Hydrolysis of Nitrophenyl and Dinitrophenyl Sulfate Esters[1]

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The pH–rate profile for the hydrolyses of *o*-, *m*-, *p*-nitrophenyl and 2,4- and 2,5-dinitrophenyl sulfates is characterized by a plateau in the pH 4–10 region preceded by a more rapid acid-catalyzed reaction and followed by feeble base catalysis. A linear free-energy plot for log k_0 (see ref 11) against the pK_a of the corresponding phenol with a slope of -1.2 was obtained. Sodium chloride, sulfate, and fluoride and copper(II) sulfate and silver perchlorate only slightly affect k_0 for 2,4-dinitrophenyl sulfate, but sodium perchlorate significantly decreases it. Acetonitrile decreases k_0 for the same ester; dioxane in concentrations up to 80% has the same effect, but, when it reaches 90%, the rate is *increased* by a factor of 70; and dimethyl sulfoxide and N,N-dimethylformamide increase it exponentially. The effects of electrolytes, acetonitrile, and dimethyl sulfoxide on the molar activity coefficients of 2,4-dinitrophenyl sulfate and its hydrolysis transition state have been separated by distribution experiments. Sodium chloride slightly "salts in," and sodium sulfate and perchlorate, and the dipolar aprotic solvents "salt out" 2,4-dinitrophenyl sulfate, but all these salts and acetonitrile destabilize the transition state while dimethyl sulfoxide has little effect on it. Linear free-energy correlations have been obtained between the acid-catalyzed rate constants, k_ψ, and the dissociation constants of the leaving groups for all three acids at all concentrations and temperatures investigated. The slopes of these plots are between 0.22 and 0.26 indicating that the acid-catalyzed hydrolysis of these sulfate esters is relatively insensitive to the electron-withdrawing power of the leaving group. The catalytic effectiveness of the acids is $H_2SO_4 > HClO_4 > HCl$. Plots of log $k_\psi + H_0$ against $H_0 + C_{H^+}$ are linear, but their slopes are different for the different acids. This behavior is rationalized by assuming that the acids, in addition to their proton-donating power, exert specific electrolyte effects on both the initial and the transition states of these hydrolyses.

Recently, considerable interest has been shown in mechanistic studies concerning the hydrolysis of sulfate esters[2–5] owing to their biochemical importance.[6] The spontaneous[2] perchloric acid,[3] base,[2] and amine[2] catalyzed hydrolyses of *p*-nitrophenyl sulfate and carboxyl group participation in salicyl sulfate hydrolysis[4] have been reported. Lack of sufficient data has frustrated attempts to compare the mechanisms of aryl sulfate hydrolyses with those of the much more widely investigated monoaryl phosphates.[7] It has been suggested that a study of the hydrolysis of sulfate esters containing good leaving groups might substantiate the proposed unimolecular mechanism.[2] Although 2,4- and 2,5-dinitrophenyl sulfates have such good leaving groups, their preparation and consequently kinetic investigations of their hydrolysis have so far eluded the attention of chemists and biochemists alike. We, therefore, have undertaken a systematic investigation of the mechanisms of hydrolysis of both mono- and dinitrophenyl sulfates and report the results of a study of their neutral and acid-catalyzed hydrolyses.

Experimental Section

Materials.—*p*-Nitrophenyl sulfate potassium salt (Eastman) was recrystallized from 90% ethanol.

o-Nitro-, *m*-nitro-, 2,4-dinitro-, and 2,5-dinitrophenyl sulfates were prepared by a modified procedure of Burkhardt and Wood.[8] Chlorosulfonic acid (35 mmol, 2.32 ml) was added dropwise with stirring to a solution of dimethylaniline (12.5 mmol, 11.73 ml) in carbon disulfide (12.5 ml) at -16 to $-21°$. The mixture was then warmed to 35–40°; the appropriate dry phenol (25 mmol) was added with stirring; and the mixture was stirred for 1–1.5 hr at 35–40° and for approximately 14 hr at room temperature. After the mixture was cooled to 0°, it was poured rapidly with stirring into cold 4 *M* KOH (50 ml). The precipitate was filtered immediately, washed at least twice with cold 95% ethanol, and dried *in vacuo*. The potassium salts of *o*- and *m*-nitrophenyl sulfates were recrystallized from 90% ethanol. The labile dinitrophenyl sulfates were purified by the addition of dry acetonitrile to the solid, centrifugation, and rotary evaporation of the solution followed by the same procedure but using a minumum amount of cold aqueous ethanol. Rapid rotary evaporation of the solvent at 10–15° and drying *in vacuo* gave shiny white crystals. The purity of all the sulfates was established to be not less than 99% by complete hydrolysis of known quantities in aqueous buffer solutions at pH 10.00, assaying the amount of phenoxide ion liberated, and by their ir and nmr spectra.

Deionized distilled water was used to make up the buffer solution and the standard acid and alkali solutions. The pH of the buffer solutions was adjusted by addition of hydrochloric acid or sodium hydroxide at 25.00° using an Orion Model 801 pH meter. The concentrations of the acid solutions were determined by titration with standard 0.10 or 1.00 *M* NaOH (BDH) using Lacmoid as the indicator. The alkali solutions were standardized by titration with standard 1.00 *M* HCl using Lacmoid as the indicator. 1,4-Dioxane was purified by the method of Fieser[9] and stored in polyethylene bottles in a refrigerator. Spectrograde dimethyl sulfoxide, N,N-dimethylformamide, and acetonitrile were used without further purification and stored over molecular sieve. The aqueous organic solutions were made up by using the appropriate volumes measured at room temperature.

Kinetics.—The hydrolysis was followed spectrophotometrically by determining either the phenoxide ion or the phenol concentration. The phenoxide ion formation was followed in the higher pH region and in alkaline solutions. At lower pH values and in the acid region advantage was taken of the fact that the extinction coefficients of the nitro- and dinitro-substituted phenol sulfates are very much smaller than those of the corresponding phenols. For a few runs in strong acid solutions, the formation of phenoxide ion was followed by adjusting the pH of the individual samples to 9.0 by the addition of buffer solutions. The rate constants for these runs agreed within 3% with those obtained by direct measurement of phenol formation. The following wavelengths (mμ) were used for following the phenoxide ion and phenol formation, respectively: *o*-nitrophenyl sulfate, 410, 290; *m*-nitrophenyl sulfate, 380, 350; *p*-nitrophenyl sulfate, 403, 320; 2,4-dinitrophenyl sulfate, 360, 320, and 2,5-dinitrophenyl sulfate, 440, 270. The Beer–Lambert law was obeyed over

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[1] (a) For a preliminary report, see E. J. Fendler and J. H. Fendler, *Chem. Commun.*, 1261 (1967). (b) Supported in part by the U. S. Atomic Energy Commission.

