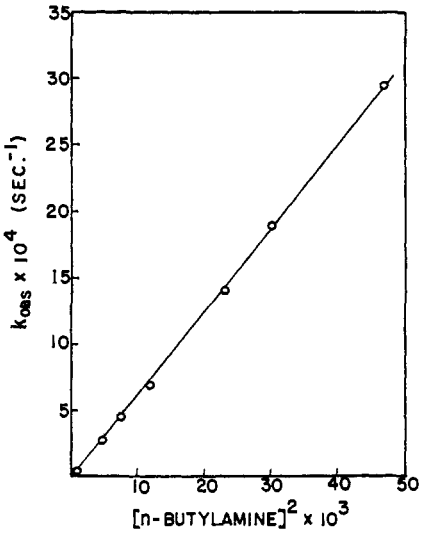


Figure 2. A plot of the observed rate constants for the reaction of *n*-butylamine with 3.25×10^{-4} *M* *p*-nitrophenyl acetate in chlorobenzene at 25.0° *vs.* the square of the *n*-butylamine concentration.

would be expected if the tertiary amine were interchangeable with *n*-butylamine as a reactive species. These results with *n*-butylamine further demonstrate the advantage of the nucleophile(s) possessing bifunctional character so that charge formation in the nonpolar medium is precluded.

The benzamidine model supports the suggestion that multifunctional catalysis by proteolytic enzymes may occur in a cyclic fashion in nonpolar regions of the active sites. Since these enzymes catalyze hydrolyses, water is obviously present in the regions of catalytic activity. This does not mean that the regions are aqueous in nature. A single water molecule within a hydrophobic environment may be bound in a position suitable for reaction with the acyl-enzyme intermediate. This water molecule could react with the carbonyl carbon, simultaneously losing a proton which would be delivered (with the aid of intervening groups such as an imidazole ring or other water molecules) to the carbonyl oxygen. In this way hydrolysis could occur without charge generation. A similar mechanism could be envisioned for the formation of the acyl enzyme, but involving the serine hydroxyl rather than a water molecule. It is just such a process that has been proposed by Bender and Kézdy.[3]

There is already substantial evidence that the binding site of α-chymotrypsin is a hydrophobic region.[14] The facility of the nucleophilic reaction of a carboxylic acid derivative in the medium of dielectric constant 5.6 raises the possibility that the *entire* active site is nonpolar in character.

Acknowledgment. The author wishes to express his gratitude to Professor Myron Bender for support of a postdoctoralship (Grant H 5726 of the National Institutes of Health) during which this project was conceived and the initial experiments were performed. We also appreciate assistance from the McCandless Fund of Emory University.

(14) J. B. Jones and C. Niemann, *Biochemistry*, **2**, 498 (1963).

A Comparative Study of the Alkaline Hydrolysis of *o*-Hydroxy-α-toluenesulfonic Acid Sultone and Phenyl α-Toluenesulfonate

O. R. Zaborsky and E. T. Kaiser[1]

Contribution from the Department of Chemistry, University of Chicago, Chicago, Illinois 60637. *Received May 24, 1966*

Abstract: The five-membered cyclic sulfonate, *o*-hydroxy-α-toluenesulfonic acid sultone, undergoes alkaline hydrolysis 7×10^5 times faster than its open-chain analog, phenyl α-toluenesulfonate. This is the second observation of a very large rate enhancement for the hydrolysis of a five-membered cyclic sulfur-containing ester.

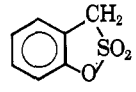
In recent years studies on the alkaline hydrolysis of five-membered cyclic esters of phosphoric, phosphonic, and sulfuric acid have been reported. An investigation on the simplest cyclic ester of phosphoric acid, ethylene phosphate, revealed that its potassium salt hydrolyzes at *ca.* 10^7 times the rate observed for the corresponding salt of the open-chain analog, dimethyl phosphate.[2] The alkaline hydrolysis of ethylene phosphate has been demonstrated to occur exclusively with P–O bond cleavage, whereas dimethyl phosphate hydrolyzes to a large extent with C–O bond cleavage.[3,4] As a result of this difference in the modes of bond cleavage, the rate enhancement for the attack at the phosphorus atom of the cyclic ester by hydroxide ion is estimated to be greater than 10^8. Further studies have shown that this large rate enhancement is not unique for five-membered cyclic esters of phosphoric acid. The five-membered cyclic ester of phosphonic acid, lithium propylphostonate, is hydrolyzed 6×10^5 times as fast as the open-chain compound, sodium ethyl

