.



Solvolysis Products. Products of complete solvolysis of 4-methoxy-1-pentyl (IP) and 5-methoxy-2-pentyl (IS) *p*-bromobenzenesulfonates were analyzed and the results are summarized in Table II. For acetolysis, the product acetates from both IP and IS were isolated after 11 reaction half-lives in 85 and 86% yields, respectively. Analysis of the two product samples by gas chromatography showed each to be a mixture of the same two components. These were identified as 5-methoxy-2-pentyl and 4-methoxy-1-pentyl acetates by comparison of infrared spectra and gas chromatographic retention times with pure authentic samples of each acetate. Both IP and IS yielded essentially identical mixtures of secondary and primary acetates in a 60:40 ratio. Analysis of a known mixture checked the weighed composition to within 0.1%. A control experiment in which 4-methoxy-1-pentyl acetate was kept in an acetic acid solution containing 0.11 *M* *p*-bromobenzenesulfonic acid for a time corresponding to eight reaction half-lives demonstrated that this observed ratio was inherent in the acetolysis reaction and was not due to isomerization of the acetate product in a strongly acid medium.

Gas chromatographic analysis of acetic acid distillates from the total acetolysis of both bromobenzenesulfonates failed to reveal the presence of any 2-methyltetrahydrofuran or methyl acetate. However, a check on the analysis with controls of known concentration indicated that yields of 2-methyltetrahydrofuran below *ca.* 5% could not be detected. The kinetic infinity titers for acetolysis of IP and IS were 97.8 ± 0.3% and 98.0 ± 0.2%, respectively. Since methyl *p*-bromobenzenesulfonate reacts at least 10^4 times slower than these compounds,[4] the upper limit of methyl ester formation is 2%. This means that no more than a 2% yield of 2-methyltetrahydrofuran could arise from this route.

In the case of ethanolysis the high boiling ether products from IP and IS were recovered in about 86% yield

(4) S. Winstein and H. Marshall, *J. Am. Chem. Soc.*, 74, 1120 (1952).

Table II. Summary of Products from the Total Solvolysis of 4-Methoxy-1-pentyl (IP) and 5-Methoxy-2-pentyl (IS) *p*-Bromobenzenesulfonates

Compd	Added solute	Reaction half-lives	Yield of ROAc, %	Compostn of acetate mixt[a] 4-MeO-1-pentylOAc, wt %	Compostn of acetate mixt[a] 5-MeO-2-pentylOAc, wt %	2-Methyltetrahydrofuran, % of theory
Acetic acid, [ROBs] 0.1 *M*, 25.2°						
IP	...	11	85	39.54	60.46	<2[b,c]
IS	...	11	86	39.80	60.20	<2[c,d]
4-MeO-1-pentyl OAc	0.11 *M* HOBs	8	93	100.00	0	...

Compd	Reaction half-lives	Yield of ROEt, %	Compostn of ether mixt[a] 2-MeO-5-EtO-pentane, wt %	Compostn of ether mixt[a] 1-MeO-4-EtO-pentane, wt %	2-Methyltetrahydrofuran, % of theory
Ethanol, [ROBs] 0.1 *M*, 25.2°					
IP	14.5	86	60.23	39.77	1.7
IS	13.5	85	58.14	41.86	1.4

[a] Determined by gas chromatography. [b] Estimate based on a 97.8 ± 0.3% kinetic infinity titer. [c] No 2-methyltetrahydrofuran was detected by gas chromatography. However, for acetolysis this technique was only sensitive to *ca.* 5%. [d] Estimate based on a 98.0 ± 0.2% kinetic infinity titer.

after 14 reaction half-lives. Gas chromatography showed two components in each product which were identified as the two isomeric methoxyethoxypentanes. The primary bromobenzenesulfonate IP afforded a mixture of 1-methoxy-4-ethoxypentane and 2-methoxy-5-ethoxypentane in a 40:60 ratio while the ratio for IS was 42:58. An analysis check on a similar mixture of known composition agreed with the weighed composition to within 0.3%. On the basis of this, it appears that the difference between the two ratios is real. It is interesting that the ratio of secondary to primary product is almost the exact opposite of the ratio in acetolysis. Gas chromatographic analysis of ethanol distillates from the total ethanolysis of IP and IS revealed that each forms about 1.5% of 2-methyltetrahydrofuran.

Discussion

k_Δ, k_s, and α- and δ-Methyl Substituent Effects. It is instructive to examine the effects of α- and δ-methyl substitution on MeO-5 participation. In understanding the factors involved, it is helpful to discuss the results in terms of: (1) k_Δ, the rate constant for anchimerically assisted ionization; (2) k_s, the rate constant for anchimerically unassisted ionization; and (3) k_c, the rate constant for an idealized process involving neither anchimeric assistance nor nucleophilic solvent participation.[1b,5,6] The ratio k_Δ/k_s measures the competition between anchimerically assisted and anchimerically unassisted solvolysis. Pertinent rate comparisons are summarized in Table III.

