Studies on the Hydrolysis of Esters of Sulfur-Containing Acids in Oxygen-18 Enriched Media

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Abstract: The hydrolyses of catechol cyclic sulfate (I), *o*-hydroxy-α-toluenesulfonic acid sultone (III), and β-*o*-hydroxyphenylethanesulfonic acid sultone (V) to give, respectively, catechol monosulfate anion (II), *o*-hydroxy-α-toluenesulfonate anion (IV), and β-*o*-hydroxyphenylethanesulfonate anion (VI) in oxygen-18 enriched aqueous alkaline solutions have been investigated. Recovery of the unchanged starting materials and analysis of their oxygen-18 content indicate that under the reaction conditions studied there is no significantin corporation of the label from the solvent. Apparently then, the reversible formation of pentacovalent intermediates in which the attacking hydroxide is bound to sulfur and the oxygens external to the ring have equilibrated does not occur to a detectable extent in these alkaline hydrolyses. Also, analysis of the oxygen-18 content of catechol isolated from the further hydrolysis of II in acidic medium provides evidence that no aryl–oxygen cleavage occurs in the alkaline hydrolysis of catechol cyclic sulfate.

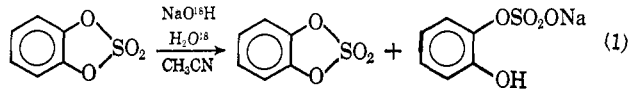
Several five-membered cyclic esters of sulfur- and phosphorus-containing acids have been shown to exhibit extraordinarily high rates of alkaline hydrolysis as compared to their acyclic and six-membered cyclic analogs.[2-9] For example, catechol cyclic sulfate, a five-membered cyclic sulfate, hydrolyzes in alkali with a rate enhancement of 2×10^7 relative to its open-chain analog, diphenyl sulfate. We have postulated[2] that nucleophilic attack at the aromatic carbon atoms in these aryl sulfates should be highly improbable and that the difference in the rates of hydrolysis should therefore represent the difference between the rates of attack of hydroxide ion at the respective sulfur atoms. A direct demonstration that aryl–oxygen cleavage does not occur in the alkaline hydrolysis of catechol cyclic sulfate was lacking, however. Also, we had not explored the possibility that during the solvolyses there might be reversible formation of pentacovalent intermediates in which the attacking hydroxide is covalently bound to sulfur. For these reasons we undertook an examination of the alkaline hydrolysis of catechol cyclic sulfate and several related compounds in oxygen-18 enriched solvent, and we report our results here.

Experimental Section

The preparation of the cyclic esters studied has already been described.[2-4] Reagent grade materials were used in all experiments. Oxygen-18 enriched water was purchased from Yeda Research and Development Co., Ltd., Rehovoth, Israel.

Hydrolysis of Catechol Cyclic Sulfate in Oxygen-18 Enriched Solvent. The following procedure was used to study the reaction shown in eq 1.

To 1.032 g (6.0×10^{-3} mol) of catechol cyclic sulfate (I) in a 100-ml, round-bottomed flask was added 24.0 ml of acetonitrile and 20.0 ml of a 0.10 *N* $NaO^{18}H$–H_2O^{18} solution (2.0×10^{-3} mol). The



I II (1)

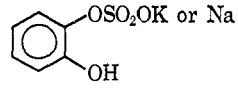
flask was stoppered, shaken vigorously, and allowed to stand at room temperature for 3 hr. No color change was observed throughout this time.

The clear, colorless *solution* (neutral pH) was transferred to a 125-ml separatory funnel, and the unreacted sulfate was extracted with a total of 100 ml of chloroform (in one 60- and two 20-ml portions). The combined chloroform solution was dried over $MgSO_4$ and filtered, the solvent evaporated at room temperature and reduced pressure, and the resulting white residue sublimed to give pure, colorless crystals of catechol cyclic sulfate. The amount of sulfate I recovered (before sublimation) was 530 mg (theoretical yield, 688 mg, based on the use of 20.0 ml of 0.10 *N* NaOH).

The water was evaporated from the aqueous solution, and it was collected and then purified by reevaporation in a two-trap system. The first trap was used to collect the residual $CHCl_3$ and some of the oxygen-18 enriched water. Then after the $CHCl_3$ had been removed (no more vigorous frothing and foaming), the other trap was quickly placed between the rotary evaporator and the pump trap, the system was evacuated up to the rotary evaporator, the water trap was placed in the liquid N_2, and finally the oxygen-18 enriched water was again collected. After most of the water had been removed, the trap was sealed off tightly at both ends by clamps which were on the rubber tubing and was removed from the system. The ice was quickly melted and brought to room temperature by holding the closed trap momentarily in steam, and after it had come to room temperature the water was transferred rapidly to a vial at which time it was sealed promptly.

