(14) We have previously followed Cooksey and Johnson[5] and used K_{ROH} in place of K_{R+}. We have now decided to use K_{R+} for the equilibrium constant for pseudobase formation since this is general practice for other cation–carbinol equilibria.
(15) A. Kaufmann and H. Hussy, *Chem. Ber.*, **41**, 1735–1742 (1908).
(16) G. B. Barlin and D. D. Perrin, *Quart. Rev., Chem. Soc.*, **20**, 75–101 (1966).
(17) As discussed later, k_{OH}/k_{H_2O} is approximately constant for these cations; this requires that $\rho(k_{H_2O}) \approx \rho(k_{OH}) \approx 0.5$ for both **3** and **5**. Also, from eq 21 one may then estimate $\rho(k_1) \approx -0.84$ for **3** and $\rho(k_1) \approx -0.62$ for **5**.
(18) P. R. Wells, "Linear Free Energy Relationships", Academic Press, New York, N.Y., 1968, p 12.
(19) C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, **2**, 323–400 (1964).

Elimination–Addition Mechanisms of Acyl Group Transfer: Hydrolysis and Aminolysis of Aryl Phenylmethanesulfonates[1]

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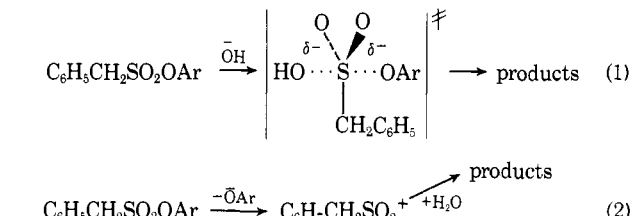
Abstract: The following evidence is consistent with an E1cB mechanism involving a sulfene intermediate for the alkaline hydrolysis and aminolysis of aryl phenylmethanesulfonates in water: (1) The Brønsted plot of hydroxide rate constant vs. phenol acidity possesses a sharp break at $pK_a \sim 6.5$. (2) Alkaline hydrolysis of the esters of weakly acidic phenols possesses a high selectivity ($\beta_{LG} = 2.4$) compared with that for esters (1.2) undergoing an addition–elimination mechanism. (3) The rate constant for phenol release is not linearly dependent on amine buffer concentration. (4) Trapping experiments with amines indicate a common intermediate for aminolysis of the esters. (5) The hydroxide rate constant for the 4-nitrophenyl ester is 1000-fold larger than for the corresponding benzene- and methanesulfonates. (6) Esters of the acidic phenols hydrolyze with general base catalysis and a high primary deuterium isotope effect. (7) Esters of the weakly acidic phenols undergo only specific base-catalyzed hydrolysis and involve no primary isotope effect. The lifetime of the conjugate base from esters of phenols with $pK_a <$ 6 is too short ($<10^{-13}$ s) for it to exist as a discrete intermediate and an E2 elimination occurs with an unsymmetrical transition state involving no S–OAr bond cleavage and half advanced proton transfer. The inactivation of α-chymotrypsin by phenylmethanesulfonyl fluoride is shown not to be via a sulfene intermediate.

Recent discussion has centered on the existence of E2 mechanisms[2] as opposed to E1 or E1cB pathways for elimination and especially on the critical evaluation of evidence previously thought to support a concerted timing.[3-5] The status of the E1cB mechanism was reviewed in 1967[6] and little evidence was available in favor of this pathway. Later, detailed studies established the stepwise path in selected systems and have led to an empirical understanding of mechanistic control.[7]

Four major types of reaction mechanism are envisaged for sulfonate group transfer. The addition–elimination mechanism (eq 1) is the process currently thought to operate for simple



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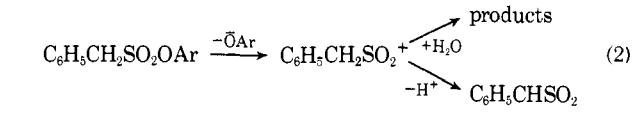