(1) To whom inquiries concerning this paper should be addressed.
(2) J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *J. Am. Chem. Soc.*, **78**, 4858 (1956).
(3) P. C. Haake and F. H. Westheimer, *ibid.*, **83**, 1102 (1961).
(4) C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3574 (1958).

ethylphosphonate.[5] The rate enhancement becomes somewhat larger when it is adjusted to represent attack at the phosphorus atom.

In attempts to explore the unusual behavior of the five-membered cyclic esters of phosphoric acid, the hydrolyses of cyclic esters of sulfuric acid have been studied.[6,7] In a recent communication from our laboratory, it was shown that the five-membered cyclic sulfate, catechol cyclic sulfate, hydrolyzes in alkali with a rate enhancement of 2×10^7 when compared to its open-chain analog, diphenyl sulfate.[7] Since nucleophilic attack at the aromatic carbon atoms in these compounds should be highly improbable, the difference in the rates of hydrolysis should represent the difference in the rate of attack of hydroxide ion at sulfur for a five-membered cyclic sulfate compared to that for the open-chain analog.

The above study led to the investigation of the alkaline hydrolysis of the five-membered cyclic sulfonate, *o*-hydroxy-α-toluenesulfonic acid sultone (I) and its open-chain analog, phenyl α-toluenesulfonate (II).[8] As in the case of catechol cyclic sulfate, nucleophilic attack of hydroxide ion at the aromatic carbon atom bonded to the oxygen atom is extremely unlikely.



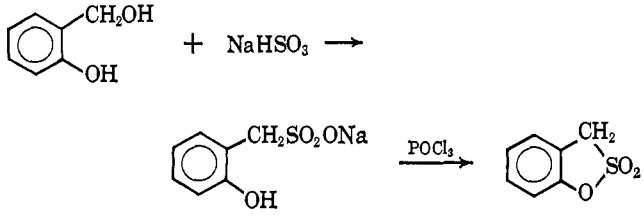
I

$C_6H_5CH_2SO_2OC_6H_5$

II

Experimental Section

Two different procedures for the preparation of *o*-hydroxy-α-toluenesulfonic acid sultone have been reported.[9,10] The method of Shearing and Smiles[10] with slight modifications was used because of the ready availability of the starting materials. The reaction sequence for the preparation of the sultone is illustrated below.



I

Sodium *o*-Hydroxy-α-toluenesulfonate. To 41.3 g (0.397 mole) of sodium bisulfite was added 49.2 g (0.397 mole) of *o*-hydroxybenzyl alcohol (Eastman) and enough water to dissolve the mixture (*ca.* 900 ml). The solution was refluxed for 8 hr, most of the excess water was removed by distillation, and the solution was evaporated to dryness on a rotary evaporator yielding a white residue which was air dried. Continuous extraction of this residue with ethanol using a Soxhlet extractor gave 78.3 g (94 % yield) of a flaky, white product. The nmr (D_2O) and infrared spectra of this material were consistent with the *o*-hydroxy-α-toluenesulfonate structure.[11]

o-Hydroxy-α-toluenesulfonic Acid Sultone. Shearing and Smiles[10] used PCl_5 to effect the cyclization of *o*-hydroxy-α-toluenesulfonate, but we found that we could obtain better yields of the sultone by using $POCl_3$ as the cyclizing agent.

To 40.0 g (0.190 mole) of sodium *o*-hydroxy-α-toluenesulfonate was added 320 g (2.09 moles) of phosphorus oxychloride. No reaction occurred at room temperature, and the reaction mixture was heated slowly to 125°. HCl fumes started to evolve at 110°, and the mixture was refluxed at 125°. Heating was continued for 1 hr, the excess $POCl_3$ was removed by distillation, and the cream-colored residue was allowed to cool.