When the water was removed from the aqueous solution as described above a white residue (II) remained. It was vacuum dried at room temperature for 8 hr and extracted with absolute ethanol. The total weight of the residue after extraction was 420 mg (theoretical yield, 424 mg, based on the use of 20.0 ml of 0.10 *N* NaOH).[10]

Degradation of the Sodium Salt of the Monosulfate II. Neither the Na salt nor the K salt of the half-ester



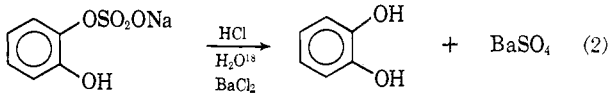
(1) Predoctoral Fellow of the National Institutes of Health.
(2) E. T. Kaiser, I. R. Katz, and T. F. Wulfers, *J. Amer. Chem. Soc.*, **87**, 3781 (1965).
(3) O. R. Zaborsky and E. T. Kaiser, *ibid.*, **88**, 3084 (1966).
(4) E. T. Kaiser, K. Kudo, and O. R. Zaborsky, *ibid.*, **89**, 1393 (1967).
(5) E. T. Kaiser and K. Kudo, *ibid.*, **89**, 6725 (1967).
(6) J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *ibid.*, **78**, 4858 (1956).
(7) J. R. Cox, Jr., R. E. Wall, and F. H. Westheimer, *Chem. Ind.* (London), 929 (1959).
(8) P. C. Haake and F. H. Westheimer, *J. Amer. Chem. Soc.*, **83**, 1102 (1961).
(9) A. Eberhard and F. H. Westheimer, *ibid.*, **87**, 253 (1965).

(10) The potassium salt corresponding to II was prepared by an independent method according to S. Yamaguchi, *Nippon Kagaka Zasshi*, **80**, 171 (1959); *Chem. Abstr.*, **54**, 24687*a* (1960); **55**, 5396*a* (1961). Studies in our laboratory by Dr. T. F. Wulfers have demonstrated that catechol cyclic sulfate (I) is hydrolyzed to the sodium salt of the monosulfate II in sodium hydroxide solution; see T. F. Wulfers, Ph.D. Thesis, University of Chicago, 1965, p 19; and ref 2.

was hydrolyzed further to catechol and inorganic sulfate by sodium hydroxide solutions. The normality of the hydroxide solutions was varied from 0.1 to 5.0 N, all samples being heated at 90° for 12 hr.

In contrast, however, the hydrolysis of the half-ester was accomplished readily with 1.0 N HCl solution and elevated temperatures.

The following degradative studies were designed to provide enough catechol to allow facile purification of this material for the determination of its oxygen-18 content. In all degradative experiments $BaCl_2$ was added initially to precipitate the inorganic sulfate as it was formed.

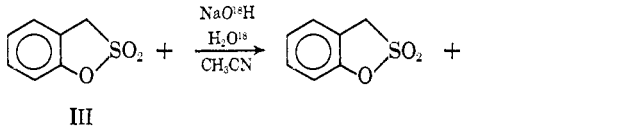


II

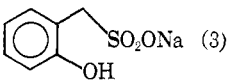
The following procedure was used. To the appropriate amount of the sodium or the potassium salt of the monosulfate (96.4 and 104 mg, respectively) in a 15-ml centrifuge tube was added 150 mg of $BaCl_2 \cdot 2H_2O$ (theoretical weight required = 111 mg) and 4.0 ml of 0.96 N HCl–H_2O^{18}. Both the Na or K salts dissolved readily giving clear, colorless solutions with no precipitation occurring at room temperature. A reflux condenser was attached to the centrifuge tube, and the tube was heated at 90° in an oil bath for 6 hr. Precipitation of $BaSO_4$ started almost immediately upon placing the sample into the oil bath. At the end of 6 hr, the $BaSO_4$ was white, but the solution had a slight pink color. The sample was removed from the bath, allowed to cool to room temperature, and worked up in the following manner.

The precipitated $BaSO_4$ was removed from the clear, pink solution by filtration, and the aqueous solution was extracted with a total of 30 ml of chloroform (three 10-ml portions). The combined chloroform extract was dried over $MgSO_4$ and filtered, the solvent was evaporated at room temperature, and the residue was sublimed twice giving pure, white crystalline catechol, mp 103.9–105.9°. In the case of the sodium salt of the monosulfate, 28.3 mg of catechol was isolated, and from the potassium salt 26.2 mg of catechol was recovered (theoretical yield of catechol = 50 mg). In our product-isolation work, the purity of the materials obtained was of utmost concern to us rather than the quantity recovered.