[2] S. J. Benkovic and P. A. Benkovic, *J. Amer. Chem. Soc.*, **88**, 5504 (1966).

[3] J. L. Kice and J. M. Anderson, *ibid.*, **88**, 5242 (1966).

[4] S. J. Benkovic, *ibid.*, **88**, 5511 (1966).

[5] R. W. Hay and J. A. G. Edmonds, *Chem. Commun.*, 967 (1967).

[6] K. S. Dodgson, B. Spencer, and K. Williams, *Biochem. J.*, **64**, 216 (1956); H. Boströn, K. Bernstein, and M. W. Whitehouse, *Biochem. Pharmacol.*, **13**, 413 (1964).

[7] J. R. Cox, Jr., and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).

[8] G. N. Burkhardt and H. Wood, *J. Chem. Soc.*, 141 (1929).

[9] L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1957, p 284.

the range of concentrations employed for all the sulfates. Kinetic runs at 14.90, 25.00, and 45.00° were followed directly in the thermostated cell compartment of a Beckman DU-2 spectrophotometer. Those at 75.00 and 100.00° were carried out in sealed tubes which were placed in a thermostat, individually withdrawn at the required times, quickly cooled, and analyzed spectrophotometrically at the appropriate wavelength. For the hydrolyses in sodium hydroxide solutions, alkali resistant glass (Corning No. 7280) was used. The temperature in the thermostats and inside the cell compartment was measured by an NBS thermometer and maintained to be ±0.02°. Examples of typical kinetic runs are shown in Figure 1.

Partitioning Experiments.—The measurement of the distribution of 2,4-dinitrophenyl sulfate between water and an immiscible organic solvent, at a constant temperature and in the presence and absence of salts or of other media, gives the effect of the electrolytes or of the media on the molar activity coefficient of the sulfate ester.[10] Water and cyclohexane, water and hexane, cyclohexane and dimethyl sulfoxide, and hexane and acetonitrile are almost completely immiscible; the salts are not extracted into the organic layer; and the density differences of these solvents readily allows them to be separated quickly and cleanly after shaking. The hydrolysis of 2,4-dinitrophenyl sulfate at 25.00° was negligible compared with the distribution time. Even in 75% dimethyl sulfoxide, representing the fastest hydrolysis rate, the half-life for the hydrolysis of 2,4-dinitrophenyl sulfate is approximately 30 min and generally the distribution was carried out in less than 2 min. Typically a known concentration of 2,4-dinitrophenyl sulfate was made up by weight in a buffer or electrolyte solution (25.00 ml), and the concentration of this solution was redetermined by measuring the absorption at 320 mμ of a suitable dilution using the appropriate blank solution. These two independently determined concentrations usually agreed within ±3%. A 10.00-ml portion of the aqueous 2,4-dinitrophenyl sulfate was vigorously mixed with 10.00 ml of cyclohexane or the same volume of hexane in a thermostated separatory funnel at 25.00°. After the two layers had separated, the concentration of 2,4-dinitrophenyl sulfate was measured spectrophotometrically in each layer at 320 mμ using the appropriate blank solution. The distribution coefficient, r, is defined as [2,4-dinitrophenyl sulfate] in cyclohexane or in hexane/[2,4-dinitrophenyl sulfate] in water or in aqueous media. The subscript o refers to water and s to salt solutions or other media. The ratio r_s/r_o is equal to the ratio f_s/f_o, where f_s is the molar activity coefficient of 2,4-dinitrophenyl sulfate in the presence of electrolytes or other media, and f_o is that in water. Six independent values for r_o were determined, and they agreed within ±5%. Furthermore, 2,4-dinitrophenyl sulfate was distributed between 3.75 *M* $NaClO_4$ and cyclohexane, and in a separate experiment hexane was used instead of cyclohexane. Excellent agreement was obtained between the values found in these two experiments (Table I).

TABLE I

ACTIVITY COEFFICIENTS OF 2,4-DINITROPHENYL SULFATE AND ITS HYDROLYSIS TRANSITION STATE IN THE PRESENCE OF ELECTROLYTES, ACETONITRILE, AND DIMETHYL SULFOXIDE[a]

Medium	f_s/f_o	f_s^*/f_o^*
1.25 *M* $NaClO_4$	1.38	1.92[b]
2.50 *M* $NaClO_4$	1.19	2.75[b]
3.75 *M* $NaClO_4$	1.37	4.25[b]
3.75 *M* $NaClO_4$[c]	1.38	4.24[b]
0.75 *M* NaCl	0.94	1.05[b]
1.50 *M* NaCl	0.91	1.00[b]
2.25 *M* NaCl	0.82	0.97[b]
0.75 *M* Na_2SO_4	1.73	1.70[b]
25.00% CH_3CN	22.40	23.40
50.00% CH_3CN	147.00	214.00
75.00% CH_3CN	200.00	372.00
25.00% DMSO	1.85	0.80
50.00% DMSO	6.23	1.30
70.00% DMSO	8.67	0.87

[a] Using cyclohexane unless otherwise stated; correlated with rate constants at 25.00° unless otherwise stated. [b] Rate constants measured at 45.00°. [c] Using hexane.

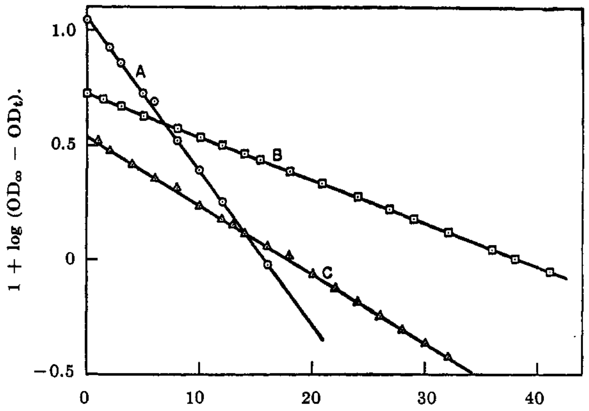

Figure 1.—Plot of 1 + log ($OD_\infty - OD_t$) against time for the neutral hydrolysis of sulfate esters. A = 2,4-dinitrophenyl sulfate; pH 5.90, 75.00°. B = *o*-nitrophenyl sulfate; pH 8.00, 100.00°; time scale in 10^2. C = 2,5-dinitrophenyl sulfate; pH 5.90, 100.00°.