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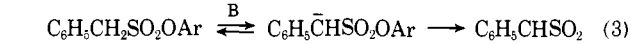

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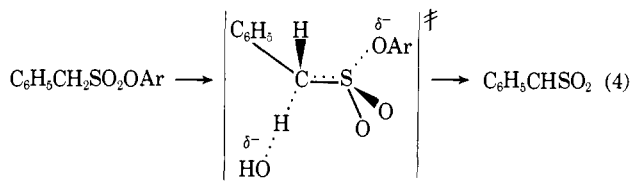


(4)

sulfonate transfers such as the hydrolysis of aryl benzenesulfonates.[8] There is some doubt, however, as to whether this process is stepwise involving a pentacovalent intermediate or concerted. The S_N1 path is a possible mechanism for sulfonyl halide hydrolysis,[9] although there is as yet no evidence for the E1 component involving proton transfer. One of the elimination mechanisms (eq 3 and 4) almost certainly participates in sulfene formation in the presence of base from sulfonyl halides possessing an α-proton.

The E1cB mechanism for acyl group transfer has recently become established,[10] but there is still no credible evidence for the operation of E2 timing for reactions in aqueous solution; we decided to investigate the possibility of E2 mechanisms of acyl group transfer for phenylmethanesulfonate esters where the intermediate is a sulfene. Regarding our knowledge of mechanistic control of the olefin forming reaction we thought that the high pK_a of the carbon acid[11] combined with an active leaving group might provide conditions for a concerted process which should be revealed in a Brønsted type plot vs. leaving group basicity; previous work[12] provides much evidence consistent with an E1cB-like (paenecarbanion) E2 process or an $E1cB_I$ (proton transfer rate limiting) mechanism for the formation of sulfenes from active sulfonates in nonaqueous solvents.

The inactivation of α-chymotrypsin by phenylmethanesulfonyl fluoride[13] is usually assumed to involve binding of the phenyl group in a hydrophobic pocket followed by an S_N2 attack of the nucleophile on the enzyme. An alternative explanation is that the enzyme catalyzes the formation of sulfene, which then attacks the nucleophile;[14] this mechanism is capable of being directly tested by use of a primary deuterium isotope effect.

Table I. Analytical and Physical Properties of Substrates

Substrate	Mp, °C	% found			% calcd		
		C	H	N	C	H	N
	Substituted Phenyl Phenylmethanesulfonates						
2-Nitro	72-73	53.3	3.9	4.9	53.2	3.8	4.8
4-Nitro[b]	106.5-107	53.1	3.6	4.6	53.2	3.8	4.8
3-Fluoro	60-61	58.5	4.5		58.7	4.2	
3-Nitro	82-83	53.5	3.9	4.8	53.2	3.8	4.8
4-Chloro	66-67	54.9	3.9		55.2	3.9	
Unsubstituted	88.5-89.5	63.2	4.7		62.9	4.9	
2,4-Dinitro[b]	84-85	46.4	3.1	8.2	46.2	3.0	8.3
2-Chloro-4-nitro	104-105	47.4	3.2	4.1	47.6	3.1	4.3
4-Chloro-2-nitro	127-128	47.9	2.9	4.5	47.6	3.1	4.3
2,6-Dinitro	147-148	46.1	2.9	8.4	46.2	3.0	8.3
4-Formyl	91-93	60.0	4.2		60.4	4.3	
3-Chloro	54-55	55.2	4.1		55.2	3.9	
2-Chloro	55-56	54.5	3.8		55.2	3.9	
4-Cyano	111-112	61.2	4.1	5.0	61.5	4.0	5.1
4-Ethoxycarbonyl	84-85	59.8	5.1		60.0	5.0	
2,5-Dinitro	119-120	45.9	3.1	8.1	46.2	3.0	8.3
4-Acetyl	90-91	61.8	5.1		62.1	4.8	
4-Methoxy[c]	96-97	60.1	4.9		60.4	5.1	
	Derivatives of Phenylmethanesulfonic acid						
Piperidide	137-138	59.9	7.0	5.7	60.2	7.2	5.9
Diethylamide	34-35	58.0	7.5	6.0	58.1	7.6	6.2
Fluoride[b]	91-92 (91-92)[17]						
Chloride[b]	88-89 (92-93)[15]						
Azide	53-54 (53-55)[18a]						
	4-Nitrophenyl Esters						
4-Nitrophenyl benzenesulfonate	90-92 (89-92[d])						
4-Nitrophenyl methanesulfonate	82-83 (83[d])						