Hydrolysis of *o*-Hydroxy-α-toluenesulfonic Acid Sultone in Oxygen-18 Enriched Solvent. The procedure for the isolation of the cyclic ester III from the reaction shown in eq 3 is given below.



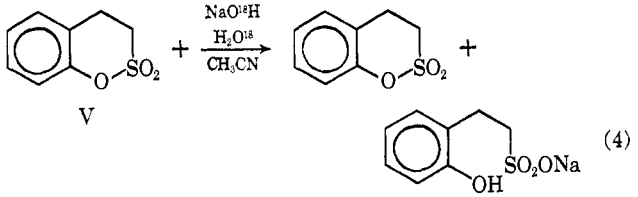
III



IV

To 340 mg (2×10^{-3} mol) of *o*-hydroxy-α-toluenesulfonic acid sultone (III) in a 25-ml erlenmeyer flask was added 6.0 ml of acetonitrile (minimum amount of organic solvent to give a homogeneous solution) and 10.0 ml of a 0.10 N $NaO^{18}H$–H_2O^{18} solution (1×10^{-3} mol). The flask was stoppered and shaken vigorously. After the base had been added, the momentarily cloudy but *colorless* mixture turned into a clear, bright yellow *solution*. This coloration decreased in intensity after *ca.* 3–4 min, but, even after 1 hr, never completely disappeared. The solution was allowed to stand at room temperature for 1 hr, then was transferred to a 60-ml separatory funnel, and the unreacted sultone was extracted with a total of 40 ml of chloroform (in one 20-ml and two 10-ml portions). The colorless chloroform solution was dried over $MgSO_4$ and filtered, the solvent evaporated at room temperature and reduced pressure, and the white residue crystallized from ether–petroleum ether (bp 30–60°). The amount of sultone recovered (before crystallization) was 169 mg (theoretical yield, 170 mg, based on 10.0 ml of 0.100 N NaOH). The melting point of the crystallized sultone was 85.5–86.8° (lit.[3] mp 86.1–87.1°).

Hydrolysis of β-*o*-Hydroxyphenylethanesulfonic Acid Sultone in Oxygen-18 Enriched Solvent. The six-membered cyclic ester, β-*o*-hydroxyphenylethanesulfonic acid (V), was prepared by Dr. K. Kudo and was recrystallized twice from ether–petroleum ether (bp 30–60°) before use (mp 110.2–111.8°). The procedure for the hydrolysis of V in the oxygen-18 enriched solvent was similar to that used for the five-membered sultone III.



V VI

To 294 mg (1.6×10^{-3} mol) of the sultone V in a 25-ml erlenmeyer flask was added 8.0 ml of acetonitrile and 8.0 ml of a 0.10 N $NaO^{18}H$–H_2O^{18} solution. Upon the addition of the base no color change was observed, and the solution remained colorless while it stood at room temperature for 17 hr. At the end of the reaction period the unreacted sultone was extracted using a total of 40 ml of chloroform (one 20-ml and two 10-ml portions). After the chloroform solution was dried and the solvent was removed by evaporation, the residue was recrystallized from ether–petroleum ether (bp 30–60°) to give material melting at 112.5–113°. From the amount of the crude sultone isolated, it could be estimated that the reaction had gone to approximately 44% completion.

Analysis of Carbon Dioxide Formed from Reaction Products. Carbon dioxide was formed from compounds I, III, V, and from catechol and water by heating samples of these materials with a mixture of mercuric cyanide and mercuric chloride in a break-seal tube at 400°.[11] Typically 40 mg of a mixture consisting of equal weight portions of mercuric cyanide and mercuric chloride (commercial material, mixed and vacuum dried at room temperature for 10 hr) was treated with 5–20 mg of the oxygen-containing compound to be analyzed. The equipment used to isolate the carbon dioxide formed in the break-seal tubes has been described elsewhere.[11b,d] The ratio of the masses 46 ($CO^{16}O^{18}$) to 44 ($CO^{16}O^{16}$) was obtained using a Consolidated Engineering Corp. mass spectrometer, Type 21-620, set at an ionizing current of 20 μA and the appropriate voltage needed to observe CO_2.

Results and Discussion

The results observed for the hydrolyses of the cyclic esters I, III, and V in oxygen-18 enriched solutions are summarized in Table I. In order to allow for the facile recovery of significant amounts of the unhydrolyzed esters, initial conditions were chosen so that the concentrations of the esters employed exceeded those of the hydroxide present. Earlier experiments in our laboratory showed that the hydrolyses of the cyclic esters are not rapid in the absence of alkali. Thus, as soon as the hydroxide originally present in a reaction mixture was consumed by the formation of the product, further reaction of the cyclic ester became slow, and the excess ester remaining could be isolated.