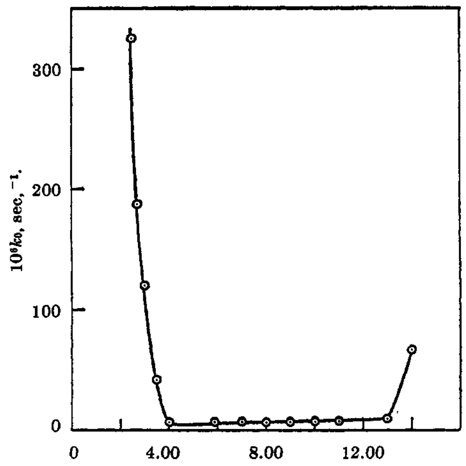

Figure 2.—Variation of k_0 with pH for *o*-nitrophenyl sulfate at 100.00°.

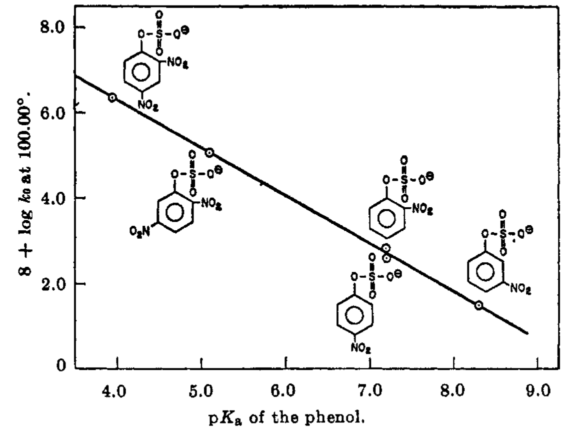

Figure 3.—Plot of 8 + log k_0 at 100.00° against pK_a of the corresponding phenol.

Results

The first-order rate constants, k_0, for the neutral[11] hydrolysis of nitrophenyl and dinitrophenyl sulfates are given in Table II. The pH–rate profile for *o*-nitrophenyl sulfate at 100.00° is in Figure 2. Figure 3

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[10] F. A. Long and W. F. McDevit, *Chem. Rev.*, **51**, 119 (1952).

[11] In this paper, the neutral hydrolysis refers to the hydrolysis of the sulfate esters, in the plateau region of the pH–rate profile, *i.e.*, from pH 4 to 12, and is symbolized by k_0.

TABLE II

HYDROLYSIS OF NITROPHENYL AND DINITROPHENYL SULFATES IN THE pH REGION

		10^6k_0, sec^{-1}						
		o-Nitrophenyl sulfate		m-Nitrophenyl sulfate	2,4-Dinitrophenyl sulfate		2,5-Dinitrophenyl sulfate	
pH	Buffer[a]	100.00°	75.00°	100.00°	75.00°	45.00°	100.00°	75.00°
1.00	0.10 M HCl	1307.0		948.0		326.0	3200.0	
2.50	0.01 M KH_2PO_4	306.0				269.0	1680.0	
2.70	0.01 M KH_2PO_4	178.0						
3.00	0.01 M KH_2PO_4	120.7		72.5			1220.0	
3.50	0.01 M KH_2PO_4	40.2					1250.0	
4.00	0.01 M $KHC_8H_4O_4$	6.78						
4.32	0.01 M $KHC_8H_4O_4$						1180.0	150.0
5.90	0.01 M $KHC_8H_4O_4$	6.80		0.31	3700.0	295.0	1180.0	148.0
6.00	0.01 M KH_2PO_4	7.10		0.32	3680.0			149.00
7.00	0.01 M KH_2PO_4	6.85	0.659	0.32	3720.0			
8.00	0.01 M $Na_2B_4O_7$	7.17		0.31		279.0		
9.00	0.01 M $Na_2B_4O_7$	6.80	0.642	0.32		278.0		
10.00	0.01 M $Na_2B_4O_7$	7.45				272.0	1160.0	
11.00	0.01 M K_2HPO_4	7.20	0.644			273.0		
13.00	0.10 M NaOH	8.40					1510.0	
14.00	1.0 M NaOH	68.10						

[a] The pH of buffers were adjusted at 25.00°.

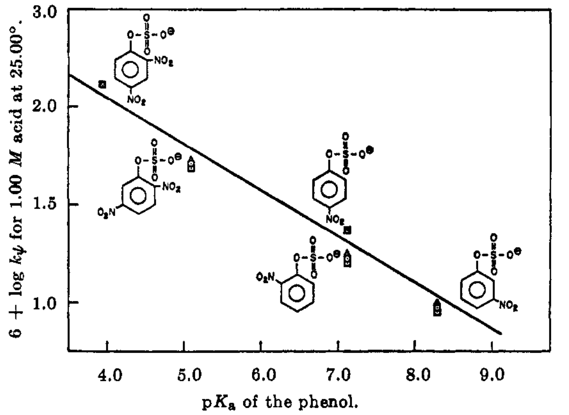

Figure 4.—Plot of 6 + log k_ψ at 1.00 M acid against pK_a of the corresponding phenol at 25.00°: ⊙, $HClO_4$; ⊡, HCl; △, H_2SO_4.

shows the linear free-energy relationship between the dissociation constant of the leaving group (nitro or dinitrophenol) and the rate constants for the neutral hydrolysis. The Arrhenius parameters for the neutral hydrolysis are collected in Table III. The effects of salts on the neutral hydrolysis of 2,4-dinitrophenyl sulfate at 45.00° are summarized in Table IV, and Table V gives the solvent effects on the hydrolysis of the same compound. The effects of electrolytes, acetonitrile, and dimethyl sulfoxide on the molar activity coefficient of 2,4-dinitrophenyl sulfate and on that of its hydrolysis transition state are collected in Table I.

