# Substituent Effects in the Alkaline Hydrolyses of Aromatic Five-Membered Cyclic Sulfonates. Hydrolyses of 5-Substituted 2-Hydroxy-$\alpha$-toluenesulfonic Acid Sultones

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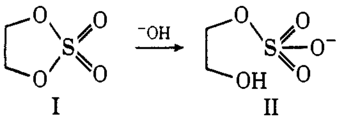
**Abstract:** A series of 5-substituted 2-hydroxy-$\alpha$-toluenesulfonic acid sultones has been synthesized, and the rate constants for the alkaline hydrolysis of these compounds have been determined at 25°. A linear relationship exists between the logarithms of these rate constants and the appropriate Hammett *para*-substituent constants, $\sigma_p$. A positive $\rho$ value of +1.23 was obtained indicating that electron-withdrawing substituents in the 5 position of the aromatic ring have an accelerating effect on the alkaline hydrolysis of aromatic five-membered cyclic sulfonates. If the mechanism of hydrolysis of the sultones involves a concerted nucleophilic displacement reaction by hydroxide ion at sulfur then our observations suggest that the sulfur–oxygen bond is significantly cleaved in the transition states for these reactions. However, we have found earlier that the formation of pentacovalent intermediates in the hydrolyses of the sultones cannot be ruled out and this possibility introduces some ambiguity in the interpretation of the linear free-energy relationship observed.

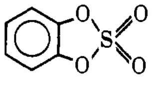
During the last few years, several reports have been published from this laboratory on the hydrolytic behavior of highly reactive cyclic sulfonates[3–5] and sulfates.[6,7] A major concern in these studies, as well as those on the analogous phosphorus systems,[8,9] was the determination of the position of nucleophilic attack by hydroxide ion.

In comparative studies on the alkaline hydrolysis of cyclic and acyclic sulfonates and sulfates attention has been focused on the relative rates of attack by hydroxide ion on the sulfur atoms in these compounds.

The alkaline hydrolysis of the aliphatic cyclic sulfate, ethylene sulfate, I, to the monosulfate, II, was found to proceed with 14% S–O bond cleavage (indicative of attack of hydroxide ion at the sulfur atom) and 86% C–O bond cleavage (indicative of attack of the nucleophile at the methylene carbon atom).[10] Since within the accuracy of the experiments performed dimethylsulfate III, the open-chain analog, appears to hydrolyze with complete C–O bond cleavage under the conditions employed, no rate comparison for attack by hydroxide ion at the sulfur atoms in I and III could be obtained. To obtain a direct comparison of the rates of hydroxide ion attack at the sulfur atom in a five-membered cyclic sulfate and an open-chain analog the alkaline hydrolyses of the aromatic sulfates catechol cyclic sulfate, IV, and diphenylsulfate, V, were studied.[6] A comparison of the second-order rate constants for the hydroxide ion catalyzed reaction of these compounds revealed that the five-membered cyclic sulfate hydrolyzes $2 \times 10^7$ times faster than the acyclic analog. This was the first observation of such an enormous rate enhancement for the hydrolysis of a five-membered cyclic ester containing a heteroatom other than phosphorus. Later, hydrolytic studies in oxygen-18 enriched solvents substantiated the assumption that hydroxide ion attack occurs at the sulfur atoms[5] in these compounds.



I    II



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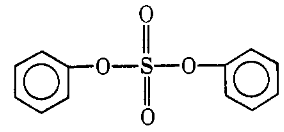

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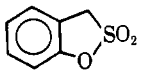
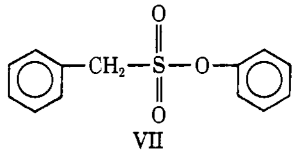
Additional studies have revealed that the hydrolyses of five-membered cyclic sulfonates also show a large rate acceleration (*ca.* a factor of $10^5$–$10^6$) relative to those of the acyclic or six-membered analogs. For instance, the alkaline hydrolysis of 2-hydroxy-$\alpha$-toluenesulfonic acid sultone, VI, is $8 \times 10^5$ faster than that of phenyl $\alpha$-toluenesulfonate, VII, the open-chain analog.[3] The hydrolysis of these sulfonates was postulated to occur *via* attack of hydroxide ion at the sulfur atom with concomitant S–O bond cleavage.