The residue was ground and transferred slowly into 600 ml of ice–water. The white material was left in contact with the water for 4 hr, then suction filtered, thoroughly washed with cold water, and finally air dried. Crystallization from ethanol gave 17.6 g (54% yield) of pure, white crystals, mp 86.1–87.1° (lit.[9,10] mp 86°). The nmr ($CDCl_3$), infrared, and mass spectra observed for this compound were all consistent with the sultone structure. *Anal.* Calcd for $C_7H_6O_3S$: C, 49.40; H, 3.55; S, 18.84. Found: C, 49.34; H, 3.55; S, 18.86.

Phenyl α-Toluenesulfonate. This compound was conveniently prepared by the following method.[12] Phenol (Merck, 15.1 g, 0.160 mole) and 15.3 g (0.080 mole) of α-toluenesulfonyl chloride (City Chem. Corp.) were dissolved in 500 ml of ether contained in a 1-l. erlenmeyer flask. The solution was cooled in a sodium chloride–ice bath, and then 42.8 ml (0.160 mole) of a 15% solution of sodium hydroxide was added dropwise with magnetic stirring over a period of 2 hr. The temperature was maintained below 5°, and vigorous stirring was continued for 4 hr after the base had been completely added. The ether layer was separated, washed twice with 10% sodium hydroxide solution, twice with water, dried over calcium chloride, and evaporated to give the crude product. Recrystallization from ether–petroleum ether (bp 30–60°) gave 11.2 g (56% yield) of a white, crystalline solid, mp 86.7–87.1° (lit.[12] mp 81–82°). The same melting point was also obtained from another solvent mixture, ethanol–water. The nmr ($CDCl_3$), infrared, and mass spectra obtained were consistent with the assigned structure. *Anal.* Calcd for $C_{13}H_{12}O_3S$: C, 62.89; H, 4.87; S, 12.91. Found: C, 62.91; H, 4.92; S, 12.91.

Kinetic Methods

***o*-Hydroxy-α-toluenesulfonic Acid Sultone (I).** The hydrolysis of I was conducted in a thermostated cell at 25.0° maintained at a constant pH by means of an automatic titrator. Two Radiometer automatic titrating assemblies were used: (1) Type SBR2C titrigraph recorder in conjunction with a Type TTTlb titrator and a GK 2021 C (KCl) electrode; (2) Type SBR2C titrigraph recorder in conjunction with a TTT-11 titrator connected with a PHM25SE pH meter equipped with a PHA925 scale expander and a GK 2021 C (KCl) electrode. The rate of hydrolysis was determined from the amount of alkali added by the titrator as a function of time. In a typical kinetic run the following procedure was used. The electrode was standardized with Fisher Certified buffer solution, 5.0 ml of the electrolyte (2.0 *M* sodium nitrate) was added to a clean, dry reaction cell, the pH was adjusted to the appropriate value with 0.2 *N* NaOH, 150–200 μl of a 3×10^{-2} *M* solution of I in spectroquality acetonitrile was added, and the titrigraph recorder was activated. The amount of acetonitrile present in the runs varied from 2.92 to 3.85% (v/v), and the assumption was made that this small amount of variation in the acetonitrile concentra-

(5) A. Eberhard and F. H. Westheimer, *J. Am. Chem. Soc.*, 87, 253 (1965).

(6) E. T. Kaiser, M. Panar, and F. H. Westheimer, *ibid.*, 85, 602 (1963).

(7) E. T. Kaiser, I. R. Katz, and T. F. Wulfers, *ibid.*, 87, 3781 (1965).

(8) Intramolecular esters of hydroxysulfonic acids are named "sultones," and the name is derived simply from the corresponding acid: *Chem. Abstr.*, 39, 5934 (1945).

(9) W. Marckwald and H. H. Frahne, *Ber.*, 31, 1854 (1898).