From previous $\rho^*\sigma^*$ treatments[1b,7] of solvolysis rates of primary and secondary arenesulfonates it is clear that fairly satisfactory estimates of k_s for the primary and secondary δ-methoxy-substituted alkyl bromobenzenesulfonates in Table III are simply the acetolysis and ethanolysis rate constants of the unsubstituted *n*-butyl or *sec*-butyl counterparts. For acetolysis, on this basis, it is clear that k_Δ/k_s is high for all of the 4-methoxy-1-alkyl bromobenzenesulfonates whether α-, δ-, or α, δ-methyl substituted. For all of these, 98% or more of the reaction goes by the k_Δ route. In the case of ethanolysis k_Δ/k_s is also substantial, but lower than in acetolysis. As is to be expected k_s plays a somewhat more important role in the more nucleophilic ethanol. In fact, for IS about 5% of the reaction proceeds by way of the anchimerically unassisted process. This kinetic estimate is substantiated by the product compositions listed in Table II, more 1-methoxy-4-ethoxypentane resulting from the secondary bromobenzenesulfonate than from the primary isomer.

It is interesting that on introduction of an α-methyl substituent k_Δ/k_s decreases considerably in acetic acid but remains essentially the same in ethanol. This difference is due to the tendency for α-methyl substitution to increase k_s more (relative to k_Δ) as the solvent changes in the direction of the limiting (*Lim*) type solvolysis.[4,6]

On scrutinizing the relative rate values (essentially relative k_Δ) of the methyl-substituted methoxybutyl bromobenzenesulfonates compared to the methoxybutyl ester, it is seen that a δ-methyl group increases rate by factors of 5.6 and 6.3 for ethanol and acetic acid, respectively. Since this methyl group is remote from the α-carbon it exerts essentially no influence on k_c or k_s, its primary action being to increase k_Δ and, consequently, k_Δ/k_s. With α-methyl substitution k_c will be increased markedly,[4,8,9] k_s may be either increased or decreased,[6,8] and k_Δ will be increased. Therefore, depending on the effect on k_s, either rate retardation or enhancement is conceivable. In the present case, an α-methyl group speeds up rate by factors of 5.9 for ethanol and 6.3 for acetic acid. This contrasts with the effect of α-methyl substitution on rate of O-5 ring closure involving a participating benzamido group[10] but agrees with that observed in Ar_1-5 participation.[11] A similar α-methyl effect is found also in the case of β-phenyl participation.[8,9,11] From the foregoing discussion it is clear that the near identity of the solvolysis rate constants of IP and IS

(5) S. Winstein, C. R. Lindegren, H. Marshall, and L. L. Ingraham, *J. Am. Chem. Soc.*, 75, 147 (1953).
(6) S. Winstein, E. Grunwald, and H. W. Jones, *ibid.*, 73, 2700 (1951).
(7) A. Streitwieser, Jr., *ibid.*, 78, 4935 (1956).
(8) S. Winstein and E. Grunwald, *ibid.*, 70, 828 (1948).
(9) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *ibid.*, 74, 1113 (1952).
(10) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, 13, 183 (1957).
(11) R. Heck and S. Winstein, *J. Am. Chem. Soc.*, 79, 3105 (1957).

Table III. Comparison of Solvolysis Rates of Some Methyl-Substituted Methoxybutyl *p*-Bromobenzenesulfonates at 25.2°

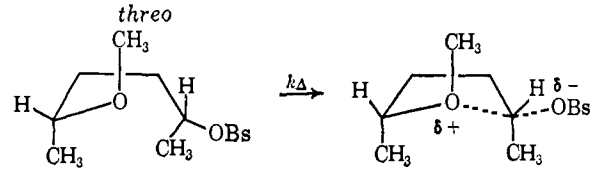
Compound	AcOH Rel rate	AcOH rel rate	k_Δ/k_s	EtOH Rel rate	EtOH rel rate	k_Δ/k_s
$CH_3(CH_2)_2CH_2OBs$	1.00[a]		0	1.00[g]		0
$CH_3OCH_2(CH_2)_2CH_2OBs$	659[b]					
	(2200)[c]	1.00	2200	18.3[h]	1.0	17
$CH_3OCH(CH_3)(CH_2)_2CH_2OBs$ (IP)	4111					
	(1.22×10^4)[d]	6.26	1.22×10^4	107	5.9	106
$CH_3OCH_2(CH_2)_2CH(OBs)CH_3$ (IS)	4135					
	(1.23×10^4)[d]	6.29	87	102	5.6	18[i]
$CH_3OCH(CH_3)(CH_2)_2CH(OBs)CH_3$						
erythro	9447	14.38	66[e]			
threo	2.28×10^4	34.70	162[e]			
$CH_3CH_2CH(OBs)CH_3$	140[f]		*Ca.* 0	5.3[i]		*ca* 0[i]

