was allowed to remain at 26° for 1.8 hours during which time the solution turned green. The ultraviolet absorption (λ_{max} 227 and 266 mμ, ε 31000 and 10000) indicated a *ca.* 50% conversion to VII. The chloroform was removed at reduced pressure and the tanish yellow residue was dissolved in 4 ml. of carbon tetrachloride and adsorbed on 100 g. of alumina ("almost neutral"). Elution with a 1/1 mixture of ether and carbon tetrachloride afforded very little material. This was followed by elution with pure ether in 7-ml. fractions. This removed 474 mg. of crude VII with a weight distribution among 15 fractions. Four of these fractions (291 mg.) under the principal part of the elution band were combined and rechromatographed on 20 g. of alumina ("almost neutral") in a similar fashion. The three fractions under the principal part of the elution band from the second chromatogram yielded crystalline material when cooled to −10° in acetone–methanol. The product melting at 98–100° weighed 119 mg. (10%). Recrystallization from acetone–methanol readily gave **5,7,9,14-anthrastatetraen-17β-ol benzoate (VII)** as colorless needles, m.p. 103–105°; λ_{max} 227, 266, 296 and 308 mμ (ε 39300, 19000, 2500 and 2100); λ_{min} 245 mμ (ε 9300), λ_{max} 12.33 μ.

Anal. Calcd. for $C_{26}H_{28}O_2$ (372.48): C, 83.83; H, 7.58. Found: C, 84.03; H, 7.77.

The alcohol VIII was obtained by hydrolysis of the benzoate VII in 5% ethanolic potassium hydroxide (30 min. at reflux). From ethanol–water it formed colorless needles, m.p. 136–138°; λ_{max} 221, 227, 266, 297 and 308 mμ (ε 24400, 25600, 17200, 2500 and 2100); λ_{min} 242 mμ (ε 5150), λ_{infl} 233 mμ (ε 16600), λ_{max} 12.30 μ.

Anal. Calcd. for $C_{19}H_{24}O$ (268.4): C, 85.03; H, 9.01. Found: C, 84.91; H, 9.27.

Acknowledgment.—We wish to thank the Schering Corporation for a generous gift of dehydroepiandrosterone acetate.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENTS OF BIOCHEMISTRY AND OF OBSTETRICS AND GYNECOLOGY, COLUMBIA UNIVERSITY, COLLEGE OF PHYSICIANS AND SURGEONS]

Kinetics and Mechanism of Solvolysis of Steroid Hydrogen Sulfates[1]

BY SHLOMO BURSTEIN AND SEYMOUR LIEBERMAN

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A kinetic study of the solvolysis of steroid hydrogen sulfates in homogeneous phase in various organic solvents has been presented. The solvolysis was found to proceed by first-order kinetics in a variety of organic solvents of low polarity and was especially fast in ethers. The effect of acid concentration and of steroid sulfate structure has been studied. Activation energies have been determined for several media. Based on the results of these studies, a mechanism has been suggested which is consistent with the observation that increasing the polarity of the medium greatly retards the rate. A transition state complex which involves the undissociated hydrogen sulfate or the dipolar ion $ROSO_3^{\oplus}{}_{H}^{\ominus}$ has been proposed.

Introduction

This paper presents a kinetic study of the solvolysis of steroid hydrogen sulfates in organic solvents in the homogeneous phase. Unlike *most* solvolytic reactions in organic media which are accelerated by increasing the polarity of the environment, the type of solvolysis described in this paper is unusual in that it is greatly retarded by polar media.

The hydrolysis of alkyl hydrogen sulfates has been the subject of numerous studies because of their industrial and biological importance. The relative stability of the simple alkyl hydrogen sulfates toward dilute aqueous alkali and acid is well known.[2,3] In acid solution, prolonged boiling is sometimes necessary to achieve complete hydrolysis and even more drastic conditions are required in alkaline media.[4] Because of the drastic conditions employed, several products in addition to the alcohol are formed and therefore a study of the mechanism of the hydrolysis of alkyl hydrogen sulfates has been difficult. Stereochemical evidence has been presented which indicates that the alkyl hydrogen sulfates are hydrolyzed by a fission of the S–O bond. Sulfates of asymmetric alcohols are hydrolyzed[4,5] without inversion and thus an attack on the central sulfur atom seems possible.