The first-order rate constants, k_ψ, for the acid-catalyzed hydrolysis of nitrophenyl and dinitrophenyl sulfates are given in Table VI. Good linear free-energy correlations have been obtained between k_ψ and the dissociation constants of the leaving groups for all three acids at all the concentrations and temperatures investigated. A typical plot for a 1.00 M acid at 25.00° is given in Figure 4. The slopes of these plots are 0.22–0.26. Plots of log k_ψ against H_0[12] generally gave good straight lines whose slopes are given in Table VII. The plot for o-nitrophenyl sulfate is illustrated in Figure 5. The scatter between the different acids might be due to the different electrolyte effects of the acids on the sulfate esters or on their hydrolysis transition states. To test this point we replotted our experimental data as suggested by Bunnett[13] and later modified by Bunnett and Olsen.[14] Plots of log k_ψ + H_0 against $-\log a_{H_2O}$ are curved and are different for the different acids; some of them show a minimum. Figure 6 shows these plots for o-nitrophenyl sulfate. In their modified treatment Bunnett and Olsen suggest that the slope, ϕ, of plots of log k_ψ + H_0 against H_0 +

TABLE III

ARRHENIUS PARAMETERS FOR THE NEUTRAL HYDROLYSIS OF NITROPHENYL AND DINITROPHENYL SULFATES

Sulfate	E, kcal/mol	$\Delta S^{\ddagger}$, eu[a]
o-Nitrophenyl	24.7	−17.4
p-Nitrophenyl	18.5[b]	−18.5[b]
2,4-Dinitrophenyl	18.8	−18.0
2,5-Dinitrophenyl	19.4	−17.4

[a] Calculated at 75.00°. [b] See ref 2.

TABLE IV

SALT EFFECTS ON THE NEUTRAL HYDROLYSIS OF 2,4-DINITROPHENYL SULFATE AT 45.00°

	Concn of salt, M	10^5k_ψ, sec^{-1}
NaCl	0.00	27.9
	1.00	25.7
	2.00	25.0
	3.00	24.8
$NaClO_4$	1.00	20.3
	2.00	15.2
	3.00	11.00
	4.00	8.19
	5.00	5.78
Na_2SO_4	1.00	28.0
$CuSO_4$	0.1	33.0
$AgClO_4$	0.1	35.0
NaF	0.5	29.5
	1.0	32.2

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(12) Values for H_0 were taken from M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957), and when available from more recently determined values such as those which have been reported by M. J. Jorgesen and D. R. Hartter, *J. Amer. Chem. Soc.*, **85**, 878 (1963), and K. Yates and H. Wai, *ibid.*, **86**, 5408 (1964).

(13) J. F. Bunnett, *ibid.*, **83**, 4956 (1961), and accompanying papers.

(14) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1917 (1966).

TABLE V

NEUTRAL HYDROLYSIS OF 2,4-DINITROPHENYL SULFATE IN AQUEOUS ORGANIC SOLVENTS

Medium	Volume % organic solvent	10^5k_ψ, sec^{-1}, at 25.00°	10^5k_ψ, sec^{-1}, at 45.00°	E, kcal/mol	$\Delta S^\ddagger$, eu, at 25.00°
CH_3CN–H_2O	0	4.00	27.9	18.8	−18.0
	25	3.85	27.4	18.6	−18.5
	50	2.74	21.0	19.2	−16.0
	75	1.86	13.1	18.4	−15.5
Dioxane–H_2O	40	5.94	50.0	20.0	−10.0
	60	4.60	49.0	22.3	−5.2
	80	3.50	42.0	24.9	0.1
	90	260.00		25.9[a]	14.0[a]
DMSO–H_2O	25	9.20	62.1	18.0	−18.0
	50	18.00	142.0	20.0	−12.0
	75	38.7	302.0	19.4	−10.5
	85	143.7	1130.0	19.5	−6.5
DMF–H_2O	25	8.62	90.8	22.2	−3.7
	50	17.6	183.0	22.1	−3.2

[a] Calculated from $10^5k_\psi = 76$ sec^{-1} at 14.90°.

TABLE VI

ACID-CATALYZED HYDROLYSIS OF NITROPHENYL AND DINITROPHENYL SULFATES[a]

		10^5k_ψ, sec^{-1}				
	Concn of acid, M	*o*-Nitrophenyl sulfate	*m*-Nitrophenyl sulfate	*p*-Nitrophenyl sulfate	2,4-Dinitrophenyl sulfate	2,5-Dinitrophenyl sulfate
HCl	1.03	1.58	0.91	2.35	13.3	5.09
	1.03[b]	17.8	12.0	43.5	135.0	45.0
	2.06	4.44	3.26	6.30	29.7	9.08
	3.06	11.2	6.47	18.0	64.7	23.3
	4.12	24.5	15.0	39.4	109.0	52.9
	5.15	48.6	34.3	85.5	276.0	98.7
	5.15[b]		387.0			
	6.18	126.5	79.5	184.0	651.0	293.0
	7.12	258.0	201.0			
$HClO_4$	1.00	1.70	0.958	2.35	12.7	5.17
	1.00[b]	22.2	13.0	45.6	126.0	53.6
	2.00	4.16	3.06	7.25	27.7	11.5
	3.00	9.92	5.67	15.2	63.6	24.5
	4.00	24.0	12.8	35.7	142.0	52.1
	5.00	60.1	28.0	68.2	300.0	105.0
	5.00[b]		297.0			
	6.00	191.0	78.7	228.0	862.0	307.0
	7.08	759.0				
H_2SO_4	1.00	1.76	0.98	2.36	13.2	5.27
	1.00[b]	20.1	11.6	44.2	151.0	49.3
	2.00	4.33	2.94	9.58	44.0	10.4
	3.00	11.2	7.13	18.5		23.4
	4.00	33.6	20.3	51.7	225.0	69.0
	5.00	92.4	54.1	138.0		182.0
	5.00[b]		456.0			
	6.00	252.0	151.0		1226.0	743.0

[a] At 25.00°, unless specified otherwise. [b] At 45.00°.

TABLE VII

ϕ VALUES[a] AND SLOPES OF LOG k_ψ *vs.* $-H_0$ PLOTS FOR THE ACID-CATALYZED HYDROLYSIS OF NITROPHENYL AND DINITROPHENYL SULFATES

		o-Nitrophenyl sulphate	*m*-Nitrophenyl sulphate	*p*-Nitrophenyl sulphate	2,4-Dinitrophenyl sulphate	2,5-Dinitrophenyl sulphate
ϕ	HCl	−0.07	−0.03	−0.05	−0.10	−0.10
	$HClO_4$	−0.20	−0.39	−0.39	−0.46	−0.38
	H_2SO_4	−0.15	−0.20	−0.20	−0.32	−0.14
Log k_ψ *vs.* $-H_0$ slope at 25.00°	HCl	0.95	0.94	0.96	0.98	1.10
	$HClO_4$	0.86	0.86	0.85	0.85	0.73
	H_2SO_4	0.86	0.85	0.83	0.86	0.73

[a] ϕ = slope of plots of log $k_\psi + H_0$ *vs.* log $C_{H^+} + H_0$ at 25.00° in the 1.00–6.00 M acid range.