[a] $k = 4.16 \times 10^{-9}$ sec^{-1} at 25.2° by extrapolation of the data of R. Glick at other temperatures ($\Delta H^\ddagger$ = 23.7 kcal/mole at 75.3°). [b] $k = 2.74 \times 10^{-6}$ sec^{-1} at 25.2° by extrapolation of the data of R. Glick at other temperatures ($\Delta H^\ddagger$ = 21.9 kcal/mole at 75.1°). [c] Based on the data of R. Glick for k^0_{ext} from the special salt effect of lithium perchlorate. [d] Based on k^0_{ext} from special salt effect of lithium perchlorate. [e] Based on *sec*-BuOBs. [f] Extrapolated from data at other temperatures; see ref 9. [g] $k = 3.60 \times 10^{-6}$ sec^{-1} at 25.2° by extrapolation of the data of R. Glick at other temperatures ($\Delta H^\ddagger$ = 20.2 kcal/mole at 50.0°). [h] $k = 6.58 \times 10^{-7}$ sec^{-1} at 25.2° by extrapolation of the data of R. Glick at other temperatures ($\Delta H^\ddagger$ = 20.8 kcal/mole at 50.0°). [i] Based on *i*-PrOBs. [j] For *i*-PrOBs. Extrapolated from data at other temperatures: R. E. Robertson, *Can. J. Chem.*, **31**, 589 (1953).

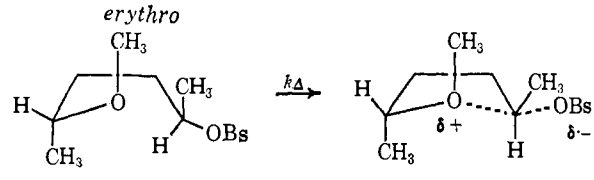
is the result of a fortuitous blending of the several structural effects.

Diastereomeric 5-Methyl-2-hexyl Systems. An examination of the relative acetolysis rates for the 5-methoxy-2-hexyl system is also informative regarding other factors which can influence ring closure. The above discussion suggests that the effects of α- and δ-methyl substitution on the rate of O-5 closure should be additive. This is approximately true for *threo*-5-methoxy-2-hexyl *p*-bromobenzenesulfonate (V) but not its *erythro* isomer VI. The *threo* ester is faster than the *erythro* isomer by a factor of 2.4. This difference can be ascribed most reasonably to a steric effect. In the transition state leading to ionization the C-methyl groups are *cis* for the *threo* diastereomer, while they are *trans* for the *erythro* isomer. Owing to the pyramidal nature of the methoxyl oxygen atom, the O-methyl group can assume a disposition *trans* to both of the other methyl groups for the *threo* transition state. On the other hand, in the *erythro* case, the O-methyl group must be *cis* to one of the other two methyl groups.[11a] This kind of interaction could plausibly account for the small reactivity differential between diastereoisomers V and VI. If this interpretation is correct it also means that a similar *trans* orientation of the O-methyl and C-methyl groups is favored for the IP–IS system.

Methylene-O and Methyl-O Cleavage. Further insight into the nature of the MeO-5 participation mechanism is provided by examination of the product data given in Table II for 4-methoxy-1-pentyl (IP) and 5-methoxy-2-pentyl (IS) *p*-bromobenzenesulfonates. The fact that these isomers give high yields of identical mixtures of secondary and primary acetates (60:40) for acetolysis and secondary and primary ethoxypentanes (40:60[12]) for ethanolysis clearly indicates that solvolysis proceeds through an intermediate common to both. The structure implied is the cyclic O-methyl-2-methyltetrahydrofuranium ion II.[11a] This is confirmed by the observation that the two isomers afford the same small yield of 2-methyltetrahydrofuran.



V



VI

These results also furnish information concerning the stability and ring opening of the cyclic oxonium ion II. Attack by solvent on the first product of ionization while the bromobenzenesulfonate anion still shields the α-carbon is precluded. If this occurred to any extent, a crossing over of products would result. All of this suggests that II is rather stable and survives long enough, even in the more nucleophilic ethanol, to become sufficiently solvated so that attack occurs at the methyl and the primary and secondary C–O carbon atoms collectively.

It is of interest to compare the Me–O and primary and secondary C–O cleavage of the O-methyl-2-methyltetrahydrofuranium ion II with the results of similar reactions which have been reported in the literature. Cyclic ion II is a ring analog of the tertiary oxonium salts (*e.g.*, dimethylethyloxonium fluoroborate) prepared and isolated by Meerwein and co-workers.[13,14]

(11a) NOTE ADDED IN PROOF. Very recently, E. R. Novak and D. S. Tarbell, *J. Am. Chem. Soc.*, **89**, 73 (1967), reported an elegant study of the stereochemical consequences of methoxyl participation in the reaction of optically active bromobenzenesulfonate IS with LiCl in pyridine. Their results point to the O-methyl-2-methyltetrahydrofuranium ion as an intermediate and confirm the inversions implied for diastereomeric V and VI and at C_2 for IS.

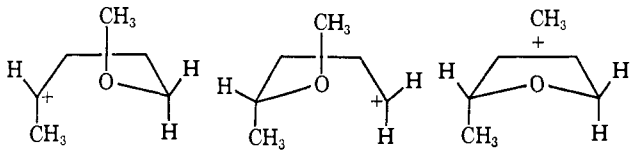
(12) Corrected for the small amount of product resulting from k_s for the IS isomer.