Since steroidal metabolites, as well as many other classes of substances, are excreted in the urine as sulfates, mild methods of hydrolysis which do not result in side reactions (dehydration, rearrangement, displacement, etc.) are desirable. One such method which has found wide use involves the continuous extraction with ether of appropriately acidified solutions of the sulfates kept at room temperature. With this method, a quantitative hydrolysis of C_{19}-ketosteroid sulfates[5,6] has been achieved. In another study[7] on the mechanism of hydrolysis by the continuous ether method it has been demonstrated that this hydrolysis occurs not in the aqueous phase but in the *ether phase*, and is thus related to the procedures of Grant and Beall[8] and Cohen and Oneson[9] who found that steroid sulfates can be quantitatively hydrolyzed in dioxane. The extreme ease with which this reaction occurs in dioxane or ether as compared to hydrolysis in

(1) Supported by a research grant (No. PHS A-1083) from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, Department of Health, Education and Welfare.

(2) C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 1-94.

(3) For kinetic data in aqueous acid see, for example: G. A. Linhart, *Am. J. Sci.*, **184**, 289 (1912); P. N. Evans and J. M. Albertson, THIS JOURNAL, **39**, 456 (1917); K. H. Bauer and W. Poethke, *J. prakt. Chem.*, [2] **126**, 296 (1930).

(4) R. L. Burwell, THIS JOURNAL, **74**, 1462 (1952); G. M. Calhoun and R. L. Burwell, *ibid.*, **77**, 6441 (1955); G. H. Green and J. Kenyon, *J. Chem. Soc.*, 1389 (1950).

(5) S. Lieberman, L. B. Hariton and D. K. Fukushima, THIS JOURNAL, **70**, 1427 (1948).

(6) S. Lieberman and K. Dobriner, *Recent Prog. in Hormone Res.*, **3**, 71 (1948); S. Lieberman, B. Mond and E. Smyles, *ibid.*, **9**, 113 (1954).

(7) S. Burstein and S. Lieberman, *J. Biol. Chem.*, **233**, 331 (1958).

(8) G. A. Grant and D. Beall, *Recent Prog. Hormone Res.*, **5**, 307 (1950).

(9) S. L. Cohen and I. B. Oneson, *J. Biol. Chem.*, **204**, 215 (1953).

aqueous media has stimulated us to undertake a more thorough study of this reaction. It has been found that this reaction represents a solvolysis of the *hydrogen sulfate* in the organic medium. Although the reaction is very fast in ethers it also proceeds rapidly in a variety of other non-polar organic solvents. Based on the kinetic data presented and a study with H_2O^{18} a probable mechanism is proposed.[10]

Experimental

Compounds.—The potassium salts of the sulfates of dehydroisoandrosterone, isoandrosterone and androsterone were prepared by treating pyridine solutions of the steroid alcohols with sulfur trioxide in pyridine according to Fieser.[11]

Anal. Calcd. for $C_{19}H_{27}O_5SK$ (potassium dehydroisoandrosterone sulfate, m.p. 219–223°): K, 9.61. Found: K, 9.02. Calcd. for $C_{19}H_{29}O_5SK$ (potassium isoandrosterone sulfate, m.p. 223–223.5°): K, 9.55. Found: K, 9.52. Potassium androsterone sulfate, m.p. 184–185°. Found: K, 9.25.[12]

Sodium cortisone sulfate and disodium hydrocortisone phosphate were made available to us by Drs. E. Chamberlain and L. H. Sarett of the Merck, Sharpe & Dohme Co.

Solvents.—All solvents were analytical reagent grade and were distilled before use without further purification with the exception of the ethers. Ethyl ether was distilled over potassium hydroxide before use. Tetrahydrofuran and dioxane were distilled twice over potassium hydroxide and were peroxide-free (tested with titanic sulfate). The other ethers used were made peroxide-free by shaking with ferrous sulfate solution, drying over calcium chloride and distilling over potassium hydroxide.