[a] Analyses by Mr. G. M. Powell using a Hewlett-Packard Model 185 CHN analyzer. Melting points are corrected and were determined with a Kofler Thermospan instrument. [b] These materials were also prepared as the α,α-dideuterio esters; melting points of these did not differ from the protio forms. [c] This ester was very unreactive and its kinetic parameters were therefore not determined. [d] G. T. Esayan and M. A. Grigorian, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki*, **13**, 433 (1960); *Chem. Abstr.*, **55**, 27 190a (1961).

Experimental Section

Materials. Phenylmethanesulfonyl chloride[15] was prepared by adding benzyl chloride (127 g) dropwise to a mixture of thiourea (76 g) in methylated spirit (150 ml). The mixture was warmed until the reaction had started and all the thiourea had dissolved, and then the reaction was refluxed gently for about 30 min. Evaporation in vacuo gave a solid which was recrystallized from ethanol. The product, *S*-benzylisothiouronium chloride, was dissolved in the minimum of water and the solution cooled in ice. Chlorine was bubbled through the stirred solution and the sulfonyl chloride precipitate filtered and recrystallized, after drying, from benzene–petroleum ether (bp 40–60 °C). The acid chloride was also prepared from the dry sodium salt of the acid by warming with an equivalent amount of PCl_5 with enough benzene to render the suspension loose.[15] Filtration followed by recrystallization gave the acid chloride. The sodium phenylmethanesulfonate was prepared by refluxing benzyl alcohol with sodium hydrogen sulfite by the method of Shearing and Smiles.[16]

The aryl esters were prepared by the following general method: phenol (10 mmol) was dissolved in dry dichloromethane (20 ml) with dry triethylamine (10 mmol). To the cooled, stirred solution was added dropwise a solution of phenylmethanesulfonyl chloride (10 mmol) in dry dichloromethane. The mixture was kept stirring overnight, extracted with dilute HCl, dried with Na_2SO_4, and the dichloromethane solution evaporated in vacuo. Phenylmethanesulfonyl piperidide and -diethylamide were prepared by a similar process.

Phenylmethanesulfonyl fluoride was prepared by gently refluxing the chloride (10 g) in xylene (10 ml) with KF in H_2O (10 ml, 70%) for about 1 h. The product was cooled, diluted with water, and the fluoride crystallized from xylene.[17]

Phenylmethanesulfonyl azide was prepared by the method of Reagan and Nickon.[18a]

Physical and analytical data for these derivatives are recorded in Table I.

Deuterium-Incorporated Compounds. 3-Nitrophenyl phenylmethanesulfonate or the chlorophenyl ester (40 g) was dissolved in dioxane (100 ml) and stirred with D_2O (100 ml) and NaOD (10.7 g) for 1 h. The material was acidified with DCl to pH 3, extracted with chloroform, then ether, and evaporated to give the sodium salt (with NaCl impurity) of the acid ($PhCD_2SO_3Na$). The material was converted to 4-chloro- and 3-nitrophenyl ester via the acid chloride and the process repeated. The final proton content of the methylene group in the acid chloride, fluoride, 4-nitrophenyl ester, and 2,4-dinitrophenyl ester was found to be less than 1% as judged from NMR spectra.