(10) E. A. Shearing and S. Smiles, *J. Chem. Soc.*, 1348 (1937).

(11) The spectra were determined on the following instruments: Varian A-60 nuclear magnetic resonance spectrometer, Beckman IR 5-A infrared spectrophotometer, and the AEI Model MS-9 mass spectrometer. The mass spectrometer was purchased in part by funds awarded to the Department of Chemistry of the University of Chicago by the National Science Foundation. All melting points were taken on a Thomas–Hoover-type capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

(12) No exact preparative procedures are reported in the easily accessible literature. Two indirect references are: G. Dougherty and R. H. Barth, U. S. Patent 2,373,298 (April 10, 1945); *Chem. Abstr.*, 39, 4094[5] (1945); and V. D. Azatyan and G. T. Esayan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauk*, 11, (5) 369 (1958); *Chem. Abstr.*, 53, 14919*i* (1959).

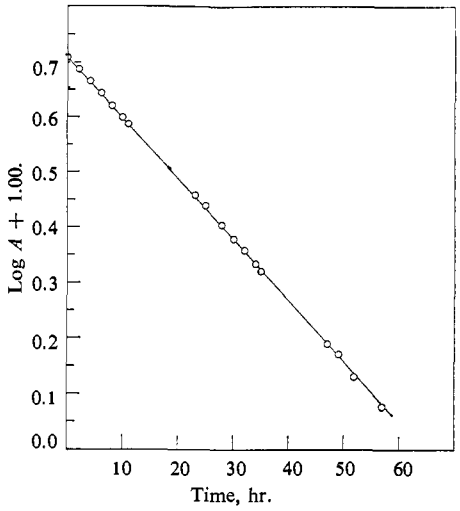


Figure 1. Plot of the data of Table I.

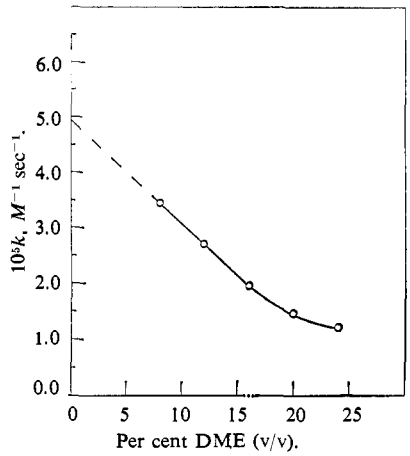


Figure 2. Effect of DME concentration on second-order alkaline rate constant.

tion did not affect the reliability of the rate measurements or the determination of the hydroxide ion concentration from the apparent pH values. The normality of the sodium hydroxide solution used for the titrations was 0.02 N, the hydroxide ion concentrations used in the reaction mixtures ranged from 1.58×10^{-6} to 1.00×10^{-5} M, and the initial concentration of the sultone ranged from 8.74×10^{-4} to 11.54×10^{-4} M.

At the end of each run, the "buffer-adjust" on the titrator was checked with standard buffer, and the data were discarded if the initial and final readings varied appreciably. In addition, all titrations were done under a constant flow of purified Linde nitrogen.

Phenyl α-Toluenesulfonate (II). The rate of hydrolysis of II was followed by means of a Beckman DU spectrophotometer. The procedure for a typical run was as follows. A 1×10^{-3} M solution of I (5.0 ml) in dry, purified 1,2-dimethoxyethane (refluxed and distilled from lithium hydride) was added to a 25.0-ml volumetric flask. Then, depending on the normality of base that was desired, the appropriate amounts of 5.0 M $NaClO_4$ and 5.0 N NaOH (Fisher certified) were pipetted into the flask, and the level of the solution in the flask was brought up to the mark by the addition of deionized water. The flask was shaken vigorously, and a portion of the clear solution was transferred to a stoppered, quartz, ultraviolet cell. The cell was placed into the thermostated compartment of the spectrophotometer, allowed to equilibrate, and readings were taken periodically at 287.0 mμ using deionized water as the reference. The rate of hydrolysis was determined by following the appearance of the phenoxide ion absorption peak at 287.0 mμ (ϵ_{max} 2600). At this wavelength only a very slight amount of extraneous absorption was due to the other components of the reaction solution, and the experimental change in absorbance agreed quite well with the calculated change due to the phenoxide ion. The reaction was studied at an ionic strength of 2.0, at base concentrations from 0.4 to 1.2 N, at 1,2-dimethoxyethane percentages varying from 8 to 24% (v/v), and at sulfonate concentrations ranging from 1.2×10^{-4} to 2.0×10^{-4} M.