Kinetic Measurements.—Ethyl acetate extracts of the steroid hydrogen sulfates, obtained by extracting a solution or suspension of the potassium steroid sulfates in 2 *N* sulfuric acid, were used for the kinetic measurements of the solvolysis. Because of the limited solubility of the potassium salts in water, suspensions were used so that concentrated solutions of the hydrogen sulfate could be obtained. Such ethyl acetate extracts contain the *steroid hydrogen sulfate* and only traces of potassium.[13] The ethyl acetate extracts are stable for *ca.* 20 minutes at 26.0° and were always prepared just before use. In most runs the ethyl acetate extract was added to the organic solvent under study within 2 minutes after extraction. Time of mixing was *ca.* 10 seconds. (Attempts to isolate the steroid hydrogen sulfate in pure form were unsuccessful.) The final concentration of mineral acid in all runs (unless otherwise stated) was determined by titration to be 10^{-4} *M*.

The solvolysis rate was determined by following the appearance of the free steroid. The separation of the C_{19}-steroid sulfates from liberated steroids was carried out by a method previously described.[7] The concentration of the free steroid was determined colorimetrically by a modification of the Zimmermann method[14] which is based upon the color produced when 17-ketosteroids are treated with an alcoholic solution of *m*-dinitrobenzene and alkali. The absorbance was measured with the Coleman junior spectrophotometer. Since the steroid hydrogen sulfate gives in the Zimmermann reaction a color of equal intensity to that given by the steroid alcohol (on a molecular basis), the initial concentration of the steroid hydrogen sulfate was determined on an aliquot withdrawn from the reaction mixture. A few drops of pyridine were added to the aliquot to prevent loss in the Zimmermann titer due to decomposition of the steroid hydrogen sulfate which occurs upon evaporation to dryness. With water-miscible solvents, extraction of the "frozen" reaction aliquot with benzene results in a volume error and therefore a correction was introduced in the following manner. A known amount of the free steroid was partitioned under precisely the same conditions and a factor was obtained which related the amount present to the amount found after partition. With this correction factor the effective, initial concentration of the sulfate could be calculated. That this method was correct was established in numerous runs by determining the final amounts of free steroid when the reaction was allowed to proceed to completion.

The rate constants were calculated from the slope of the curve of $\log (a - x)$ *vs.* time. The specific rates agreed within ±8%. The activation energies E^* were calculated from the rates at two different temperatures and corresponded within ±5%. The entropies of activation were calculated from the absolute rate equation.[15]

Typical Run of Solvolysis of Dehydroisoandrosterone Hydrogen Sulfate.—Potassium dehydroisoandrosterone sulfate (16.0 mg.) was suspended in 1.5 ml. of 2 *N* sulfuric acid and extracted with 4.5 ml. of ethyl acetate. The ethyl acetate layer was filtered through glass wool to free the extract of adhering aqueous droplets; 3 ml. of the ethyl acetate extract was added to 47 ml. of a mixture of isopropyl ether and ethanol (10% by weight) and mixed thoroughly. Two-ml. aliquots of the reaction mixture were withdrawn at the time intervals indicated in Table I and plunged into glass-stoppered tubes containing 8 ml. of ice-cold 1% sodium bicarbonate solution and 4 ml. of benzene. The mixtures were shaken immediately. The organic layers were filtered through filter paper and the concentration of dehydroisoandrosterone determined on 3-ml. aliquots following evaporation to dryness. An estimate of the initial sulfate concentration (a) by the Zimmermann reaction gave an absorbance of 0.81. Since no volume error occurred with this solvent mixture, a = 0.81. The results obtained are listed in Table I and are plotted in Fig. 1B.

TABLE I

RATE OF SOLVOLYSIS OF DEHYDROISOANDROSTERONE HYDROGEN SULFATE IN ISOPROPYL ETHER–ETHANOL (10% BY WEIGHT) (a = 0.81)

Time, min.	X^a	Time, min.	X^a	Time, min.	X^a
1	0.04	7	0.18	18	0.37
2	.06	9	.23	22	.43
3	.09	11	.26	26	.49
4	.11	13	.30	40	.63
5	.15	15	.35	50	.68

[a] Absorbance of liberated steroid alcohol determined by the Zimmermann color reaction.