(13) H. Meerwein, G. Hinz, P. Hofmann, E. Kronig, and E. Pfeil, *J. Prakt. Chem.*, **147**, 257 (1937).

(14) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *ibid.*, **154**, 83 (1939).

These investigators found that one of the alkyl groups of such salts could be readily removed by some nucleophile. For instance, the salts are hydrolyzed by water and give ethers and acetates with acetic acid. In nucleophilic substitution it was observed that methyl is cleaved in preference to the ethyl group.[15] Another reaction similar in some respects to the ring opening of II by solvent is the cleavage of alkyl ethers in aqueous hydrobromic acid. The reactive form here is the dialkylhydronium ion, $RR'O^+H$, and the displacing species is thought to be Br^- or $BrHBr^-$. Burwell and Fuller[16] found that the reactivity of isopropyl *vs.* *n*-propyl increased with increasing concentration of hydrobromic acid. The same effect was shown for cyclopentyl compared to *n*-butyl.

Me–O cleavage is favored distinctly in the reactions of open-chain tertiary oxonium salts while primary and secondary C–O cleavage is greatly preferred in the cyclic oxonium ion intermediate II. This difference can be ascribed quite plausibly to a decrease in steric hindrance and an increase in reactivity due to some eclipsing strain when the primary and secondary C–O carbons are constrained to a five-membered ring. As regards the disposition of the positive charge in ion II, more of it is on oxygen, but the methyl and the primary and secondary C–O carbons also bear some of the positive charge with IIa, b, and c contributing to the resonance hybrid. Of these, it is to be expected that the contribution of IIc is smaller, but nevertheless important.



IIa IIb IIc

The influence of solvent on the ratio of primary to secondary C–O cleavage is qualitatively reminiscent of the relative rates of solvolysis of ethyl and isopropyl derivatives.[6,9] At 50° the rate sequence EtBr:*i*-PrBr is 1:0.76 in ethanol, 1:1.38 in 80% ethanol, and 1:10 in water. At 75° the rate sequence EtOTs:*i*-PrOTs is 1:5 in ethanol, 1:50 in acetic acid, and 1:200 in formic acid. The order changes from a descending trend to a slightly increasing one, and then to a more ascending one as the ionizing power of the solvent increases or solvent nucleophilicity decreases and the reaction changes in the direction of the limiting type solvolysis.[4,6] For the case of cyclic ion II, the ratio of primary to secondary C–O cleavage product is 1:0.66 in ethanol and 1:1.5 in acetic acid. Thus, as solvent is changed from ethanol to acetic acid the reaction becomes more limiting in character and structure IIa contributes more to the transition state leading from the cyclic intermediate to final product.

The preceding discussion has neglected mention of the important contribution of ion pair return to the behavior of cyclic oxonium ion II in acetic acid. This phenomenon will be treated in detail in another paper, but it should be pointed out that the ratio of primary to secondary C–O cleavage by return of the *p*-bromobenzenesulfonate anion to covalent ester is in the same direction. Both compounds approach the same 1:2.2 mixture of primary and secondary bromobenzenesulfonates.

(15) D. Kastner, "Newer Methods of Preparative Organic Chemistry," 1st ed, Interscience Publishers, Inc., New York, N. Y., 1948, pp 311–312.

(16) R. L. Burwell and M. E. Fuller, *J. Am. Chem. Soc.*, **79**, 2332 (1957).

Experimental Section

4-Methoxy-1-pentanol. 1-Chloro-3-methoxybutane, bp 126°, $n^{25}D$ 1.4127, was prepared in 90% yield by the method of Doering and Young.[17] Gaseous formaldehyde generated by heating paraformaldehyde (dried over phosphorus pentoxide) to *ca.* 180° was passed with a slow stream of nitrogen into the stirring Grignard reagent prepared from 245.2 g (2.0 moles) of the chloride and 52 g (2.14 g-atoms) of magnesium in 1500 ml of anhydrous ether. Addition of formaldehyde was stopped when Gilman's color test[18] showed a negative result. The reaction complex was neutralized by slowly adding 320 ml of saturated ammonium chloride solution. After filtering off the salt cake and thoroughly washing with ether, the combined solution was dried with magnesium sulfate. The solvent was removed and the concentrate fractionally distilled to give 188 g (76.6%) of 4-methoxy-1-pentanol, bp 84.2–85.0° (14.5 mm), 184–184.5° (754 mm), $n^{25}D$ 1.4224 (lit.[17] bp 185–186°, $n^{25}D$ 1.4232).

4-Methoxy-1-pentyl *p*-Bromobenzenesulfonate (IP). 4-Methoxy-1-pentanol was converted to the *p*-bromobenzenesulfonate by the low-temperature method described previously.[19] During the work-up and recovery of this product, the temperature was kept below room temperature. Recrystallization was at −20° from ether–pentane solvent, mp 20.5–21.0°.

Anal. Calcd for $C_{12}H_{17}O_4SBr$: C, 42.73; H, 5.08. Found: C, 42.63; H, 5.08.

Since IP appeared to be somewhat unstable on storing for extended periods of time, even at −20°, several different batches were prepared as required.