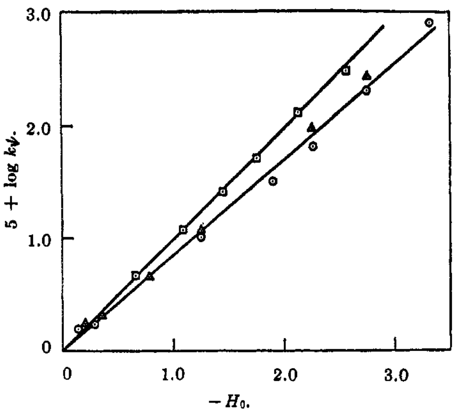

Figure 5.—Plot of 5 + log k_ψ against $-H_0$ for *o*-nitrophenyl sulfate at 25.00°: ⊙, $HClO_4$; ⊡, HCl; ◬, H_2SO_4.

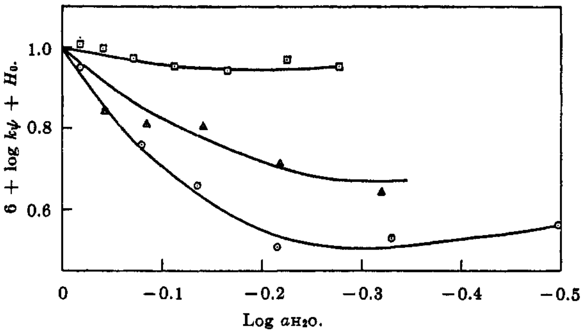

Figure 6.—Plot of 6 + log k_ψ + H_0 against log a_{H_2O} for *o*-nitrophenyl sulfate at 25.00°: ⊙, $HClO_4$; ⊡, HCl; ◬, H_2SO_4.

log C_{H^+} indicates the effect of activity coefficient ratios on the reaction rate.[14] Figure 7 shows such plots for *o*-nitrophenyl sulfate. Corresponding plots for the other sulfate esters are similar. The slopes of these plots are given in Table VII. The energies and entropies of activation are collected in Table VIII.

TABLE VIII

ENERGIES AND ENTROPIES OF ACTIVATION FOR THE ACID-CATALYZED HYDROLYSIS OF NITROPHENYL AND DINITROPHENYL SULFATES

Sulfate	Solvent	*E*, kcal/mol	$\Delta S^\ddagger$, eu at 25.00°
o-Nitrophenyl	1.03 *M* HCl	22.9	−5.7
	1.00 *M* $HClO_4$	23.9	−5.5
	1.00 *M* H_2SO_4	21.6	−9.0
m-Nitrophenyl	1.03 *M* HCl	27.8	1.0
	5.15 *M* HCl	22.4	−0.4
	1.00 *M* $HClO_4$	25.2	1.6
	5.00 *M* $HClO_4$	22.3	−1.4
	1.00 *M* H_2SO_4	23.4	−1.0
	5.00 *M* H_2SO_4	20.1	−7.0
p-Nitrophenyl	1.03 *M* HCl	22.6	−2.0
	1.00 *M* $HClO_4$	22.2	−6.0
	1.00 *M* H_2SO_4	23.1	−1.5
2,4-Dinitrophenyl	1.03 *M* HCl	21.8	−1.5
	1.00 *M* $HClO_4$	21.6	−5.0
	1.00 *M* H_2SO_4	22.9	−1.3
2,5-Dinitrophenyl	1.03 *M* HCl	21.0	−8.0
	1.00 *M* $HClO_4$	21.2	−6.0
	1.00 *M* H_2SO_4	21.9	−7.0

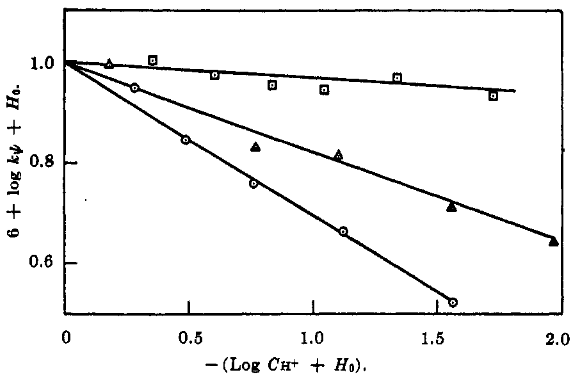

Figure 7.—Plot of 6 + log k_ψ + H_0 against −(log C_{H^+} + H_0) for *o*-nitrophenyl sulfate at 25.00°: ⊙, $HClO_4$; ⊡, HCl; ◬, H_2SO_4.

Errors, standard deviations, in individual rate constants are not greater than ±4%; those in *E* are approximately ±0.7 kcal mol^{-1}; and those in $\Delta S^\ddagger$ are ±2 eu. We consider values for the molar activity coefficients of 2,4-dinitrophenyl sulfate to be accurate within ±10%, although the errors are smaller for the electrolytes. Errors for the transition-state activity coefficient ratios are inevitably compounded, but even for acetonitrile, representing the most complex system, the results are correct within ±25%.

Discussion

Neutral Hydrolysis.—The pH-rate profile for the hydrolysis of aryl sulfate esters involves a plateau, pH 4–12, preceded by a more rapid acid-catalyzed reaction and followed by an exponential curve (see Figure 2) due to the incursion of base catalysis.[15] Superficially this hydrolytic behavior is very similar to that which has been observed for the hydrolysis of alkyl,[7] aryl,[16,17] and acyl[18,19] phosphate dianions.

The present results on the hydrolysis of nitrophenyl and dinitrophenyl sulfate anions will be discussed with respect to the hypotheses that (a) the rate-determining step involves unimolecular sulfur–oxygen bond fission with the elimination of SO_3, (b) the hydrolysis proceeds by bimolecular nucleophilic attack of water on sulfur, and (c) water molecules participate in the transition state by ion–dipole or dipole–dipole interactions or by hydrogen bonding to such an extent that the molecularity of the reaction is a matter of its academic definition.

The sensitivity of the rate of hydrolysis to changes in substituents in the leaving group (ρ) has been found to be a useful mechanistic probe in studies of phosphate ester hydrolysis.[16,17,19] We have found that a plot of log k_0 for the sulfate anion hydrolysis against the pK_a of the corresponding phenol is linear with a slope of −1.2 (Figure 3). Such a relatively large substituent effect is consistent with a unimolecular mechanism, since in this case the only requirement for hydrolysis is sulfur–oxygen bond breaking. However, for the hydrolysis of phosphate monoanions, which exhibits many characteristics of a unimolecular reaction but

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[15] The powerful base catalysis at high pH values might involve a change from a unimolecular to a bimolecular mechanism involving attack by hydroxide ion on both carbon and sulfur.[2] In addition, these processes could be complicated by specific electrolyte effects of the alkali metal hydroxide. Clearly our data on the base-catalyzed hydrolysis are insufficient to elucidate the base-catalyzed mechanism in greater detail.