Rate of Solvolysis of Cortisone Hydrogen Sulfate.—Because of the low partition coefficient of cortisone hydrogen sulfate between ethyl acetate and acidic solutions, the solvolysis of this compound was studied only in tetrahydrofuran, a solvent which quantitatively extracts this sulfate from a 20% sodium chloride solution acidified to *p*H 1. Again the rate of hydrolysis was followed by measuring the appearance of the free steroid; separation of the free steroid from the sulfate was achieved by partitioning an aliquot of the reaction mixture between ethyl acetate and 1% sodium bicarbonate solution, the free steroid being extracted quantitatively by the ethyl acetate. The liberated steroid was measured in methanol at 239 mμ with the Beckman DU spectrophotometer following evaporation of appropriate aliquots of the ethyl acetate phase. The initial concentration was determined by diluting the reaction mixture with methanol and measuring at 239 mμ. Appropriate blanks were used throughout.

Solvolysis of Hydrocortisone Dihydrogen Phosphate.—Since the extraction properties of hydrocortisone dihydrogen phosphate are very similar to those of cortisone hydrogen sulfate the same method was used to study the solvolysis of this phosphate. Conditions under which cortisone hydrogen sulfate hydrolyzed completely in about 3 hours produced no solvolysis of the phosphate even after 17 hours.

Solvolysis in the Presence of H_2O^{18}.—The potassium salts

(10) While this report was in typescript, a paper by J. McKenna and J. K. Norymberski, *J. Chem. Soc.*, 3889 (1957), appeared in which a study of the solvolysis of the Na, K and pyridinium salts in a non-homogeneous phase of some sulfated cholesterol derivatives was reported.

(11) L. F. Fieser, THIS JOURNAL, **70**, 3232 (1948).

(12) The analyses were done by Mr. J. Alicino, Metuchen, N. J.

(13) Potassium was determined by flame photometry by Miss Cecile Weiss.

(14) A. F. Holtorff and F. C. Koch, *J. Biol. Chem.*, **135**, 377 (1940).

(15) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processses," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.

of the sulfates of dehydroisoandrosterone and isoandrosterone (40 mg.) each were suspended in 1.5 ml. of H_2O^{18} (containing 1.4 atom per cent. excess of O^{18}) containing 1.5 moles/l. of hydrogen chloride and extracted with 4.5 ml. of anhydrous ethyl acetate. To this solution 100 ml. of anhydrous ether was added and then the mixture was kept at room temperature for 24 hours. The ether now was washed with alkali and water and the free steroid isolated. The semicarbazones of these products were prepared[16] to remove O^{18} that may have been introduced into the carbonyl oxygen at C_{17}. These derivatives (dehydroisoandrosterone semicarbazone, m.p. 254–257°; isoandrosterone semicarbazone, m.p. 271–273°) were analyzed for O^{18}.[17] No excess O^{18} was found in the dehydroisoandrosterone and an insignificant amount (0.008%) was found in the isoandrosterone.

Results

As described above, the rates of solvolysis were determined by following only the appearance of the liberated steroid.[18] In most cases the kinetics were strict first order up to about 70% reaction. A few examples are given in Fig. 1. The deviation from linearity above 70% reaction was not further investigated and the rates given were obtained from the linear portion of the curves. In all runs dehydroisoandrosterone was isolated and its identity established by infrared spectrophotometry. Products other than the steroid alcohols were not detected by chromatographic and infrared analysis.

The rate of solvolysis of dehydroisoandrosterone hydrogen sulfate under various conditions is given in Table II. Because of solubility difficulties, runs in benzene, cyclohexane, $CHCl_3$ and furan could be carried out only by adding ethanol; otherwise a non-homogeneous system results with most of the steroid sulfate in the aqueous phase. Table II also lists the energies and entropies of activation.

The effect of hydrogen ion concentration on the solvolysis rates of dehydroisoandrosterone hydrogen sulfate in tetrahydrofuran–10% EtOH is given in Fig. 2.

Table III presents the effect of structure of the sulfate upon rates of solvolysis.

Discussion

A. Rate of Solvolysis as a Function of the Nature of the Solvent.—Table II shows that the nature of the solvent has a determining effect upon the rate of solvolysis. The rate is strongly influenced by the ionizing power of the solvent; the less polar the medium, the faster the rate. Thus, in water acidified to 2 *N* with sulfuric or hydrochloric acid, no reaction occurred at room temperature even when left for as long as 9 days.[7] Indeed the sulfate which hydrolyzed fastest, cortisone hydrogen sulfate (see Table III), when left in water made *p*H 1 for 24 hours remained unchanged. The stability of dehydroisoandrosterone hydrogen sulfate in methyl sulfide is probably due to the formation of a salt,[19] and this ionized species apparently resists solvolysis. As the polarity of the medium is decreased there is an acceleration in rate (compare 3 with 6, 9, 10, 13 in Table II). Approximately a 16-fold increase in rate occurred by changing from ethanol to benzene–10% ethanol (3 *vs.* 6). It is noteworthy that only about a 2.5-fold increase over ethanol was found when $CHCl_3$–10%