4-Methoxy-1-pentyl Acetate. This acetate product was prepared by slowly adding 7.7 g (0.098 mole) of acetyl chloride in 20 ml of anhydrous ether to a stirring mixture of 8.9 g (0.075 mole) of 4-methoxy-1-pentanol and 9.3 g (0.118 mole) of dry pyridine at 0 to −10°. After stirring at 0° the reaction mass was poured into 50 ml of ice water. The acetate was recovered by extraction with ether and then washed with 5% hydrochloric acid, 5% sodium bicarbonate, and water. After drying over magnesium sulfate, the product was fractionated through an 8.0 mm × 80 cm concentric tube column to give 8.8 g (73%) of 4-methoxy-1-pentyl acetate, bp 90.5° (19 mm), $n^{25}D$ 1.4131.

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.72; H, 10.00.

2-Methoxy-5-ethoxypentane. The sodium salt of 4-methoxy-1-pentanol was made by treating 10.0 g (0.085 mole) of alcohol with a stirring slurry of 2.6 g (0.11 mole) of sodium hydride in 50 ml of ether. After a reflux period of 24 hr, most of the ether was distilled off and 17.1 g (0.11 mole) of ethyl iodide was added. The temperature was gradually increased until reaction occurred. The excess sodium hydride was decomposed with water and the product recovered by extraction with ether. After drying with magnesium sulfate, the ether was removed and the concentrate fractionally distilled under vacuum to give 6.4 g (51.5%) of 2-methoxy-5-ethoxypentane, bp 63° (19.7 mm), $n^{25}D$ 1.4042.

Anal. Calcd for $C_8H_{18}O_2$: C, 65.72; H, 12.41. Found: C, 65.56; H, 12.43.

5-Methoxy-2-pentanol. 1-Chloro-3-methoxypropane, bp 111–111.8°, $n^{25}D$ 1.4108, was obtained in 70% yield by the procedure of Letsinger and Schnizer.[20] To the Grignard reagent from 188.9 g (1.74 moles) of chloride and 46.7 g (1.92 g-atoms) of magnesium made in the usual manner in 600 ml of ether was added, with stirring, 80 g (1.81 moles) of acetaldehyde in 600 ml of ether. The reaction complex was hydrolyzed with 275 ml of saturated ammonium chloride solution. The product was recovered from the salt cake by decantation of the ether solution followed by washing with fresh ether. After drying the combined ether solu-

(17) W. E. Doering and R. W. Young, *ibid.*, 74, 2997 (1952).

(18) H. Gilman and A. H. Blatt, Ed., "Organic Synthesis," Coll. Vol. II, 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1947, p 189.

(19) S. Winstein and R. Heck, *J. Am. Chem. Soc.*, 78, 4801 (1956).

(20) R. L. Letsinger and A. W. Schnizer, *J. Org. Chem.*, **16**, 704 (1951).

tion over magnesium sulfate, the ether was removed and the concentrate fractionally distilled to give 134 g (66.5%) of 5-methoxy-2-pentanol, bp 77.0–77.2° (15 mm), $n^{25}D$ 1.4212.

Anal. Calcd for $C_6H_{14}O_2$: C, 60.98; H, 11.94. Found: C, 60.69; H, 11.78.

5-Methoxy-2-pentyl *p*-Bromobenzenesulfonate (IS). For stability reasons the IS bromobenzenesulfonate was prepared as needed from 5-methoxy-2-pentanol by the low-temperature procedure.[19] Care was taken to keep the temperature of the product below room temperature during work-up and recovery. Purification was attained by three recrystallizations from ether–pentane solvent at −20°, mp 31.5–32.0°.

Anal. Calcd for $C_{12}H_{17}O_4SBr$: C, 42.73; H, 5.08. Found: C, 42.49; H, 5.06.

Approximately equal portions of IP and IS showed a mixture melting point of 6–10°.

5-Methoxy-2-pentyl Acetate. This substance was prepared by the same method used for the isomeric 4-methoxy-1-pentyl acetate. Reaction of the same quantities of starting materials yielded 8.4 g (70%) of 5-methoxy-2-pentyl acetate, bp 85.0° (19 mm), $n^{25}D$ 1.4106.

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.69; H, 10.32.

1-Methoxy-4-ethoxypentane. This material was prepared by the procedure used for 2-methoxy-5-ethoxypentane. Reaction of 14.6 g (0.1 mole) of ethyl iodide with the sodium alcoholate prepared from 2.5 g (0.11 mole) of sodium hydride and 8.87 g (0.075 mole) of 5-methoxy-2-pentanol in 75 ml of ether gave 5.24 g (48%) of 1-methoxy-4-ethoxypentane, bp 61.5–62.2° (20 mm), $n^{25}D$ 1.4040.

Anal. Calcd for $C_8H_{18}O_2$: C, 65.72; H, 12.41. Found: C, 65.63; H, 12.39.