VI



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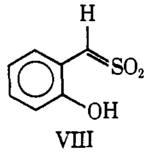
However, another process could be envisioned whereby S–O bond fission occurs, but where attack of hydroxide ion occurs at the $\alpha$-methylene position and not at the sulfur atom. This process would involve the intermediacy of the sulfene VIII.[3]



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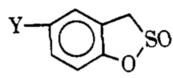

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[1] Predoctoral Fellow of the National Institutes of Health.

[2] Fellow of the Alfred P. Sloan Foundation to whom inquiries concerning this paper should be addressed.

[3] O. R. Zaborsky and E. T. Kaiser, *J. Amer. Chem. Soc.*, **88**, 3084 (1966).

[4] E. T. Kaiser, K. Kudo, and O. R. Zaborsky, *ibid.*, **89**, 1393 (1967).

[5] E. T. Kaiser and O. R. Zaborsky, *ibid.*, **90**, 4626 (1968).

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

[7] F. P. Boer, J. J. Flynn, E. T. Kaiser, O. R. Zaborsky, D. A. Tomalia, A. E. Young, and Y. C. Tong, *ibid.*, **90**, 2970 (1968).

[8] P. C. Haake and F. H. Westheimer, *ibid.*, **83**, 1102 (1961).

[9] A. Eberhard and F. H. Westheimer, *ibid.*, **87**, 253 (1965).

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

Much of our recent attention has been devoted to determining whether such an intermediate occurs along the reaction path in the hydrolysis of sulfonates possessing labile α-methylene protons. From various experimental observations, we have concluded that the results are most consistent with nucleophilic displacement by hydroxide at sulfur, and that a sulfene intermediate is not obligatory in these hydrolyses.[11] Although we cannot presently eliminate hydrolysis mechanisms proceeding through the intermediacy of sulfenes altogether, there is ample evidence available to support the argument that sulfene formation certainly is not the dominant pathway for hydrolysis of sulfonates (if it exists at all).

The presently described investigation of the hydrolysis of 5-substituted 2-hydroxy-α-toluenesulfonic acid sultones was undertaken in order to explore further the factors affecting the reactivity of these very labile sultones. A classical Hammett study of substituent effects could give pertinent information about the electronic requirements of the transition states in the hydrolyses of the five-membered sultones IX.

## Experimental Section

The synthesis of 2-hydroxy-α-toluenesulfonic acid and sultone, VI,[3] and 5-nitro-2-hydroxy-α-toluenesulfonic acid sultone, IXa,[12] has been described by previously. The 5-amino derivative, IXb, was obtained by reduction of the 5-nitro sultone.[13,14]

**5-Methyl-2-hydroxy-α-toluenesulfonic Acid Sultone, IXc.**[15] To 148 g (1.18 mol) of sodium sulfite in 350 ml of water was added 33.4 g of 36% formaldehyde solution (0.40 mol) and 43.2 g (0.40 mol) of *p*-cresol. The light yellow mixture was refluxed for 10 hr, cooled, and acidified to pH 7 with 6 *N* sulfuric acid. The small amount of precipitate formed was filtered, and the clear solution was evaporated under reduced pressure to give a tan residue. Continuous extraction of this material with ethanol, using a Soxhlet extractor, gave 27.1 g (30% yield) of the cream colored sodium salt of 5-methyl-2-hydroxy-α-toluenesulfonic acid.

The cyclization of the sodium salt to the sultone was accomplished with phosphorus oxychloride as described elsewhere.[3] Repeated crystallization from ethanol gave a white, crystalline solid (35% yield), mp 96.1–96.5° (lit.[15] mp 91.5°).