TABLE II

RATES OF SOLVOLYSIS OF DEHYDROISOANDROSTERONE HYDROGEN SULFATE UNDER VARIOUS CONDITIONS[a]

No.	Temp., °C.	Solvent	k, sec.$^{-1}$	E^*, kcal./mole	ΔS^*, e.u.
1	27-30	H_2O (0.1 *M* or 2.0 *M* H^+)	Immeasurably slow		
2	27.0	CH_3SCH_3			
3	26.0	EtOH	3.2×10^{-5}[b]		
4	35.0	EtOH	2.1×10^{-5}		
5	55.5	EtOH	4.0×10^{-4}	29	+11
6	26.0	Benzene, 10% EtOH	5.1×10^{-5}		
7	29.5	Benzene, 10% EtOH	1.0×10^{-4}		
8	50.0	Benzene, 10% EtOH	2.7×10^{-3}	31	+24
9	26.0	Cyclohexane, 10% EtOH	3.5×10^{-5}		
10	27.0	$CHCl_3$, 0.75% EtOH	2.7×10^{-5}		
11	26.5	$CHCl_3$, 10% EtOH	$\sim 8 \times 10^{-6}$		
12	26.0	CH_2Cl_2	1.2×10^{-4}		
13	28.0	CH_2Cl_2, 10% EtOH	3.5×10^{-5}		
14	26.0	EtOAc	1.2×10^{-4}		
15	1.0	Acetone	3.0×10^{-5}		
16	26.0	Acetone	1.5×10^{-3}		
17	29.5	Acetone	2.5×10^{-3}	26	+12
18	26.0	Methyl ethyl ketone	1.6×10^{-3}		
19	25.0	Cyclohexanone	1.1×10^{-6}		
20	26.0	Cyclopentanone	1.1×10^{-3}		
21	27.0	Ethyl ether	2.1×10^{-3}		
22	28.0	Ethyl ether, 10% EtOH	2.6×10^{-3}		
23	26.0	Ethyl ether satd. with H_2O	4.3×10^{-5}		
24	26.0		4.1×10^{-5}[c]		
25	26.0	Isopropyl ether, 10% EtOH	5.9×10^{-4}		
26	26.0	*n*-Butyl ether, 10% EtOH	5.6×10^{-4}		
27	29.0	Tetrahydrofuran	$\sim 7 \times 10^{-2}$		
28	1.0	Tetrahydrofuran, 10% EtOH	3.9×10^{-4}		
29	25.0		1.1×10^{-2}	23	+13
30	27.0	Dioxane, 10% EtOH	7.0×10^{-3}		
31	26.0	Anisole	1.7×10^{-4}		
32	27.0	Furan, 4% EtOH	5.7×10^{-5}		
33	26.0	Tetrahydrofuran, 3% H_2O	3.4×10^{-4}[b]		
34	31.0	Tetrahydrofuran, 3% H_2O	8.4×10^{-4}		
35	42.0	Tetrahydrofuran, 3% H_2O	4.7×10^{-3}	30	+23
36	26.0	Tetrahydrofuran, 6% H_2O	1.7×10^{-5}[b]		
37	40.0	Tetrahydrofuran, 6% H_2O	3.1×10^{-4}		
38	53.0	Tetrahydrofuran, 6% H_2O	3.7×10^{-3}	39	+46
39	26.0	Tetrahydrofuran,	5.9×10^{-5}		
40	40.0	6% H_2O +	6.0×10^{-4}		
41	52.5	0.07 *M* H^+	2.8×10^{-3}	25[d]	+ 4
42	24.0	Methyl Cellosolve	2.0×10^{-4}		