Other materials were of analytical reagent grade or were purified by distillation or crystallization of the bench grade materials. Water was twice distilled from glass and D_2O (99.95%) was obtained from Prochem Ltd. Biebrich scarlet was obtained from Messrs. Hopkins and Williams and was recrystallized according to the method of Jayaran and Rattee;[18b] α-chymotrypsin was obtained from Boehringer (Mannheim).

Methods. Infrared spectra (Unicam-SP 200 and Perkin-Elmer Model 237 instruments) were used routinely to check the identity of products. NMR spectra (Perkin-Elmer R10 machine) were also used for identification and occasionally a Joel 100 Mc/s instrument, operated by Dr. D. O. Smith, was employed. pH measurements were made using a Pye-Dynacap instrument calibrated with E.I.L. standard pH powders. Mass spectra were recorded on an A.E.I. MS 902 high resolution mass spectrograph by Dr. R. B. Turner of this laboratory.

The labeling experiments were carried out as follows: the ester, in acetonitrile/alcohol solution, was added slowly to a stirred solution of NaOH (0.1 M), allowing complete solution before further addition. The phenol was then extracted with chloroform after acidification, isolated, and submitted for mass spectral analysis. Abundancies were estimated directly from the peak heights in the photographic traces.

Table II. Fission of 4-Nitrophenyl and 2,4-Dinitrophenyl Phenylmethanesulfonate in ^{18}O-Enriched Water [f,g]

Product	Natural		Control,	Enriched,	S-O,	Ar-O,
	Calcd[c]	Obsd	obsd[d]	obsd	calcd[e]	calcd[e]
4-Nitrophenol[a]	0.818	0.890	0.893	0.808	0.818	2.583
2,4-Dinitrophenol[b,h]	1.255	1.390	1.300	1.405 (A)	1.255 (B)	3.020 (C)

[a] Product from the hydrolysis of 4-nitrophenyl phenylmethanesulfonate in 0.01 M NaOH, 25 °C, 1 M ionic concentration made up with NaCl. [b] Product from 2,4-dinitrophenyl phenylmethanesulfonate under the conditions of footnote *a*. [c] Calculated from the natural abundance (R. C. Weast, Ed., "Handbook of Chemistry", 51st ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1970-1971). [d] Products treated with enriched water. [e] Calculations based on an ^{18}O enrichment of 1.969%. [f] Figures represent the abundance of the $(M + 2)^+$ ion as a percentage of the M^+ ion. [g] An estimate of the errors may be obtained by comparing the observed and calculated natural percent abundance of the $(M + 2)^+$ ion. [h] An estimate of 8% for the reaction proceeding via Ar-O cleavage may be obtained using the figures in the last three columns and the equation: % Ar-O = (A − B)100/(A − C); this value must be regarded as an *upper limit* only because of the relatively large error observed in the measurements compared with the total effect.

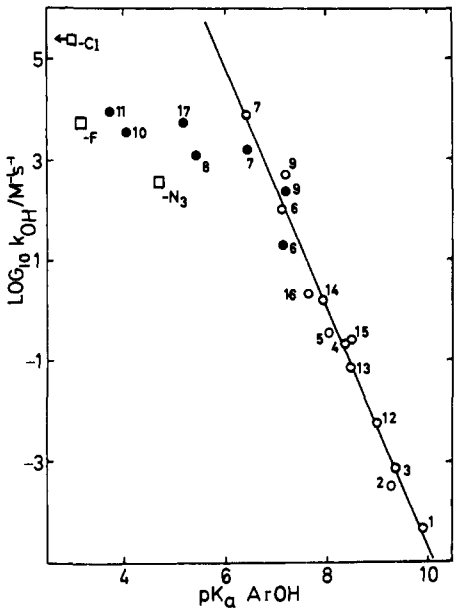


Figure 1. Plot of log k_{OH} vs. pK_a of the leaving phenol in the hydrolysis of substituted phenyl phenylmethanesulfonates. Data are from Table III; open circles represent buffer independent rate constants. Points for azide, chloride, and fluoride are included for comparison purposes; the numbering system for identification is given in Table III.