5-Methoxy-2-hexanols. To the Grignard reagent from 84.5 g (0.69 mole) of 1-chloro-3-methoxybutane and 17.0 g (0.70 g-atom) of magnesium, prepared in 500 ml of ether, was added 33.5 g (0.76 mole) of acetaldehyde in 100 ml of ether. The reaction mass was decomposed with 120 ml of saturated ammonium chloride solution. On fractionation, the crude concentrate yielded 57.6 g (63%) of a mixture of *erythro*- and *threo*-5-methoxy-2-hexanols, bp 77.5° (9 mm), $n^{25}D$ 1.4242, $n^{18}D$ 1.4267 [lit.[21] bp 79–80° (9 mm), $n^{18}D$ 1.4263].

Kinetic results from the acetolysis of the mixed *p*-bromobenzenesulfonates indicated that the *erythro*:*threo* ratio was *ca.* 0.8.

5-Methoxy-2-hexyl *p*-Bromobenzenesulfonates. The diastereomeric mixture of 5-methoxy-2-hexanols was converted by the usual low-temperature technique[19] to the mixed *p*-bromobenzenesulfonates. All attempts to crystallize the isolated product failed. The crude liquid product was 97.5% pure by equivalent weight in acetolysis.

2,5-Hexanediols. A 411-g (3.65 moles) quantity of distilled 2,5-hexanedione was reduced with a slurry of 79 g (2.08 moles) of lithium aluminum hydride in 2400 ml of ether. The mixture was decomposed by dropwise addition of 158 ml of water followed by 136 ml of 10% sodium hydroxide solution. After standing, the white solid was removed by filtration and washed with ether and the combined ether solution dried with magnesium sulfate. The ether was flashed off and the concentrate vacuum fractionated to give 337 g (81%) of a mixture of *meso*- and *dl*-2,5-hexanediols, bp 119.5–120.5° (12 mm), $n^{25}D$ 1.4460 (lit.[22] $n^{25}D$ 1.4453).

The *meso*-glycol was isolated from the mixed 2,5-hexanediols by fractional crystallization in ether at −20° according to the procedure of Serck-Hanssen and co-workers.[23] Three recrystallizations from ether gave 100 g of *meso*-2,5-hexanediol, mp 37–39° (lit.[23] after four recrystallizations, mp 40–41°).

***dl-erythro*-5-Methoxy-2-hexanol.** The monosodium salt of *meso*-2,5-hexanediol was prepared by adding 6.6 g (0.29 g-atom) of freshly cut sodium to a stirring solution of 100 g (0.85 mole) of the glycol and 100 ml of *p*-xylene at 115–125°. The resulting mixture was cooled to 100° and 46 g (0.32 mole) of methyl iodide was added. After stirring for 1 hr at this temperature, the reaction was cooled to room temperature and filtered to remove the sodium iodide. The solvent was distilled off and the product isolated by fractionation through an efficient column at reduced pressure, bp 77.5° (9 mm), $n^{25}D$ 1.4240.

***dl-erythro*-5-Methoxy-2-hexyl *p*-Bromobenzenesulfonate.** The usual low-temperature method[19] was used to prepare *dl-erythro*-5-methoxy-2-hexyl *p*-bromobenzenesulfonate from the corresponding alcohol. After recrystallization from the ether–pentane solvent at −10°, the melting point was 33.0–33.8°.

Anal. Calcd for $C_{13}H_{19}O_4SBr$: C, 44.45; H, 5.45. Found: C, 44.68; H, 5.60.

***p*-Bromobenzenesulfonic Acid.** This arenesulfonic acid was prepared as described previously.[8b] The neutralization equivalent was 98.9% in acetic acid.

Kinetic Measurements. Acetic acid solvent containing 0.01 *M* acetic anhydride was prepared as described earlier.[24] Absolute ethanol containing less than 0.004% water by Karl Fischer titration was prepared according to the procedure outlined by Fieser.[25] Titrations in acetic acid were with standard sodium acetate in acetic acid.[24] For ethanol, standard sodium methoxide in methanol was the titrant. In both cases brom phenol blue was used as the indicator.[6,24]

All acetolysis rate determinations at 25.2° were carried out in glass-stoppered 50- or 100-ml volumetric flasks. The acetic acid solvent was equilibrated at 25° before making up the rate solution. For rates faster than *ca.* 5×10^{-5} sec^{-1}, the 5-ml aliquot point was quenched in 20 ml of purified dioxane. At 50.0° the rate measurement for *dl-erythro*-5-methoxy-2-hexyl *p*-bromobenzenesulfonate also was effected in a stoppered volumetric flask. The flask was warmed to 50° and acetic acid which had been prewarmed to 54° was used to make up the solution. After shaking for 1 min, the temperature was 50.0°. The sample was immersed in the 50.0° bath and pulling of aliquots was begun immediately. These were quenched by delivery into dioxane; titrations were completed after all of the aliquots had been taken. Other acetolysis rates at 50° were carried out by the usual sealed-ampoule technique. The sealed-ampoule method was used also for the ethanolysis study at 25°. Anhydrous ethanol which had been thermostated at 25° was used to make up the solutions.

In all rate measurements, except for the diastereomeric mixture of 5-methoxy-2-hexyl *p*-bromobenzenesulfonates, the average deviation throughout a run was less than ±2%. A typical example is shown in Table IV.