*Anal.* Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.38; S, 17.41. Found: C, 52.46; H, 4.26; S, 17.35.

**5-Methoxy-2-hydroxy-α-toluenesulfonic Acid Sultone, IXd.** The sodium salt of 5-methoxy-2-hydroxy-α-toluenesulfonic acid was obtained in 36% yield from the reaction of *p*-methoxyphenol, formaldehyde, and sodium sulfite. Cyclization of the sodium salt with phosphorus oxychloride gave (after repeated crystallizations from ethanol) a colorless, crystalline product (54% yield), mp 81.0–81.5°.

*Anal.* Calcd for $C_8H_8O_4S$: C, 47.99; H, 4.03; S, 16.02. Found: C, 47.90; H, 3.98; S, 16.00.

The infrared spectrum of IXd (KBr disk) showed weak bands at 3.50 and 7.72 μ; medium bands at 3.40, 6.21, 6.70, 7.92, 8.42, 8.75, 9.69, 10.8, 11.6, 13.3, and 14.5 μ; strong bands at 7.32, 8.20, 8.60, and 12.4 μ. The nmr spectrum ($CDCl_3$) showed a singlet (3 H) at δ 3.80, a singlet (2 H) at δ 4.46, and a multiplet (3 H) centered at δ 6.9.[16,17]

**5-Bromo-2-hydroxy-α-toluenesulfonic Acic Sultone, IXe.**[13] To a mixture of 5.00 g ($2.94 \times 10^{-2}$ mol) of 2-hydroxy-α-toluenesulfonic acid sultone and 0.30 g of iron fillings in 25 ml of chloroform was added, with magnetic stirring, 5.17 g ($3.23 \times 10^{-2}$ mol) of bromine dissolved in 10 ml of chloroform. The mixture was heated to moderate reflux, and white fumes could be seen evolving from the condenser head after 1 hr. Refluxing was continued for 26 hr, the volume of chloroform was reduced, the mixture cooled, and the tan, crystalline solid was filtered, washed, and vacuum dried. Crystallization from ethanol gave 3.98 g (54% yield) of white crystals, mp 148.0–149.0° (lit.[13] mp 147°).

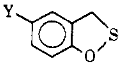
*Anal.* Calcd for $C_7H_5O_3SBr$: C, 33.75; H, 2.02; S, 12.87. Found: C, 33.69; H, 2.14; S, 12.80.

**Kinetic Methods.** The hydrolysis of VI as well as the various five-substituted derivatives was conducted in a thermostated cell at 25.0° maintained at a constant pH by means of an automatic titrator. A description of the equipment and exact experimental procedure used has already been given.[3]

## Results and Conclusions

In the hydrolysis of VI and its various 5-substituted derivatives, the hydroxide ion concentration was kept constant during the course of a given run by means of a titrator. Therefore, pseudo-first-order kinetics were observed in these hydrolyses. The second-order rate constants for hydroxide ion catalysis were determined by studying the dependency of pseudo-first-order rate constants on the hydroxide ion concentrations. The results obtained are summarized in Table I.

**Table I.** Second-Order Rate Constants for the Base-Catalyzed Hydrolysis of 5-Substituted 2-Hydroxy-α-toluenesulfonic Acid Sultones (IX–IXe)[a]

| Substituent, Y | Second-order rate constant for 5-substituted sultone,  $k_{OH} - Y$ ($M^{-1}$ sec$^{-1}$) | Log $k_{OH}-Y/k_{OH}-H$ | *para*-σ substituent constant,[b] $\sigma_p$ |
|---|---|---|---|
| H | 37.4 | 0.000 | 0.00 |
| $NH_2$ | 13.6 | −0.439 | −0.66 |
| $OCH_3$ | 21.3 | −0.244 | −0.27 |
| $CH_3$ | 24.0 | −0.193 | −0.17 |
| Br | 95.1 | 0.405 | 0.23 |
| $NO_2$ | $1.43 \times 10^3$ | 1.582 | 1.24[c] |

[a] At 25.0° and in 0.50 *M* $NaClO_4$, ionic strength 0.50. [b] C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 334 (1964). [c] $\sigma^-$ value. The fact that $\sigma^-$ must be used for the *p*-$NO_2$ substituent strongly suggests that considerable charge has developed on oxygen in the transition state for the solvolysis of the nitro-substituted sultone.