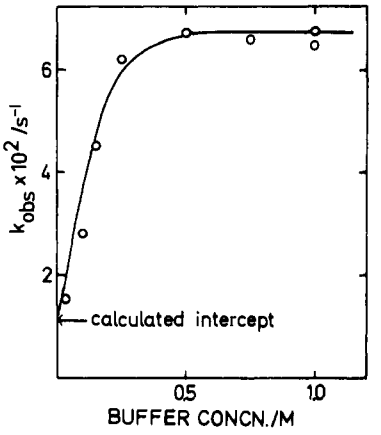


Figure 2. Plot of rate constant for release of 4-nitrophenol from 4-nitrophenyl phenylmethanesulfonate in diethylamine buffers of increasing concentration. Conditions: 50% base, ionic strength made up to 1 M with NaCl, pH 10.82 ± 0.02, 25 °C. The intercept marked is calculated from the data inTable III using the pH; the buffer-independent line is also calculated from data in Table III.

Reaction kinetics were measured spectrophotometrically using the following technique: ester (50 λ), ca. 10 mg dissolved in 0.25 ml of acetonitrile and made up to 5 ml with absolute alcohol, was mixed with aqueous buffer in a silica cell in the thermostatted cell compartment of the instrument (Beckman-DBG or Unicam-SP 800) using the flattened tip of a glass rod as a stirrer. It was necessary to use ethanol as solvent for the stock as the substrate in acetonitrile tended to precipitate when added to the buffer; the purpose of the acetonitrile in the stock is to solubilize the ester, as solution does not readily take place with ethanol alone (the maximum organic solvent content in the reaction mixture was 2% in ethanol with 0.1% in CH_3CN). The wavelength for kinetic studies was determined previously using the automatic scanning mode of the Unicam-SP 800 instrument; repetitive scanning also gave an indication of the cleanness of the reaction.

A pH stat (Radiometer, Copenhagen) was used to follow chloride, fluoride, and azide hydrolyses: a stock solution of the derivative in acetonitrile was added to a solution of 9 ml of 1 M NaCl solution in the thermostatted cell and the pH maintained at a set value by titration with 0.1 M NaOH. The amount of acid released allowed a check on the stoichiometry of the reaction.

Reaction of phenylmethanesulfonyl fluoride with chymotrypsin was followed by measuring the change in absorbance at 550 nm caused by release of Biebrich scarlet bound at the active site of the enzyme. Dye solution (50 λ) was added to a solution of the enzyme in buffer (2.5 ml) and the trace at 550 nm recorded with a Servoscribe potentiometric recorder. The inhibitor, in acetonitrile, was then added (50 λ) and the trace, involving dye expulsion, measured. The magnitude of the dye-enzyme complex absorbance compared with the dye alone was used as an internal measure of the enzyme concentration.

Results

The esters liberated phenol in buffers via a pseudo-first-order rate law up to about 90% of the total reaction. In the case of the 4-nitrophenyl esters the reaction was shown to give a stoichiometric amount of product as judged from the absorbance at 400 nm and the known extinction coefficient of 4-nitrophenol in base. Spectral scanning also indicated that the reaction was a simple A → B type in those cases where isosbestic wavelengths were observed. pH stat experiments in the case of azide, chloride, and fluoride showed that the stoichiometric amount of acid was liberated.