Table IV. Acetolysis of 0.0309 *M* *dl-erythro*-5-Methoxy-2-hexyl *p*-Bromobenzenesulfonate at 50.0°

Time, sec	0.0368 *M* NaOAc,[a,b] ml	10^4k, sec^{-1}
0	1.546	...
188	1.873	6.69
421	2.241	6.85
675	2.553	6.68
960	2.870	6.75
1269	3.145	6.76
1993	3.620	6.90
∞ (>ten half-lives)	4.323	Av 6.77 ± 0.07

[a] Per 5.140-ml aliquot. [b] *p*-Dioxane used as a quench.

Derivation of Kinetic Eq 2. Equation 2 was used for the kinetic analysis of the acetolysis of a mixture of *threo*- and *erythro*-5-methoxy-2-hexyl *p*-bromobenzenesulfonates. Let x and y refer to the concentrations, in milliliters of titrating reagent, of the *threo* and *erythro* diastereomers, respectively, while z is the total concentration $(x + y)$, all at time t. The corresponding initial concentrations are x_0, y_0, and z_0. From these definitions the following relations are apparent.

$$x = z - y \tag{3}$$

$$x/x_0 = (z/x_0) - (y/x_0) \tag{4}$$

$$y_0 = z_0 - x_0 \tag{5}$$

The first-order rate of disappearance of the *erythro* isomer is given by eq 6; this is converted to eq 7 by appropriate substitution from

(21) B. Helferich, *Ber.*, **52B**, 1808 (1919).
(22) S. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).
(23) K. Serck-Hanssen, S. Stallberg-Stenhagen, and E. Stenhagen, *Arkiv Kemi*, **5**, 203 (1953).
(24) S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Am. Chem. Soc.*, 70, 821 (1948).
(25) L. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 286.

relations 3, 4, and 5. The rate of disappearance of the *threo* isomer may be expressed in the form of eq 8. With the aid of eq 8, eq 7

$$y = y_0 e^{-k_y t} \quad (6)$$

$$x/x_0 = (z/x_0) - [(z_0/x_0) - 1]e^{-k_y t} \quad (7)$$

is modified to give eq 2. The latter is an expression in terms of the known total concentration z, the concentration of the *threo* isomer

$$\ln (x/x_0) = -k_x t \quad (8)$$

$$-k_x t = \ln [(z/x_0) - [(z_0/x_0) - 1]e^{-k_y t}) \quad (2)$$

x, and the rate constants of both isomers k_x and k_y. Since the rate constant k_x is known for the *erythro* diastereomer, different values of x_0 can be tried by successive approximations until the rate constant for the *threo* isomer k_x is constant throughout a kinetic run. Table V illustrates the results.

Table V. Acetolysis Rate Constant of *threo*-5-Methoxy-2-hexyl *p*-Bromobenzenesulfonate Calculated[a] from the Acetolysis of a Diasteromeric Mixture of 5-Methoxy-2-hexyl *p*-Bromobenzenesulfonates (0.0315 *M*) at 25.2°

Time, sec	% reaction $(x + y) = z$	0.0368 *M* NaOAc,[b] ml	z	$e^{-k_y t}$ [d]	$10^5 k_x$, sec^{-1}
0	6.22	0.275	4.148[c]	...	...
2313	19.52	0.864	3.560	0.9131	9.43
2895	22.55	0.997	3.426	0.8924	9.48
4550	30.44	1.346	3.077	0.8361	9.51
5835	35.62	1.580	2.843	0.7951	9.43
10700	52.40	2.317	2.106	0.6567	9.54
13716	59.88	2.648	1.775	0.5833	9.43
20608	72.50	3.206	1.217	0.4449	9.42
24121	77.27	3.417	1.006	0.3875	9.58
32487	84.80	3.750	0.673	0.2789	9.42
∞	97.50	4.423	...	...	...
					Av 9.47 ± 0.05

[a] Using eq 2 with x_0 as 2.085 ml at 6.22% reaction. [b] Per 5.140 ml of aliquot. [c] The z_0 value at 6.22% reaction. [d] k_y for the *erythro* isomer is $3.93 \pm 0.02 \times 10^{-5}$ sec^{-1}.

Examination of Solvolysis Products. Analytical gas chromatography for acetolysis was performed with a 2 m × 0.6 mm copper tube column packed with 30% by weight Dow Corning silicone 550 on sieved 100-mesh Celite. For ethanolysis, a 2 m × 0.6 mm stainless steel column packed with 30% by weight Carbowax 1500 on sieved 40–60-mesh Firebrick was used. All comparisons of unknown mixtures with authentic samples were performed at the same time, under identical experimental conditions.