It is readily apparent from an inspection of the second column in Table I that substituents in the 5 position of the aromatic ring do have a profound effect on the rate constants for hydrolysis of five-membered cyclic sulfonates. Sultones possessing electron-withdrawing aromatic substituents like the nitro group show a substantial enhancement in the rate constant for hydrolysis, while sultones which have electron-donating aromatic substituents, like the methyl group, show a slight retardation. The rate constants for alkaline hydrolysis can be satisfactorily correlated by a quantitative relationship. A linear relationship exists between the logarithms of the alkaline rate constants for hydrolysis and either Hammett *para*-substituent constants, $\sigma_p$ (Figure 1), or the p$K_A$'s of the parent phenols. Figure

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(11) P. Müller, D. F. Mayers, O. R. Zaborsky, and E. T. Kaiser, *J. Amer. Chem. Soc.*, **91**, 6732 (1969).

(12) K. W. Lo and E. T. Kaiser, *Chem. Commun.*, 834 (1966).

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

(14) The authors wish to thank Dr. K. W. Lo for a sample of the 5-nitro- and 5-amino-2-hydroxy-α-toluenesulfonic acid sultone.

(15) E. A. Shearing and S. Smiles, *J. Chem. Soc.*, 1348 (1957).

(16) Only the spectral data for the heretofore unknown 5-methoxy derivative are given. All other compounds mentioned gave satisfactory analyses, and their infrared and nmr spectra were totally consistent with the assigned structures.

(17) The spectra were determined on the following instruments: Varian A-60 nuclear magnetic resonance spectrometer, Perkin-Elmer 137 infrared spectrophotometer, and a Beckman IR-5 infrared spectrophotometer. 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.

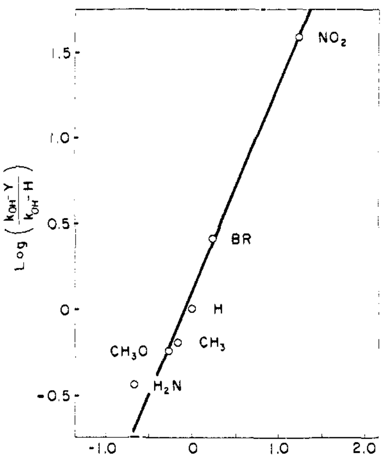
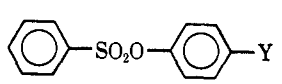


Figure 1. Dependence of log $k_{OH}$ $-$Y/$k_{OH}$ $-$H on *para-σ* substituent constant, $\sigma_p$, at 25.0° and ionic strength 0.50 ($NaClO_4$). Data from Table I.

1 gives the dependency of log $k_{OH} - Y/k_{OH} - H$ on the *para-σ* substituent constants and shows that a linear free-energy relationship indeed exists for the solvolyses of the five-membered cyclic sulfonates. The positive $\rho$ value of $+1.23$, of course, indicates that the rate constants for hydrolysis are increased by electron-withdrawing groups in the 5 position of the aromatic ring which are *para* to the incipient phenolic oxygen.[18]

The only derivative for which a deviation is observed from the linear relationship of Figure 1 is 2-hydroxy-5-amino-α-toluenesulfonic acid sultone. This deviation may be due to hydrogen bonding of the solvent to the amino group. Hydrogen bonding of the water protons to the nitrogen atom would reduce the electron density on the latter atom. This would decrease the extent of electron donation from the nitrogen into the aromatic ring and could therefore cause the observed hydrolysis rate constant for the amino derivative to be larger than that predicted from the amino $\sigma_p$ value.