From Table I it can be seen that under the conditions employed *the hydrolyses of catechol cyclic sulfate (I), o-hydroxy-α-toluenesulfonic acid sultone (III), and β-o-hydroxyphenylethanesulfonic acid sultone (V) were not accompanied by any significant exchange into the starting esters.* Our results show that in the hydrolysis reactions there is no detectable reversible formation of pentacovalent intermediates such as VII in which the oxygens attached to sulfur and external to the ring have become equilibrated. Of course, the data do not rule out the possibility that pentacovalent intermediates are formed irreversibly. Alternatively, pentacovalent

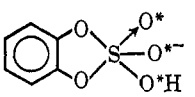
(11) (a) M. Anbar and S. Guttmann, *Int. J. Appl. Radiat. Isotopes*, **5**, 233 (1959); (b) F. R. Williams and L. P. Hager, *Science*, **128**, 1434 (1958); (c) E. T. Kaiser, M. Panar, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 602 (1963); (d) E. T. Kaiser, Ph.D. Thesis, Harvard University, 1959, pp 82–83.

Table I. Reactions of Esters of Sulfur-Containing Acids in Oxygen-18 Enriched Media[a]

Ester	Exptl conditions (initial)[b]	Excess O^{18} in in H_2O, %	Excess O^{18} in recovered ester, %	Atom of O^{18} introduced in recovered ester	Excess O^{18} in hydrolysis product, %	Atom of O^{18} introduced in product
Catechol cyclic sulfate	0.136 *M* ester + 0.045 *M* NaOH	1.325 1.362	0.004 0.007	0.00 0.01		
o-Hydroxy-α-toluene-sulfonic acid sultone	0.125 *M* ester + 0.0625 *M* NaOH	1.421 1.353 1.375	−0.003 −0.003	0.00 0.00		
β-*o*-Hydroxyphenylethane-sulfonic acid sultone	0.100 *M* ester + 0.05 *M* NaOH	1.401 1.395	−0.001 0.001	0.00 0.00		
Potassium catechol monosulfate	0.114 *M* ester + 0.96 *M* HCl	1.255			0.005[c,d]	0.00[c,d]
Sodium catechol monosulfate	0.114 *M* ester + 0.96 *M* HCl	1.325 1.362			0.013[d,e] 0.009[d,e]	0.02[d,e] 0.01[d,e]

[a] Reactions were carried out at room temperature. [b] Except for those cases for which solution pH values are listed, the pH values of reaction mixtures were not kept constant. When an excess of the ester was employed in the alkaline hydrolyses this was done in order to conveniently recover some unreacted ester at the conclusion of the reaction. [c] This experiment was carried out on catechol monosulfate prepared by the method of Yamaguchi (see ref 10). [d] The product of the acidic hydrolysis reaction for which the extent of oxygen-18 incorporation was measured was catechol. [e] These experiments were carried out using the catechol monosulfate samples isolated from the hydrolyses of catechol cyclic sulfate in oxygen-18 enriched alkaline solutions.

intermediates might be reversibly formed in the hydrolyses of I, III, and V, and the oxygens external to the ring might not equilibrate during the lifetimes of



VII

* represents one-third of the oxygen-18 label

these intermediates. In any event, with the data now in hand, there is certainly no compelling evidence to support the postulation of pentacovalent intermediates in the hydrolyses of the cyclic esters.[12]

(12) As noted in a recent paper by Bordwell, *et al.*, there appears to be no evidence in the literature for the addition of nucleophiles such as hydroxide or alkoxide to the S=O bonds of compounds like our sulfate and sulfonate esters. These workers have postulated, however, that the methoxide ion promoted decomposition of some episulfones may involve the addition of the alkoxide to the S=O bond of the sulfone group: F. G. Bordwell, J. M. Williams, Jr., E. B. Hoyt, Jr., and B. B. Jarvis, *J. Amer. Chem. Soc.*, **90**, 429 (1968).

Finally, we had assumed in our earlier kinetic work[2-4] that the cyclic esters I, III, and V undergo S–O bond cleavage when they are hydrolyzed in alkali. We have tested this assumption now by taking catechol monosulfate (II) isolated from the hydrolysis of the cyclic sulfate in an oxygen-18 enriched medium (initially alkaline) and then hydrolyzing the monosulfate further to catechol in an acidic oxygen-18 enriched solution. Measurements on the oxygen-18 enrichment of the catechol obtained indicated that maximally 0.02 atom of oxygen from the solvent was introduced into the phenolic hydroxyl group of catechol monosulfate from the hydrolysis of the cyclic ester I. Thus, our assumption that hydroxide attacks at sulfur in the hydrolysis of I is confirmed by the experimental evidence.

Acknowledgment. The support of the National Science Foundation is gratefully acknowledged.