The site of fission in the ester hydrolyses in base is at the S-O bond for 4-nitrophenyl phenylmethanesulfonate, but for the 2,4-dinitrophenyl ester 8% of the reaction is via Ar-O cleavage. The accuracy on this is not very high judging from the control data in Table II, but it is sufficient to show that S-O cleavage is the predominant pathway. Reaction of the 4-nitrophenyl ester in amine buffers gave sulfonamide by comparison of the melting point and spectral characteristics of the product with authentic samples (piperidide and diethylamide) also indicating S-O fission (see later for trapping experiments).

Base Catalysis. The least reactive phenyl ester showed only specific base-catalyzed hydrolysis, whereas general base catalysis was also observed for the most reactive esters. The bimolecular rate constants for specific base catalysis are plotted in Figure 1 vs. the pK_a of the leaving phenol. The 4-nitrophenyl,

Table III. Rate Parameters for Substrates

	Substrate	pK_a^{ArOH} [b]	pK_{SH} [i,l]	k_{OH}, [j,d,h] M^{-1} s^{-1}	k_2, [k] s^{-1}	λ, nm
			Substituted Phenyl Phenylmethanesulfonates			
1	Unsubstituted	9.92	22.8	4.9×10^{-5} [m] (4)	2.9×10^4	270
3	4-Chloro	9.38	22.6	7.7×10^{-4} (6)	2.7×10^5	245
4	3-Nitro	8.39	22.2	0.23 (5)	3.3×10^7	355 or 290
5	4-Acetyl	8.05	22.0	0.40 (4)	4.2×10^7	325
6	4-Nitro	7.15	21.7	110, 22[c] (15)	5.0×10^9	400
7	2-Nitro-4-chloro	6.46	21.4	5900, 2100[c] (10)	1.4×10^{11}	400
8	4-Nitro-2-chloro	5.45		1300[c] (10)		400
9	2-Nitro	7.23	21.7	520, 270[c] (10)	2.5×10^{10}	400
10	2,4-Dinitro	4.11		3800[c,e] (10)		400
11	2,6-Dinitro	3.77		10 000[c] (9)		430
12	3-Chloro	9.02	22.4	6.2×10^{-3} (3)	1.6×10^6	230
13	2-Chloro	8.48	22.2	0.077 (3)	1.2×10^7	290
14	4-Cyano	7.95	22.0	1.7 (3)	1.6×10^8	275
15	4-Ethoxycarbonyl[a]	8.50	22.2	0.27 (3)	4.3×10^7	300
			Derivatives of Phenylmethanesulfonic Acid			
18	Chloride	−7		2.6×10^5 [c,f] (4)		pH stat
19	Azide	4.72		390[c,f] (6)		pH stat
20	Fluoride	3.17		5800[c,f,g] (8)		pH stat
			4-Nitrophenyl Esters			
21	Benzenesulfonate			0.016 (4)		400
22	Methanesulfonate			0.040 (5)		400