Kinetic Results and Comparison of Rates

In the study of the hydrolyses of both I and II the hydroxide ion concentrations were kept constant during the course of a given run. With I the hydroxide ion concentration was maintained constant by means of an automatic titrator, while with II it was kept constant by using a large excess of the base. Therefore, in a given run pseudo-first-order kinetics were observed in the hydrolyses of both compounds.

Sodium o-hydroxy-α-toluenesulfonate was produced from the alkaline hydrolysis of I in sodium hydroxide solution. Calculation of the second-order rate constant for the hydroxide ion catalysis from various pseudo-first-order rate constants obtained at different hydroxide ion concentrations gave a value of 33.6 M^{-1} sec^{-1}.

Alkaline hydrolysis of II in sodium hydroxide solution gave the sodium salts of α-toluenesulfonic acid and phenol. Results from a typical run are tabulated in Table I and plotted in Figure 1. Since II is extremely insoluble in water, a cosolvent, 1,2-dimethoxyethane had to be used. A study of the effect of the concentration of the organic solvent upon the second-order rate

Table I. Sample Run: Base-Catalyzed Hydrolysis of II at 25.0[a]

Time, hr	Absorbance at time t, A_t	Concn of I remaining at time t, $A = A_\infty - A_t$	Log A + 1.00
0	0.051	0.511	0.708
2	0.076	0.486	0.687
4	0.100	0.462	0.665
6	0.123	0.439	0.642
8	0.145	0.417	0.620
10	0.166	0.396	0.598
11	0.176	0.386	0.587
23	0.275	0.287	0.458
25	0.288	0.274	0.438
28	0.309	0.253	0.403
30	0.323	0.239	0.378
32	0.334	0.228	0.358
34	0.340	0.216	0.334
35	0.353	0.209	0.320
47	0.408	0.154	0.188
49	0.414	0.148	0.170
52	0.427	0.135	0.130
57	0.443	0.119	0.076
inf.	0.562	...	...

[a] Ionic strength 2.0, 0.6 N NaOH, 24% DME, and sulfonate concentration of 2×10^{-4} M.

Table II. Effect of DME Concentration on Second-Order Alkaline Rate Constant

1,2-Dimethoxyethane (DME), % (v/v)	Second-order alkaline rate constant, 10^5k (M^{-1} sec^{-1})
8	3.45
12	2.69
16	1.95
20	1.45
24	1.21

constants observed was made, and extrapolation of these measurements to 0% 1,2-dimethoxyethane gave a value of 4.94×10^{-5} M^{-1} sec^{-1} for the rate constant (Table II and Figure 2.)

Thus, a comparison of the rate constants for the two sulfonates shows that the five-membered cyclic sulfonate (I) hydrolyzes 6.8×10^5 times faster than its open-chain analog (II). This is then the second observation of a very large rate enhancement for the hydrolysis of a five-membered cyclic sulfur-containing ester.

A comparison of the phosphorus and sulfur systems reveals an interesting trend; the ratios of the rates for the cyclic esters compared to their acyclic analogs are lower when a methylene group is directly attached to the hetero atom (phostonates and sultones) than those which have been observed for the phosphates and sulfates. Studies on the origin of the extraordinary lability of the cyclic sulfur-containing esters and the mechanism involved in their hydrolyses are being pursued.[13,14]

(13) X-Ray investigations on the structures of the sulfonate esters are in progress in the laboratory of Professor E. B. Fleischer at the University of Chicago.

(14) The support of the National Science Foundation is gratefully acknowledged. O. Z. wishes to thank the National Institutes of Health for a Predoctoral Fellowship.