[16] C. A. Bunton, E. J. Fendler, and J. H. Fendler, *J. Amer. Chem. Soc.*, **89**, 1221 (1967).

[17] A. J. Kirby and A. G. Varvoglis, *ibid.*, **89**, 415 (1967).

[18] G. DiSabato and W. P. Jencks, *ibid.*, **83**, 4400 (1961).

[19] A. J. Kirby and W. P. Jencks, *ibid.*, **87**, 3209 (1965).

involves a proton transfer to the leaving group, the slope of a corresponding plot is −0.32.[20] In this case, a small substituent effect is reasonable since leaving groups which weaken the phosphorus–oxygen bond decrease the basicity of the ester oxygen atom and *vice versa*. In addition, the magnitude of the slope for sulfate anions is considerably greater than seems probable for a mechanism involving bimolecular displacement by a water molecule. Indeed, the bimolecular reaction between hydroxide ion and a series of fully substrated phosphates with different leaving groups displays little sensitivity to the nature of the leaving group; *i.e.*, a plot of log k against the pK_a of the leaving group has a slope of −0.43.[21] However, the effect of substituents in the leaving group on the rate of hydolysis of nitro and dinitrophenyl sulfates is quite similar to that found for the hydrolysis of the dianions of substituted acetyl, benzoyl, and aryl phosphates for which the corresponding slope is −1.2.[16–19] Considerable evidence supports the conclusion that the hydrolysis of these phosphates proceeds by unimolecular phosphorus–oxygen bond fission with elimination of the metaphosphate ion.[7] Thus, the available evidence for substituent effects suggests that the hydrolysis of nitro and dinitrophenyl sulfates proceeds by a unimolecular mechanism, but it does not exclude the alternative formulation mentioned in hypothesis c.

The presence of sodium chloride (up to 3.00 M), sodium sulfate (1.00 M), and sodium fluoride (1.00 M) only slightly affects the rate constant for the neutral hydrolysis of 2,4-dinitrophenyl sulfate, but the addition of sodium perchlorate significantly decreases it (Table IV). The addition of sodium perchlorate, chloride, and sulfate was found to increase the rate of hydrolysis of the dianion of 2,4-dinitrophenyl phosphate, but this effect was more specifically dependent on the cation than on the anion.[16] The available data concerning the effects of 0.8 M potassium iodide, 0.8 M sodium fluoride, and 0.25 M sodium sulfite on the hydrolysis of p-nitrophenyl sulfate at 75.00°[2] has been interpreted as evidence supporting a unimolecular mechanism.[22] However, *an intercomparison of these salt effects between the various sulfate and phosphate esters is somewhat meaningless since they can only be described in terms of free-energy changes of the initial state relative to the transition state.* Such changes are best described by the Brønsted–Bjerrum rate equation which relates the rate constant in the presence of electrolytes, k, to the rate constant in their absence, k_0, and to the ratio of activity coefficients of the initial and transition states, f_s/f^*, which follows.

$$k = k_0 f_s/f^* \tag{1}$$

A meaningful interpretation of electrolyte and medium effects on reaction rate must necessarily involve a separation of the activity coefficient terms in eq 1 rather than a gross comparison of the observed rate constants for seemingly similar reactions. We have attempted to do this by partitioning 2,4-dinitrophenyl sulfate between cyclohexane or hexane and the aqueous solution (see Experimental Section). Combining $r_s/r_0 = f_s/f_0$ with eq 1 one obtains

$$k_0 r_s/k_s r_0 = f_s^*/f_0^* \tag{2}$$

which allows separation of the activity coefficient ratios for both the initial and transition states. Sodium chloride slightly "salts in" and sodium perchlorate and sulfate "salt out" 2,4-dinitrophenyl sulfate, but all these salts destabilize the transition state (Table I). The significant rate deceleration caused by sodium perchlorate (Table IV) is explicable in terms of a very pronounced transition-state destabilization which is not canceled by initial state interactions. It is not surprising that sodium chloride and sulfate affect the hydrolysis rate insignificantly since the former salt only slightly alters the molar activity coefficient of the initial and transition state and interactions of the latter with the initial state and transition state cancel.

Copper(II) and silver(I) ions have no significant effect on the hydrolysis of 2,4-dinitrophenyl sulfate (Table IV).[23] Recently, a considerable copper(II) ion catalysis was reported for 8-hydroxyquinoline sulfate.[5] Although the exact nature of metal ion catalysis is not perfectly understood, rate enhancement is generally discussed in terms of chelation with the substrate[7] or charge neutralization in the transition state.[25] Not unexpectedly, metal ions do not seem to chelate with 2,4-dinitrophenyl sulfate nor do they enhance its hydrolysis rate by any other mechanism.

In their recent study Benkovic and Benkovic[2] have reported that the rate constant for p-nitrophenyl sulfate hydrolysis was a factor of two slower in 50% aqueous acetonitrile than in water. Indeed, these authors used this fact as one of their mechanistic probes to substantiate the proposed unimolecular mechanism[2] since similar effects have been reported for hydrolysis of acetyl phosphate dianion.[18] On the other hand, the hydrolysis rate of 2,4-dinitrophenyl phosphate was found to increase by a factor of four in aqueous 50% acetonitrile,[17] and considerable enhancement of the hydrolysis rate of steroid sulfates[26] by moist dioxane has been noted for some time. These conflicting effects of dipolar aprotic solvents on the hydrolysis of sulfate and phosphate esters question the validity of the use of solvent effects as mechanistic criteria, at least for these compounds. We, therefore, have examined the effect of acetonitrile, dimethyl sulfoxide, dioxane, and N,N-dimethylformamide on hydrolysis of 2,4-dinitrophenyl sulfate (Table V). Changing the aqueous medium to aqueous acetonitrile steadily decreases the hydrolysis rate. Dioxane has the same effect up to 80% dioxane concentration, but, when the water content of the medium is 10%, the neutral rate is increased by a factor of 70. Dimethyl sulfoxide and N,N-dimethylformamide increase the rate of the neutral hydrolysis exponentially.

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[20] C. A. Bunton, E. J. Fendler, E. Humeres, and K-U Yang, *J. Org. Chem.*, **32**, 2806 (1967).

[21] D. F. Heath, "Organophosphorus Poisons," Pergamon Press, New York, N. Y., 1961, p 79.