[a] Unless otherwise indicated, all runs contained 6% (by volume) ethyl acetate, *ca.* 0.1 *M* water (determined by Karl Fischer titration) and *ca.* 10^{-4} *M* sulfuric acid. The water concentration in the tetrahydrofuran runs 27–29 was *ca.* 0.27 *M*. In runs 39–41 the specified concentration of *p*-toluenesulfonic acid was added. The initial concentration of steroid sulfate ranged between 0.32×10^{-5} *M* and 0.55×10^{-3} *M*. All percentages are by weight with the exception of runs 10, 11, 13 and 32 which were expressed by volume. In runs 10, 12 and 21 a slight cloudiness was present after mixing the ethyl acetate extract of the hydrogen sulfate with the solvent. The presence of an aqueous phase may have slowed these reactions. [b] These slow rates were not experimentally measured but were calculated for the specified temperature from the activation energy and were included for comparison. [c] In this run the ethyl acetate concentration was 0.6% and steroid sulfate concentration was 0.05×10^{-3} *M*. [d] This value was obtained from runs 40 and 41. The *calculated* value for 26° was 8.9×10^{-5}.

(16) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p. 85.

(17) We wish to thank Miss Laura Pontecorvo for carrying out these analyses according to the method of D. Rittenberg and L. Pontecorvo, *J. Appl. Radiation & Isotopes*, **1**, 208 (1956).

(18) In runs 3–11 and 13 (Table I) no immediate $BaSO_4$ precipitation was observed upon the addition of $BaCl_2$ at the end of the reaction and it is reasonable to assume that ethanolysis occurred in these experiments similarly to the methanolysis which occurred when chondroitin sulfate was treated with methanolic hydrogen chloride; see T. G. Kantor and M. Schubert, THIS JOURNAL, **79**, 152 (1957).

(19) I. A. Usov, M. Z. Finkelshtein and V. N. Below, *J. Gen. Chem. (U.S.S.R.)*, **17**, 2253 (1947), have shown that aliphatic thioethers form sulfonium compounds with alkyl sulfates.

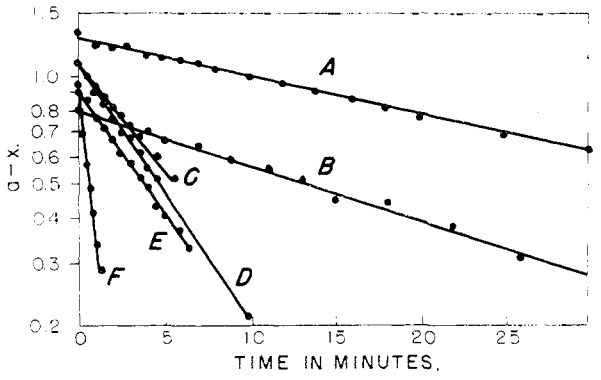


Fig. 1.—Some rate data for the solvolysis of dehydroisoandrosterone hydrogen sulfate: A, EtOH, 55.5°; B, isopropyl ether, 10% EtOH, 26.0°, curve was linear to 50 minutes (see Experimental); C, ethyl ether, 26.0°; D, benzene–10% EtOH, 50.0°; E, acetone, 29.5°; F, tetrahydrofuran–10% EtOH, 25.0°.

EtOH was the medium (3 *vs.* 11) as compared to the 9-fold increase observed with methylene chloride (3 *vs.* 13).

TABLE III

EFFECT OF STRUCTURE ON SOLVOLYSIS RATE OF STEROID HYDROGEN SULFATES

Hydrogen sulfate of	$k \times 10^5$ sec.$^{-1}$ (26.0°) in Tetrahydrofuran 6% H_2O, 10^{-4} M H^+	Tetrahydrofuran 6% H_2O, 0.07 M H^+[a]	Ether 10^{-4} M H^+	Ether satd. with H_2O, 10^{-4} M H^+
Androsterone	1.2	1.9	67	
Isoandrosterone	2.9	5.9		4.3
Dehydroisoandrosterone		5.9	210	4.3
Cortisone		30		

[a] *p*-Toluenesulfonic acid.