Bridged Polycyclic Compounds. XXXVI. Rearrangements in the Acetolysis of *exo*-Dehydro-2-norbornyl *p*-Bromobenzenesulfonate[1]

Stanley J. Cristol, Terence C. Morrill, and Robert A. Sanchez

Contribution from the Department of Chemistry, University of Colorado, Boulder, Colorado 80302. *Received December 30, 1965*

Abstract: *exo*-3-Deuteriodehydro-2-norbornyl *p*-bromobenzenesulfonate (VIIb) solvolyzes in glacial acetic acid to give about 7% of an equimolar mixture of *exo*-3-deuteriodehydro-2-norbornyl acetate (VIId) and 7-deuteriodehydro-2-norbornyl acetate (VIIId), along with about 93% of deuterated 3-nortricyclyl acetate (IId). The acetolysis is accompanied by a considerably more rapid scrambling of the *p*-bromobenzenesulfonate by internal return to 7-deuteriodehydro-2-norbornyl *p*-bromobenzenesulfonate (VIIIb), without attendant formation of deuterated nortricyclyl *p*-bromobenzenesulfonate (IIb). The data are consistent with the assumption that ion pairs involving a symmetrical nonclassical cation such as IV are produced in the ionization process, or with the assumption that *rapidly* equilibrating nonsymmetrical cations such as V and VI are involved, but are not consistent with the suggestion made earlier that the nonsymmetrical cation V is formed in the ionization step and isomerizes relatively slowly to its Wagner–Meerwein isomer VI.

Solvolyses of derivatives of *exo*-dehydro-2-norborneol (Ia) and of its homoallylic isomer 3-nortricyclenol (IIa) have been of interest since the initial reports of their reactivities and interconversions,[2,3] in particular as one of the key examples of a homoallylic cationic system.[4] The high reactivity of the *exo*-*p*-bromobenzenesulfonate Ib compared with its *endo* epimer in acetolysis[3] or of the corresponding *exo* chloride in solvolysis in 80% aqueous ethanol[5] compared with its *endo* epimer has been attributed[2-6] to anchimeric assistance to ionization provided by the electron cloud of the 5,6 double bond (homoallylic interaction) at the developing cationic center at C_2. In addition, it has been suggested that a portion of the driving force for increased reactivity may be ascribed to participation of the σ 1,2 bond,[4b] similar to that assumed in the *exo*-2-norbornyl case,[7,8] where there is much evidence supporting the concept that the symmetrical nonclassical cation III[4] (or a variant thereof) is produced in the ionization process.

Solvolyses of Ib and IIb in methanol and in acetic acid have been shown to give mixtures of dehydronorbornyl and nortricyclyl ethers and esters containing largely II isomers.[9] These mixtures contained slightly

(1) Previous paper in series: S. J. Cristol, J. K. Harrington, and M. S. Singer, *J. Am. Chem. Soc.*, **88**, 1529 (1966).

(2) J. D. Roberts, W. Bennett, and R. Armstrong, *ibid.*, **72**, 3329 (1950).

(3) S. Winstein, H. M. Walborsky, and K. Schreiber, *ibid.*, **72**, 5795 (1950).

(4) (a) S. Winstein and R. Adams, *ibid.*, 70, 838 (1948); (b) M. Simonetta and S. Winstein, *ibid.*, **76**, 18 (1954); (c) S. Winstein and E. M. Kosower, *ibid.*, **81**, 4399 (1959).

(5) J. D. Roberts and W. Bennett, *ibid.*, **76**, 4623 (1954).

(6) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *ibid.*, 77, 4183 (1955).

(7) S. Winstein and D. Trifan, *ibid.*, **74**, 1147, 1154 (1952).

(8) For a recent summary of the evidence available on the norbornyl ion, see S. Winstein, E. Clippinger, R. Howe, and E. Vogelfanger, *ibid.*, **87**, 376 (1965).

(9) S. J. Cristol, W. K. Seifert, D. W. Johnson, and J. B. Jurale, *ibid.*, **84**, 3918 (1962).