[22] These salt-effect studies were carried out, however, at a constant ionic strength of one using potassium chloride which seriously complicates any interpretation of the effect of 0.8 M added electrolyte on the rate of hydrolysis.

[23] However, the presence of 0.01 M cetyltrimethylammonium bromide, a cationic micelle, increases the rate of both the neutral and the base-catalyzed hydrolysis by a factor of two but very significantly decreases the acid-catalyzed rate of pH 2.0, whereas 0.01 M sodium lauryl sulfate, an anionic micelle, slightly decreases the rate of the neutral hydrolysis.[24]

[24] E. J. Fendler and J. H. Fendler, to be published.

[25] C. H. Oestreich and M. M. Jones, *Biochem.*, 2926, 3151 (1966); 1515 (1967).

[26] J. McKenna and J. K. Norymberski, *J. Chem. Soc.*, 3889 (1957).

The effects of these dipolar aprotic solvents on the hydrolysis of 2,4-dinitrophenyl sulfate is revealed strikingly by their entropies of activation. Supported by a large body of experimentally determined entropies of activation for reactions of known mechanism, positive $\Delta S^{\neq}$ values have been assigned to unimolecular mechanisms and negative ones to bimolecular mechanisms.[27] The entropies of activation for the neutral hydrolysis of nitrophenyl and dinitrophenyl sulfates are more negative than those generally associated with a unimolecular mechanism (Table III). The interpretation of the magnitude of entropy effects for unimolecular reactions is, however, less straightforward than that for bimolecular reactions. The ordering effect in the latter case arises from the covalently bound water in the transition state, while the former situation is a composite of two opposing effects. The one-step process of forming sulfur trioxide and phenoxide ion results in a decrease in the order of the system, hence an increase in the entropy. On the other hand, the internal mobility of the solvent is reduced by a greater solvation of the entities in the transition state resulting in a decrease in entropy. Apparently for aryl sulfate esters, the net effect on the entropy difference between the initial and the transition state due to these opposing factors results in a moderatively negative entropy of activation. Several reactions whose mechanisms have been independently established to be unimolecular have fairly considerable negative entropies of activation.[28,29] The hydrolysis of 2,4-dinitrophenyl sulfate in aqueous solvent mixtures containing dipolar aprotic solvents exhibits significantly higher entropies of activation (Table V). The effectiveness of the solvents in increasing the entropies of activation is dioxane > N,N-dimethylformamide > dimethyl sulfoxide > acetonitrile. Tentatively one may ascribe the entropy increase to a decrease in transition-state solvation.[28]

Medium effects, however, are best described in terms of eq 1 which allows a separation of the activity coefficient effects in the initial and transition states. We have attempted to do this for the acetonitrile and dimethyl sulfoxide systems (Table I). It is evident that, although acetonitrile considerably increases the molar activity coefficient of 2,4-dinitrophenyl sulfate, the corresponding transition-state destabilization largely compensates for this effect. The significant "salting out" effect of dimethyl sulfoxide on 2,4-dinitrophenyl sulfate, however, is not compensated by the over-all transition-state stabilization. Recently, activity coefficients have been measured for *t*-butyl acetate, ethyl acetate, and acetal in various water–DMSO mixtures and have been correlated with their hydrolysis rate constants.[30] The results showed that, while dimethyl sulfoxide decreased the activity coefficient of acetal and ethyl acetate, the transition state of the acid-catalyzed hydrolysis of the former (an A-1 reaction) was stabilized to a greater extent than that of the latter (an A-2 reaction). Although estimates of activity coefficient ratios for different bimolecular reactions in several dipolar aprotic solvents have been made,[31] once again, meaningful comparisons of these effects must await the accumulation of further data.

The effects of electrolytes and dipolar aprotic solvents on the molar activity coefficient of 2,4-dinitrophenyl sulfate and on its hydrolysis transition state are likely to originate from their ability to alter the structure of liquid water,[32] and hence the degree of ground- and transition-state solvation. In studying electrolyte and medium effects, therefore, it is best to consider only the degree and type of water involvement in the rate-determining step.

Acid-Catalyzed Hydrolysis.—The hydrolyses of nitrophenyl and dinitrophenyl sulfates are catalyzed to a great extent by acids, and the order of their catalytic power is $H_2SO_4 > HClO_4 > HCl$ (Table VI). It is unlikely that this order is dependent on the nucleophilicity of the anions of the acids since sodium chloride and sulfate have little effect, whereas perchlorate ions markedly decrease the rate of spontaneous hydrolysis (Table IV). For an A-1 hydrolysis with a fast equilibrium protonation, eq 1 can be written as

$$k_\psi = k_0 a_{H^+} f_s / f^* \qquad (3)$$

where a_{H^+} is the activity of the hydrogen ion. Taking the logarithm of eq 3 and adding and subtracting H_0 gives eq 4 where f_B is the activity coefficient of the

$$\log k_\psi = -H_0 + \log (f_s f_{BH^+})/(f^* f_B) + \text{constant} \qquad (4)$$

neutral indicator base used in the experimental determination of H_0 and f_{BH^+} is the activity coefficient of its conjugate acid. The above equation is, in fact, the basis of the well-known Zucker–Hammett hypothesis,[33] which states that a plot of log k_ψ against H_0 is linear with a slope of one for an A-1 reaction assuming that the activity coefficient ratio remains constant.[34] The use of this assumption has been justified by the selection of acidity function indicators whose structures were similar to those of the compounds under investigation. Nevertheless, inconsistencies in the Zucker–Hammett criteria have been noted,[13] and in several cases good correlations with H_0 values obtained using neutral indicators have been found for charged and protonated substrates.[3,7,35] The rate-determining step in the acid-catalyzed hydrolysis of aryl sulfate esters was proposed to be the unimolecular fission of the rapidly formed zwitterion.[3] Although we have obtained good linear Hammett plots (see Figure 5), we do not wish to attribute undue significance to this observation. Bunnett proposed that a plot of log $k_\psi + H_0$ against log a_{H_2O} is often linear and its slope,

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(27) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

(28) Indeed, the interpretation is further complicated, as suggested by a referee, by the relative ground- and transition-state solvation for the neutral hydrolysis. The transition state for this reaction may be less extensively solvated than the ground state since the former may have a highly dispersed negative charge while the charge in the latter resides on at most three oxygen atoms. However, the small deuterium solvent isotope effect of $k_{H_2O}/k_{D_2O} = 1.26$[2] suggests a transition state in which little bond formation between the solvent and the substrate has occurred and is consistent with those effects generally associated with unimolecular reactions.[29] Relative ground- and transition-state solvation in mixed aqueous–nonaqueous solvents, naturally, tends to be even more complex.