Although by decreasing the polarity of the medium acceleration of solvolysis may be achieved, it is evident from Table II that a prediction of the effects of the medium based entirely on the dielectric constant theory[20] is not possible. Thus, the largest acceleration in solvolysis was observed with the ethers (*e.g.*, 21, 27, 30, etc.) and it is apparent that a more specific solvent effect is playing an important role. The fastest rate was observed with tetrahydrofuran (27) in which the rate was 22,000 times larger than the rate in ethanol (3 *vs.* 27). The *availability* of the electrons of the ethers seems to be of decisive importance. The less hindered the ether the faster was the rate (compare 22, 25, 26, 29, 30). Participation of the electrons in ring resonance decreased the rate appreciably (29 *vs.* 31 and 32). This latter effect was especially well shown by the aromatic furan in which the rate was approximately 1/200 as fast as in tetrahydrofuran–10% ethanol. It is of interest that the rate in furan was only slightly higher than observed in benzene (32 *vs.* 6). Although the ethers could be placed in a separate class of their own with respect to their large solvolysis acceleration, appreciable rates were observed with the ketones (16, 18, 19, 20) and with the only ester studied (14). That the decrease in ionization of the sulfate is of importance was further demonstrated in runs 33 and 36 in which it was shown that an increase in the concentration of water retards the solvolysis greatly.

(20) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953; (b) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953; (c) A. Streitwieser, *Chem. Revs.*, **56**, 571 (1956); (d) J. E. Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956; *J. Org. Chem.*, **20**, 1202 (1955).

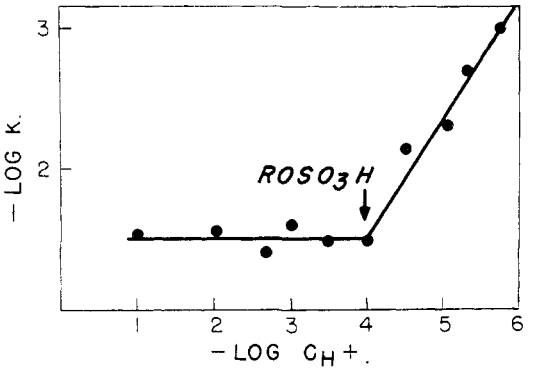


Fig. 2.—Effect of acid concentration on solvolysis rate of dehydroisoandrosterone hydrogen sulfate in tetrahydrofuran–10% EtOH. The acid concentration lower than $-\log C_{H^+} = 4$ (obtained by adding known amounts of pyridine to the reaction mixture) was calculated from the Henderson equation, using the pK_a value of 5.22 for pyridine in aqueous media (J. D. Cox and E. F. G. Herrington, *Trans. Faraday Soc.*, **50**, 918 (1954)). Acidities higher than $-\log C_{H^+} = 4$ were obtained by adding *p*-toluenesulfonic acid to the indicated stoichiometric concentrations. The value shown by the arrow is the stoichiometric concentration of the steroid hydrogen sulfate.

B. Rate of Solvolysis as a Function of Hydrogen Ion Concentration.—Figure 2 shows that, with tetrahydrofuran–10% EtOH as solvent, increasing the stoichiometric concentration of acid over a wide range produced no significant change in rate. These results may be interpreted as being due to the existence of the steroid hydrogen sulfate in this medium in the form of a closely associated ion-pair or a similar aggregate. An increase in the hydrogen ion concentration would then produce no change in the concentration of the effective reactive species and thus would not influence the rate. In a study of the course of polar reactions under non-polar conditions, Ingold and associates[21] have observed similar effects. The addition of pyridine to the reaction mixture resulted in a decrease in rate which is undoubtedly due to salt formation and is thus similar to the effect of water.[22]

C. Rate of Solvolysis as a Function of Sulfate Structure.—From Table III it is obvious that the primary sulfate, cortisone-21-hydrogen sulfate, is solvolyzed at the fastest rate with the solvent 2. On the other hand, the slowest rate was observed with androsterone hydrogen sulfate, that compound whose O–SO_3H group is in the more hindered axial (3α, 5α) conformation. The presence of the β,γ-double bond in dehydroisoandrosterone has less effect upon the rate than does the stereo-

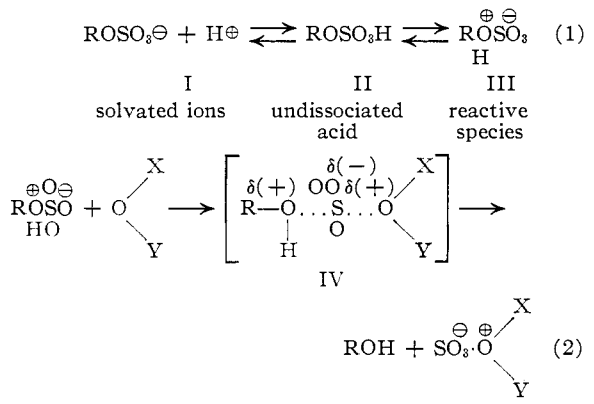
(21) *Cf.* C. K. Ingold, *Proc. Chem. Soc.*, 279 (1957).