Total Acetolysis of 4-Methoxy-1-pentyl *p*-Bromobenzenesulfonate (IP). A 9.26-g sample of IP was dissolved in 250 ml of anhydrous acetic acid, and the solution was kept at 25.2° for 121 hr (10.8 reaction half-lives). The *p*-bromobenzenesulfonic acid was then neutralized with 1.45 g of sodium carbonate and almost all of the acetic acid was distilled off at 30-mm pressure through an 18-in., glass helices packed column. Care was taken to keep the kettle temperature below 50°. After taking up the residue in 20 ml of ether, about 20 ml of water was added and the mixture neutralized to a pH of 6–7 with saturated sodium carbonate solution. Following 15 hr of continuous ether extraction of the neutralized mixture, the extract was dried over magnesium sulfate and concentrated by evaporation. Rapid distillation of the remaining concentrate at 20-mm pressure through a 6 × ⅜ in. Vigreux column gave 3.62 g (85%) of acetate product, $n^{25}D$ 1.4116. Product fractionation was avoided by distilling to dryness and heating the column above the acetate boiling point. The product infrared spectrum showed no alcohol was present and gas chromatographic analysis indicated only two components corresponding to a 60.46:39.54 ratio of 5-methoxy-2-pentyl acetate and 4-methoxy-1-pentyl acetate, respectively. Identity of these product acetates was established by direct comparison of retention times with pure authentic samples of each. The analytical precision was checked by analysis of an accurately weighed mixture of 61.91% 5-methoxy-2-pentyl acetate and 38.09% 4-methoxy-1-pentyl acetate. The results of gas chromatography showed a 61.97:38.03 ratio.

2-Methyltetrahydrofuran was looked for by atmospheric distillation of a 5-ml sample of totally solvolyzed (and then neutralized) product solution. Analysis of the acetic acid distillate failed to show the presence of cyclic ether or methyl acetate. However, examination of acetic acid solutions of known concentrations indicated that yields of cyclic ether below *ca.* 5% could not be detected.

Total Acetolysis of 5-Methoxy-2-pentyl *p*-Bromobenzenesulfonate (IS). A solution of 9.23 g of IS in 250 ml of anhydrous acetic acid was kept at 25.2° for 121 hr (10.8 reaction half-lives). Following this the mixture was worked up in a manner identical with the above-described acetolysis of the IP isomer. The recovered yield of acetate product was 3.67 g (86%), $n^{25}D$ 1.4115. No alcohol was present as shown by the infrared spectrum. Gas chromatographic analysis revealed only two components, a 60.20:39.80 ratio of 5-methoxy-2-pentyl acetate and 4-methoxy-1-pentyl acetate, respectively.

Analysis of the acetic acid distillate showed no 2-methyltetrahydrofuran or methyl acetate.

Control Experiment for Acetolysis of IP and IS. In a control experiment, a solution of 4.62 g of 4-methoxy-1-pentyl acetate in 250 ml of acetic acid containing 0.112 *M* *p*-bromobenzenesulfonic acid was kept at 25.2° for 91 hr (equivalent to *ca.* eight acetolysis half-lives for IP). The product was worked up in the above-described manner to yield 4.29 g (93%) of acetate, $n^{25}D$ 1.4131. The infrared spectrum was identical with that of the starting acetate and analysis by gas chromatography showed only one component corresponding to 4-methoxy-1-pentyl acetate.

Total Ethanolysis of 4-Methoxy-1-pentyl *p*-Bromobenzenesulfonate (IP). A solution of 4.70 g of IP in 125 ml of anhydrous ethanol was placed in a constant temperature bath at 25.2° for 72 hr (14.5 reaction half-lives). After this the *p*-bromobenzenesulfonic acid was neutralized with the calculated amount of sodium ethoxide in ethanol. When the sodium *p*-bromobenzenesulfonate had settled, the solid was removed by filtration and the ethanol was distilled off through an 18-in., glass helices packed column. The residue was taken up in ether and filtered again to remove the remaining sodium *p*-bromobenzenesulfonate. After evaporating off the ether, the concentrate was rapidly distilled (72 mm) through a 6-in. Vigreux column to give 1.75 g (86%) of high boiling ether product. Analysis by gas chromatography showed only two constituents corresponding to a 60.23:39.77 ratio of 2-methoxy-5-ethoxypentane and 1-methoxy-4-ethoxypentane, respectively. Identities of the ether products were fixed by comparison of retention times with authentic pure samples of each. The analytical precision was checked by analysis of an accurately weighed mixture of 46.82% 2-methoxy-5-ethoxypentane and 53.18% 1-methoxy-4-ethoxypentane. The gas chromatographic results showed a 46.61:53.39 ratio.

To a 5-ml quantity of an ethanol solution of IP (0.10 *M*) which had reacted for 13 reaction half-lives was added just enough sodium to neutralize the *p*-bromobenzenesulfonic acid. The solution was distilled to dryness and the ethanol distillate analyzed for 2-methyltetrahydrofuran by gas chromatography. A very small amount of the cyclic ether, corresponding to *ca.* 1.4% yield, was found.

Total Ethanolysis of 5-Methoxy-2-pentyl *p*-Bromobenzenesulfonate (IS). A 4.69-g quantity of IS in 125 ml of anhydrous ethanol was kept at 25.2° for 71 hr (13.5 reaction half-lives). It was worked up by the procedure outlined for the ethanolysis of IP. The recovered yield of high boiling ether product was 1.70 g (85%). Gas chromatographic analysis showed a mixture of 2-methoxy-5-ethoxypentane and 1-methoxy-4-ethoxypentane in a 58.14:41.86 ratio.