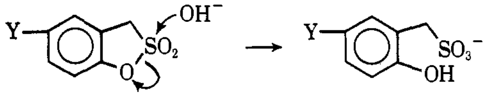
Substituent effects on the rate constants for the alkaline hydrolyses of phenolic benzenesulfonates (structure X) have been examined.[19] Although the experimental conditions used (70% dioxane–$H_2O$ at 50 and



X

70°) were quite different from those employed in our study, the effects of substituents on the rate constants were similar to those we found. The ratios of the second-order alkaline rate constants at 50° in 70% dioxane–$H_2O$ were 1.0:6.6:205 for the parent unsubstituted ester (Y = H, structure X), *p*-chloro (Y = Cl) and *p*-nitro (Y = $NO_2$) derivatives, respectively. From these limited data a $\rho$ value of $+1.8$ can be calculated, a value quite comparable to that we have found for our highly reactive cyclic sulfonates.

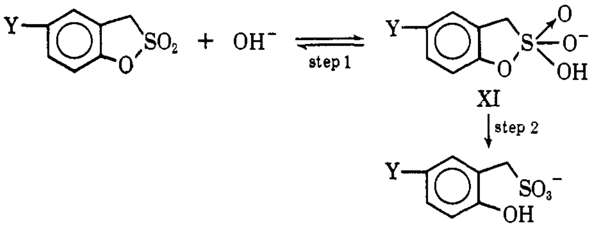
The evidence presently available to us is completely consistent with the postulation of the mechanism shown in eq 1 for the hydrolyses of the aromatic five-membered sultones, IX. This mechanism involves a concerted nucleophilic displacement reaction by hydroxide ion at sulfur. If this proposal is correct then the $\rho$ value we have found suggests that the sulfur–oxygen bond is significantly cleaved in the transition states for the hydrolyses of the sultones. In other words the



(1)

transition state must have considerable polar character.

As discussed by us earlier,[5] studies on the hydrolysis of 2-hydroxy-α-toluenesulfonic acid sultone in oxygen-18 enriched aqueous alkaline solutions show that during hydrolysis there is no detectable reversible formation of pentacovalent intermediates like XI in which the oxygens attached to sulfur and external to the ring have become equilibrated. However, we cannot rule out the possibility that pentacovalent intermediates are formed irreversibly in the sultone hydrolyses or that the oxygens external to the ring in structures such as XI do not equilibrate during the lifetimes of these intermediates. In the event that pentacovalent intermediates do lie along the pathway for the alkaline hydrolysis of sultones the interpretation of the $\rho$ value we have found becomes somewhat ambiguous. Nevertheless, it seems likely to us that the $\rho$ value for the first step in the hydrolysis mechanism given in eq 2 would not be large and that our observed $\rho$ value would reflect primarily the effects of substituents on the reaction of step 2 in which the pentacovalent intermediate undergoes ring opening to give the product sulfonic acid. According to this hypothesis, the transition state for the ring-opening reaction (step 2) would be quite polar.



(2)

Since no compelling evidence now exists which allows us to rule out the intermediacy of species like XI in the hydrolyses of the sultones (subject to the qualifications mentioned above), we cannot distinguish between the alternative interpretations we have offered for our observation of a sizeable positive $\rho$ value in these reactions. Our observations do suggest however that the transition state in at least one step in the hydrolyses of the five-membered cyclic sulfonates must be very polar.

**Acknowledgments.** The support of the Petroleum Research Fund of the American Chemical Society is gratefully acknowledged.

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[18] It has been pointed out by a referee that the $\rho$ value of $+1.23$ observed is smaller than that generally found for an elimination type reaction (usual values $+2$ to $+3.8$, see J. F. Bunnett, *Angew. Chem. Intern. Ed. Engl.*, **1**, 225 (1962)). This may be considered as additional evidence against a sulfene mechanism in the hydrolysis of the sultone.

[19] R. V. Vizgert, *Zh. Obshch. Khim.*, **28**, 1873 (1958); English Version, **28**, 1917 (1958).