(22) The results reported by McKenna and Norymberski (*cf.* ref. 10) thus constitute a special case of the present study, namely, a study in the alkaline region.

chemical conformation of the sulfate group, since both dehydroisoandrosterone sulfate and isoandrosterone sulfate solvolyze at about the same rate which is in turn greater than that of androsterone sulfate.

D. Probable Mechanism.—As mentioned earlier, asymmetric organic sulfates are hydrolyzed in either aqueous medium[4] or in ether[6] with complete retention of configuration of the asymmetric carbon atom. These stereochemical observations were employed as evidence for the cleavage of the S–O bond. Since, however, this kind of evidence cannot be considered final, for retention could have resulted from two inversions,[23] experiments with H_2O^{18} were carried out. The absence of O^{18} in both the saturated product (isoandrosterone) and the β,γ-unsaturated compound (dehydroisoandrosterone) proves that the C–O bond remains intact during solvolysis. The fact that dehydroisoandrosterone sulfate solvolyzes at the same rate as isoandrosterone sulfate is also evidence against a mechanism involving a carbonium ion intermediate. The latter might have been expected to have derived anchimeric assistance from the double bond at 5,6 as is the case in solvolytic reactions of cholesteryl bromide and tosylate.[24]

A probable mechanism for the solvolysis of steroid hydrogen sulfates, consistent with these experimental facts, could involve an attack on the central sulfur atom. Attack of hydrolytic reagents on the *central* hetero-atom has been postulated for tetraalkyl titanates,[25] organic phosphates,[26] boric acid esters,[27] phenyl methanesulfonates,[28] cyclic sulfites[29] and alkyl hydrogen sulfates.[4] Based on the experimental findings of the present paper this mechanism is proposed



According to this scheme the unstable dipolar ion III is considered to be the reactive species which gives rise to the free alcohol by reaction with a nucleophilic reagent XOY by sequence 2. From the data obtained in this study, it is impossible to define precisely the nature of XOY, which, depending upon the circumstances, may be water, alcohol or ether (*cf.* 18). According to this scheme the S–O bond is severed and these reactions are thus consistent with the H_2O^{18} experiments. Any change in environment that will shift the equilibrium in sequence 1 to the right will increase the rate of solvolysis. In media of high dielectric constant the hydrogen sulfate will exist primarily as solvated ions formulated as I. As the polarity of the medium is decreased the equilibrium will shift to the right with the formation of II—the undissociated acid—and consequent increase in the concentration of the reactive moiety. Since in all experiments of this study there was at least a 0.1 *M* concentration of water, II would probably be more nearly correctly formulated as the closely associated ion-pair $ROSO_3^{\ominus}$ $H_3O^{\oplus}$ or similar aggregate.[30]

The formulation of the unstable dipolar ion III as the "reactive species" in the solvolysis is strongly corroborated by the positive entropies of activation found (*cf.* Table II). A large positive entropy effect is found in reactions where there is recombination of oppositely charged ion reactants with concomitant "defreezing" of solvent molecules due to desolvation of the transition state.[20] Whether the unstable dipolar ion III is a true intermediate which reacts in sequence with an attacking nucleophile X–O–Y going through the transition complex IV according to reaction 2 cannot be answered from this study. As predicted by the dielectric constant theory of Hughes and Ingold,[20a] the formation of both the dipolar ion III and the transition state complex IV would be favored by non-polar media.

As was pointed out above, certain oxygen-containing solvents (especially the ethers) accelerated the solvolysis to a much larger extent than would be predicted from their dielectric constants. It is not possible to say whether these solvents actually participate in the reaction diagrammatically shown in (2). That participation of the solvents is plausible, however, is suggested by the existence of well-characterized ether:sulfur trioxide compounds.[2,31] The appreciably lower activation energies found for tetrahydrofuran (Table I, 29) would also favor (2).

It is noteworthy that hydrocortisone phosphate did not hydrolyze under the conditions used for the solvolysis of cortisone sulfate.

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