

Department of Chemistry, Columbia University

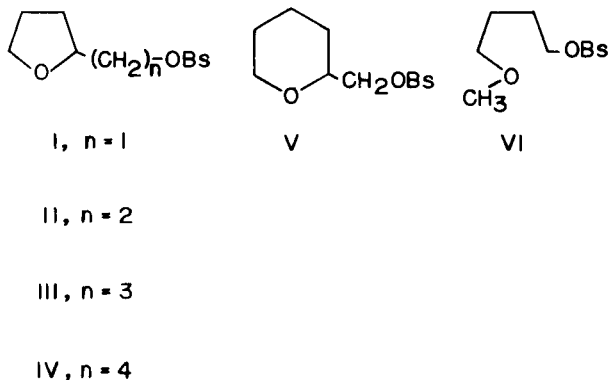
Neighboring Group Participation by the Tetrahydrofuran Ring (1)

George T. Kwiatkowski (2a), Spiro J. Kavarnos (2b), and W. D. Closson

Neighboring group participation in the solvolytic reactions of a series of ω -(2-tetrahydrofuran)alkyl *p*-bromobenzenesulfonate esters has been investigated. Anchimeric assistance to solvolysis is most pronounced in the case of 3-(2-tetrahydrofuran)propyl *p*-bromobenzenesulfonate where a 1-oxabicyclo[3.3.0]octane cation can form. A "special salt effect" and an "induced common ion effect" were observed in the acetolysis of this ester. It appears that the tetrahydrofuran ring is about twice as effective as the methoxyl group in neighboring group participation.

Considering the recent interest in the basicity (3), nucleophilicity (4), and electron-donor properties (5) of cyclic ethers, we would like to report some of our results concerning the intramolecular nucleophilicity of the tetrahydrofuran ring.

A series of ω -(2-tetrahydrofuran)alkyl *p*-bromobenzenesulfonates (I-IV) was prepared from the known alcohols (6) by standard methods. All were liquid at room temperature and liberated *ca.* 90% of the theoretical amount of acid on solvolysis. In addition, the *p*-bromobenzenesulfonate ester of 2-tetrahydropyranmethanol (V) was prepared (m.p. 76-77°) as well as that of 4-methoxybutanol (VI) (liquid).



In Table I are presented the experimental solvolytic rate constants. The acetolysis rate measurements were conducted titrimetrically while ethanolysis constants were determined conductimetrically (7). Data for certain reference compounds (cyclopentanemethyl (VII), cyclohexanemethyl (VIII), and 3-cyclopentane propyl brosylate (IX)) are also included.

The variation of acetolysis rates of the ω -(2-tetrahydrofuran)alkyl brosylates as a function of chain length exhibits the same pattern as observed for the ω -methoxyalkyl brosylates (8), indicating that participation through formation of a five-membered ring is most favorable. That participation does occur in the acetolysis of the propyl and butyl members of the series (III and IV) is quite definite since their rates are *ca.* 780 and 90 times as fast, respectively,

as that of a typical primary brosylate, IX. Investigation of the acetolysis products of III indicated that only 3-tetrahydrofuranpropyl acetate was formed.

The effect of lithium perchlorate on the rate of acetolysis of III was investigated and the results are given in Table II. Although a plot of rate *vs.* LiClO_4 concentration shows considerable scatter it is obvious that a special salt effect (9) exists. It can be estimated that the value of k_{ext}^2/k_t^2 (9) is very roughly two. This is quite similar to the values of two to three found for several systems where $\text{MeO} - 5$ assisted acetolysis occurs (8). Good confirming

evidence for the existence of a special salt effect in the acetolysis of III is the fact that an induced common ion effect (10) can be observed. Thus, a large concentration of lithium brosylate (0.0278 M) by itself has essentially no effect on the titrimetric rate constant (k_t), but after k_t has been approximately doubled by addition of a small amount of lithium perchlorate the further addition of a sizeable amount of brosylate ion (0.026-0.040 M) will bring k_t down to a value only 25% higher than at zero salt concentration. This 25% increase in k_t is presumably the normal salt effect of 25.3×10^{-4} M lithium perchlorate.