(29) C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, **83**, 3207 (1961).

(30) B. G. Cox and P. T. McTigue, *Aust. J. Chem.*, **20**, 1815 (1967).

(31) A. J. Parker, *Advan. Phys. Org. Chem.*, **5**, 173 (1967), and references cited therein.

(32) J. L. Kavanau, "Water and Solute–Water Interactions," Holden-Day, Inc., San Francisco, Calif., 1964, and references cited therein.

(33) L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.*, **61**, 2791 (1959).

(34) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957); K. Wiberg, "Physical Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1964, p 430; E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

(35) S. D. Batts, *J. Chem. Soc., B*, 551 (1966).

w, is the difference in hydration between the initial and transition states and is characteristic of the mechanism involved. Although approximately 100 reactions were examined, some anomalies had been noted.[13] We have obtained curves, sometimes with a minimum, using the Bunnett plot for the acid-catalyzed hydrolysis of nitrophenyl and dinitrophenyl sulfates (Figure 4 and Results). More significantly, we noted that the catalytic efficiency of the different acids varied. An examination of *w* values for those few A-1 reactions, where data for all three strong acids (HCl, $HClO_4$, H_2SO_4) are available,[13] strikingly reveals the significant differences between the catalytic power of the different acids for a given reaction. Clearly the assumption that the activity coefficient ratio in the Zucker–Hammett equation[33] remains constant is untenable, at least for these reactions, and may well fortuitously cancel for some other reactions.

The difficulty is further compounded by the differential effects of acids on the activity coefficients of the Hammett indicators used.[36] We have found that the activity coefficients of *o*-nitroaniline, 4-chloro-2-nitroaniline, and 2,4-dinitroaniline decreased to a different extent as a function of acid concentration.[37]

Bunnett and Olsen have recently modified their original treatment and showed that plots of log $k_\psi + H_0$ against $H_0 + C_{H^+}$ are linear, and that their slopes, ϕ, are related to the effect of activity coefficients on the reaction rate (*i.e.*, to f_s/f^*). Using this treatment we obtained good linear correlations for all the sulfate esters (Figure 7). The ϕ values (Table VII) correspond to little or no water participation in the transition state,[14] but more significantly it is apparent that perchloric acid has the most pronounced effect on the activity coefficient ratio. This is confirmed by the negative salt effect of sodium perchlorate on the spontaneous hydrolysis of 2,4-dinitrophenyl sulfate (Table IV). The acids, therefore, not only affect the reaction rate by their proton-donating power but also by virtue of their electrolyte effects which are specific and are likely to be similar to those of the anions of their sodium salts.

The acid-catalyzed hydrolysis of nitrophenyl[38] and dinitrophenyl phosphate[16] showed a high degree of dependence on water activity and exhibited rate maxima in the 4–8 *M* region, but for the dinitrophenyl sulfates plots of log $k_\psi + H_0$ against $H_0 + C_{H^+}$ were linear and gave parallel straight lines for HCl, $HClO_4$, and H_2SO_4 even at different temperatures. One can conclude that the acid-catalyzed hydrolysis of phosphate and sulfate esters follow different mechanisms.

The linear free-energy relationship for the acid-catalyzed hydrolysis of sulfate esters has a slope of approximately 0.3 (Figure 4). The acid catalysis for sulfate ester hydrolysis is therefore less dependent on the electron-withdrawing power of the leaving group than the neutral hydrolysis, where the corresponding slope is 1.2. For phosphate esters the acid hydrolysis is more sensitive to electron-withdrawing substituents than is the monoanion reaction, but less sensitive than the dianion reaction.[16]

Registry No.—*o*-Nitrophenyl sulfate, 17396-91-7; *m*-nitrophenyl sulfate, 3233-64-5; 2,4-dinitrophenyl sulfate, 17396-93-9; 2,5-dinitrophenyl sulfate, 17396-94-0; NaCl, 7647-14-5; $NaClO_4$, 7601-89-0; Na_2SO_4, 7757-82-6; $CuSO_4$, 7758-98-7; $AgClO_4$, 7783-93-9; NaF, 7681-49-4; acetonitrile, 75-05-8; dimethyl sulfoxide, 67-68-5; HCl, 7647-01-0; $HClO_4$, 7601-90-3; H_2SO_4, 7664-93-9.

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[36] E. M. Arnett and G. W. Mach, *J. Amer. Chem. Soc.*, **89**, 1177 (1967).

[37] Unpublished work of C. A. Bunton and J. H. Fendler.

[38] P. W. C. Barnard, C. A. Bunton, D. Kellerman, M. M. Mhala, B. A. Silver, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, *B*, 227 (1966).

Bromine Telomerization

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Readily polymerizable olefins such as vinyl chloride, ethyl methacrylate, and styrene can be telomerized with bromine by means of the bromine adducts of certain polyhaloethylenes which act as bromine donors. The tri- and tetrachloro- and bromo- and chlorobromoethylenes were especially efficient for this purpose. The vinyl chloride–bromine dimer and trimer have been separated and characterized. A mechanism has been proposed for this reaction which involves the disproportionation of a polyhaloethyl radical to an olefin and a bromine radical. Efficient bromine donors appear to be those materials which contain bulky electronegative substituents that weaken the carbon–bromine bond and which, in the radical form, lack energy delocalization mechanisms such as resonance and rotation about the carbon–carbon bond.

The feasibility of telomerizing olefins with bromine using bromine donors has been suggested previously.[1] The mechanism in Scheme I was proposed for the free-radical induced reaction between 1,1,2,2-tetrabromoethane and ethylene. In that reaction 1,2-dibromoethylene, 1,2-dibromoethane, and 1,4-dibromobutane were obtained as well as material believed to be 1,6-dibromohexane.

The above reaction scheme represents a free-radical chain telomerization of ethylene (the taxogen) by bromine (the telogen) with 1,2-dibromoethylene acting as a bromine carrier. Although proof of this mechanism was not obtained at the time, the material balance was in agreement with the proposed reaction course. The identification of 1,6-dibromohexane, which would have proved telomerization, was only putative, owing to its low concentration in the product.

Further work in these laboratories has now shown that certain olefins can indeed be telomerized with bromine by the use of materials which can act as bromine donors in such systems. High conversions have been obtained with vinyl chloride. Ethyl methacrylate

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[1] M. Rogozinski and L. M. Shorr, *J. Org. Chem.*, **29**, 948 (1964).