It is obvious from the data in Tables I and II that intramolecular nucleophilic participation by the oxygen atom of the tetrahydrofuran ring, as in the case of methoxy group (8), is most important when formation of a five-membered ring is possible. Direct comparison of k_t for III and 4-methoxybutyl brosylate (VI) indicates that the tetrahydrofuran ring is about three times more effective than the methoxyl group in both acetic acid and ethanol, but if one considers the values of k_{ext}^2 for the acetolysis reaction of the two compounds ($15 - 16 \times 10^{-5} \text{ sec.}^{-1}$ for VI (11) and *ca.* $24 \times 10^{-5} \text{ sec.}^{-1}$ for III, both at 50°) it can be seen that the two groups are about equally effective. Since Arnett and Wu have shown that 2-methyltetrahydrofuran is only about fifteen times as basic as dimethyl ether (3), this similarity of results is not unexpected. It is of interest that the bicyclic oxonium ion X is of about the same stability as the monocyclic ion XI. Both must be of appreciable stability in acetic acid as evidenced not only by their

TABLE I
Rates of Solvolysis of Bromobenzenesulfonate Esters

Compound	Solvent	Temp.	Addend	$10^5 k, \text{ sec.}^{-1}$ (a)	
I	Acetic acid	80°	-	0.094	± 0.008
"	"	"	0.045 M NaOAc (b)	0.088	± 0.002
II	"	"	0.030 M NaOAc (b)	0.193	± 0.02
III	"	"	-	188	± 5
"	"	70°	-	75.6	± 1.6
"	"	50°	-	12.0	± 0.3
"	Ethanol	"	-	42.6	± 0.8
IV	Acetic Acid	80°	-	21.5	± 0.3
"	"	50°	-	1.03	± 0.02
"	Ethanol	80°	-	45.1	± 0.7
"	"	50°	-	2.85	± 0.08
V	Acetic Acid	80°	-	0.0139	± 0.0013
VI	"	50°	-	4.58	± 0.10
"	Ethanol	"	-	13.0	± 0.5
Cyclopentane- methyl (VII)	Acetic Acid	80°	-	0.903 (c)	
Cyclohexane- methyl (VIII)	"	"	-	0.150 (c)	
3-Cyclopentane- propyl (IX)	"	"	-	0.240	± 0.001
"	Ethanol	"	-	13.1 (d)	

(a) Values are either the average of two or more independent experiments, or the average of the values from a single determination. (b) Sodium acetate. (c) Data from ref. 17. (d) W. D. Closson and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, 86, 1887 (1964).

TABLE II
Effects of Salt on Acetolysis of
3-(2-Tetrahydrofuran)propyl Brosylate at 50°

Salt Concentration x 10^4 M		$10^5 k, \text{ sec.}^{-1}$ (a)
-		12.0 ± 0.3
278	LiOBs (b)	11.8 ± 0.3
3.16	LiClO ₄	20.5 ± 1.0
6.32	"	21.8 ± 0.5
15.8	"	24.6 ± 1.1
25.3	"	28.4 ± 0.4
34.8	"	29.5 ± 0.5
44.2	"	30.0 ± 0.7
63.2	"	31.5 ± 0.8
265	LiOBs (b)	16.1 ± 0.2
25.3	LiClO ₄	
401	LiOBs (b)	15.1 ± 0.2
25.3	LiClO ₄	

(a) Values of k_t are either the average of two or more independent experiments, or the average of the values from a single kinetic run. (b) Lithium Brosylate.

TABLE III
Preparation of *p*-Bromobenzenesulfonate Esters

Ester (a)	Yield (b)	Physical State	Purity (c)
I	94%	oil	94%
II	46%	oil	82%
III	90%	low melting solid	94%
IV	50%	oil	93%
V	78%	solid, m.p. 76-77°	(d)
VI	40%	oil	90%

(a) 3-Cyclopentanepropyl brosylate was available from previous work, (ref. d, Table I). (b) Crude yield of brosylate. (c) Percent of theoretical amount of sulfonic acid liberated on acetolysis. On solution in acetic acid at room temperature all of the brosylates were neutral to bromphenol blue. (d) *Anal.* Calcd. for C₁₂H₁₅BrO₄S: C, 42.99; H, 4.51. Found: C, 42.61; H, 4.55.

TABLE IV

Acetolysis of Tetrahydrofuranpropyl Brosylate at 70°

Time (sec.)	[ROBs] x 10 ²	10 ⁵ k, sec. ⁻¹
0	2.60	-
180	2.27	76.7
360	1.98	75.5
600	1.63	77.8
780	1.37	82.0
900	1.33	75.0
1020	1.17	78.7
1800	0.634	78.4
2400	0.456	73.0
		77.1 ± 2.2

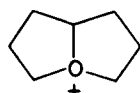
TABLE V

Ethanolysis of Tetrahydrofuranpropyl Brosylate at 50°

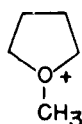
Time, Ksec.	Conductance, mhos	10 ⁵ k, sec. ⁻¹
0	452	-
0.660	780	45.7
0.900	837	40.4
1.440	1050	44.7
1.860	1152	43.6
2.520	1288	43.4
3.180	1380	42.0
3.780	1454	42.0
5.040	1557	41.4
6.600	1622	40.3
∞	1710	-
		42.6 ± 1.5 (a)

(a) The titrimetric rate constant under identical conditions was $40.0 \times 10^{-5} \text{ sec.}^{-1} \pm 1.7 \times 10^{-5} \text{ sec.}^{-1}$.

rates of formation from substrate, but also by the special salt effect III and VI exhibit (12).



X



XI

The three-fold increase in rate for III, IV, and VI on going from acetic acid to ethanol is worth noting. Normally, S_N1 reactions proceed more rapidly in acetic acid. Since the ethanolysis rates of all three compounds are many times those of reasonable non-oxygenated analogs one can be sure that the reaction mechanism is unchanged. In certain systems where MeO-5 participation occurs at a secondary carbon this modest rate enhancement is not observed (13). This suggests that the enhancement is due to

an increase in the nucleophilicity of the ether oxygen in ethanol since this would have a greater effect with a primary system. A likely cause of this would be the expected difference in degree of hydrogen bonding of the ether oxygen in the two solvents. An entirely different explanation, though, may be that the rate at which the solvent-separated ion pair dissociates or reacts with solvent is slightly faster in ethanol.

Tetrahydrofurfuryl brosylate (I) and tetrahydropyranmethyl brosylate (V) both solvolyze in acetic acid at one-tenth the rate of their carbocyclic analogs. It is known that both I and cyclopentanemethyl brosylate (VII) solvolyze in polar solvents with considerable ring expansion (14,15), while the two six-ring compounds do not (15,16). This ring expansion accounts for the six-fold rate enhancements of the five-ring compounds over the corresponding six-ring brosylates (14,17). It is amusing that replacement of a γ -methylene by oxygen has exactly the same kinetic effect in these two systems even though their overall reaction mechanisms are quite different.

EXPERIMENTAL

p-Bromobenzenesulfonate Esters.

The alcohols used in this work were all known compounds and were either obtained from commercial sources or prepared by standard methods (6). They were converted to *p*-bromobenzenesulfonate esters (brosylates) by the following procedure: To a stirred solution of the alcohol in five times its volume of pyridine at -10° was slowly added one equivalent of *p*-bromobenzenesulfonyl chloride. The mixture was stirred at -10° to 0° for ca. 4 hr., then one ml. of water was added to the mixture, stirring continued for a few minutes, and the mixture then poured into ice-HCl. The brosylate was extracted with ether and the ether solution washed with dilute acid, dilute carbonate solution, and saturated brine, and then dried with MgSO₄. Concentration under reduced pressure yielded the ester. Most of the brosylates were liquids and were not purified further. Some could be recrystallized from ether or pentane at low temperatures. Yields and other data are shown in Table III.

3-(2-Tetrahydrofuran)propyl Acetate.

This compound was prepared by treating 5.0 g. (0.038 mole) of 3-(2-tetrahydrofuran)propanol in 8 g. of pyridine with 8.1 g. (0.08 mole) of acetic anhydride. The mixture was stirred overnight at room temperature, poured into water, and extracted with ether. The extract was washed with dilute acid, dilute carbonate solution, and saturated brine, then dried with MgSO₄. Concentration and distillation yielded 4.9 g. (0.0285 mole) of 3-(2-tetrahydrofuran)propyl acetate; b.p. 144° (48 mm.), n_D^{25} 1.4394 (lit. (18) b.p. 99° (2 mm.), n_D^{25} 1.4380).

Acetolysis Products of 3-(2-Tetrahydrofuran)propyl Brosylate.

About 2 g. of the brosylate (III) was dissolved in 190 ml. of dry acetic acid and heated at 100° for 1 hr. The solution was cooled and poured into 700 ml. of ice-water. The resulting mixture was continuously extracted with pentane for 48 hrs. The pentane extract was washed with saturated sodium carbonate solution, and concentrated, yielding a yellow oil. Gas-chromatographic analysis (silicone oil column) of the oil indicated the presence of only one high boiling component which had a retention time identical with that of 3-(2-tetrahydrofuran)propyl acetate. A sample of the material was purified by preparative gas-chromatographic technique and shown to have an infrared spectrum identical with that of authentic acetate.

Kinetic Experiments.

Anhydrous acetic acid was prepared by refluxing reagent grade glacial acetic acid with the calculated amount of acetic anhydride and a trace of sodium acetate, followed by distillation. Reagent grade absolute ethanol was used without further treatment. Anhydrous lithium

perchlorate was obtained from the G. F. Smith Chemical Co. and dried for 12 hrs. under vacuum at 78° prior to use. Lithium *p*-bromobenzenesulfonate was prepared by refluxing methyl brosylate in methanol with one equivalent of lithium hydroxide for 27 hrs. Evaporation of the methanol yielded lithium brosylate which was recrystallized from ethanol-acetone and dried under vacuum.

A. Acetolysis.

Acetolyses were carried out by means of the ampule technique. Titrations of liberated sulfonic acid were performed using 0.020 M sodium acetate in acetic acid and bromphenol blue indicator. The acetolysis of I, II, and V were carried out in the presence of sodium acetate. In these cases the aliquots were acidified with a measured amount of standard perchloric acid in acetic acid and then back-titrated with sodium acetate solution. A typical kinetic experiment is shown in Table IV. In general, reactions were followed to about 80% of completion. In most cases, duplicate experiments yielded rate constants that were within 4% of each other. The acetolysis constants obtained for the very unreactive brosylates (I and V) have a much poorer precision (ca. 10%) since it was inconvenient to follow the reactions over as large a fraction of total reaction.

B. Ethanolysis.

The ethanolysis rates were determined conductimetrically, using an Industrial Instruments, Inc. conductivity bridge, Model RC 16B2, and a simple sealed conductance cell. Ethanolysis rates tended to drift downward with time, presumably due to a somewhat nonlinear conductivity-concentration relationship for bromobenzenesulfonic acid in ethanol. Even so, reproducibility compared well with that of the acetolysis experiments and rate constants determined titrimetrically were always within 7% (usually 5%) of the value obtained conductimetrically. A typical kinetic experiment, using the conductance technique, is shown in Table V.

REFERENCES

- (1) This work was supported in part by the Petroleum Research Fund, administered by the American Chemical Society (Grant No. 1272-A4).
- (2) (a) National Institutes of Health Predoctoral Fellow, 1963-1965. (b) Undergraduate research student, School of General Studies, Columbia University, 1963.
- (3) E. M. Arnett and C. Y. Wu, *J. Am. Chem. Soc.*, **84**, 1680, 1684 (1962).
- (4) H. Weiner and R. A. Sneen, *Tetrahedron Letters*, 1309 (1963).
- (5) S. Searles and M. Tamres, *J. Am. Chem. Soc.*, **73**, 3704 (1951); M. Tamres, S. Searles, Jr., and J. M. Goodenow, *ibid.*, **86**, 3934 (1964); M. Brandon, M. Tamres, and S. Searles, *ibid.*, **82**, 2129 (1960); M. Tamres and M. Brandon, *ibid.*, **82**, 2134 (1960).
- (6) (a) Commercial sources supplied tetrahydrofurfuryl alcohol and 3-(2-tetrahydrofuran)propanol. (b) 2-(2-Tetrahydrofuran)ethanol: T. Francis and E. von Rudloff, *Can. J. Chem.*, **37**, 972 (1959). (c) 4-(2-Tetrahydrofuran)butanol: K. Arh-Lipovac and R. Seiwerth, *Monatsh.*, **84**, 992 (1953).
- (7) While it has been shown that the linear conductivity-concentration relationship for electrolytes in ethanol is rather unsatisfactory (J. B. Hyme and R. E. Robertson, *Can. J. Chem.*, **35**, 623 (1957), we have found that ethanolysis constants determined from this relationship are almost always within 5% of the titrimetric rate constant.
- (8) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).
- (9) S. Winstein, E. Clippinger, A. H. Fainberg, and G. C. Robinson, *J. Am. Chem. Soc.*, **76**, 2597 (1954).
- (10) S. Winstein, P. E. Klinedinst, Jr., and G. C. Robinson, *ibid.*, **83**, 885 (1961).
- (11) Computed from the ratio $k_{\text{ext}}/k_{\text{t}}$ from ref. 8 and the acetolysis rate constant (k_{t}) of VI from Table I.
- (12) C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom", Elsevier Publishing Co., New York, 1963, p. 141.
- (13) D. S. Noyce and B. N. Bastian, *J. Am. Chem. Soc.*, **82**, 1246 (1960).
- (14) D. Gagnaire, *Bull. soc. chim. France*, 1813 (1960).
- (15) G. LeNy, *Compt. rend.*, 250, 368 (1960).
- (16) R. S. Bly, Jr., and H. L. Dryden, Jr., *Chem. and Ind.* 1287 (1959).
- (17) H. Felkin and G. LeNy, *Bull. soc. chim. France*, 1169 (1957).
- (18) R. H. Bray and R. Adams, *J. Am. Chem. Soc.*, **49**, 2102 (1927).

Received October 26, 1964

New York, New York