[a] Measured with piperidine buffers; aminolysis reaction at the carboxyl ester is absent, since the rate constants are buffer independent. [b] Ionization constants obtained from W. P. Jencks and J. Regenstein in the "Handbook of Biochemistry", 2d ed, H. A. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1970, Section J-187; Kortüm, Vogel, and Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution", Butterworths, London, 1961; the value for chloride is taken from R. P. Bell, "The Proton in Chemistry", 2d ed, Chapman and Hall, London, 1973, p 86. [c] Obtained from the intercept at zero buffer concentration. [d] Except where stated these are buffer-independent rate constants (i.e., derived from rate data at buffer concentrations where the rate is buffer independent); values in parenthees are the numbers of runs for each parameter: errors in the parameters no greater than 10%; aqueous buffers. [e] Corrected for a small amount of AR–O cleavage (see text and Table II); the correction is barely above the experimental error. [f] Medium contains 3% ethanol. [g] I. G. Knunyants and G. A. Sokolski, *Angew. Chem., Int. Ed., Engl.*, **11**, 583 (1972), find a value 912 M^{-1} s^{-1} under different conditions from our experiments. [h] Buffer species involved in the measurements are as follows: piperidine (4, 5, 6, 13, 14, 15, 16); tris(hydroxymethyl)aminomethane (6, 7, 8, 10, 17); hydroxide ion (1, 2, 3, 12, 21, 22); β-alanine (9); diethylamine (6); bicarbonate (6); borate (6); dinitrophenyl phenylmethanesulfonate parameters were also derived from intercepts (at zero buffer concentration) in the presence of buffer species noted in Table IV. All except esters 8, 10, 11, 12, 6, 7, 9 had buffer-independent rates. [i] The proton transfer step catalyzed by hydroxide ion follows the equation $\log k_1 = 5.5 - 0.4pK_a^{ArOH}$, which defines the line (Figure 7) for k_{OH} at zero buffer concentration for esters 7, 8, 10, 11, 17 and the "corrected" exchange rate (see discussion of α-proton acidity and legend to Figure 7) for ester 6 in H_2O. The value of pK_{SH} may be calculated from the equation $pK_{SH} = 2 \times 10^{10}/(1 + 10^{-(pK_{acceptor} - pK_{donor})})$, from R. S. Molday and R. G. Kallen, *J. Am. Chem. Soc.*, **94**, 6739 (1972), assuming protonation of the conjugate base by water has the diffusion-controlled rate 2×10^{10} M^{-1} s^{-1}. We utilize $pK_w = 14$ for proton dissociation from H_2O to allow for the 55.5 M concentration of water in the calculation of pK_{SH}. The linear free energy relationship $pK_{SH} = 18.8 + 0.4pK_a^{ArOH}$ governs the carbon acidity. [j] The buffer-independent specific base term is governed by the equation $\log k_{OH} = 19.3 - 2.4pK_a^{ArOH}$ [k] The decomposition of the carbanion is governed by the linear free energy relationship $\log k_2 = 24 - 2.0pK_a^{ArOH}$. [l] The values for pK_{SH} are close to those for similar compounds in Me_2SO solvent ($C_6H_5CH_2SO_2CH_2C_6H_5$, 24; $C_6H_5SO_2CH_3$, 25.5). We are indebted to Professor F. G. Bordwell for communicating these unpublished results (July 1975). [m] This value is close to that found by O. R. Zaborsky and E. T. Kaiser, *J. Am. Chem. Soc.*, **88**, 3084 (1966).

2-nitrophenyl, and 2-nitro-4-chlorophenyl phenylmethanesulfonates possessed two specific base-catalyzed terms: as the buffer concentration is increased the general base term vanishes (Figure 2) and the buffer independent rate constant as well as the intercept at zero buffer concentration is proportional to hydroxide ion concentration. The nonlinearity in the buffer-rate constant relationship was shown to exist for diethylamine and piperidine buffers for the 4-nitrophenyl ester, tris(hydroxymethyl)aminomethane for the 2-nitro-4-chlorophenyl ester, and β-alanine for the 2-nitrophenyl ester.

The general base catalytic terms were measured for a series of buffer species for the 2,4-dinitrophenyl ester. The catalysis by tris(hydroxymethyl)aminomethane was measured at three different buffer ratios (Figure 3) and found to be proportional only to the concentration of basic species. The other buffer effects were measured at a constant pH varying the concentration of the base species in question, and the results (Table IV) for the bimolecular term calculated assuming only base catalysis. For the most reactive base species the pH was kept constant with tris(hydroxymethyl)aminomethane buffer and the proportion of base present estimated from the pK_a of the conjugate acid. No curvature was observed in the buffer-rate plots for esters of phenols with $pK_a < 6$.

Trapping Experiments. Analysis of the product stoichiometry in the reaction between diethylamine or piperidine buffers (1 M total buffer concentration, 1 M ionic strength, 25 °C, fraction base = 0.5) and the 4-nitrophenyl phenylmethanesulfonate was carried out by extracting the acidified reaction mixture with chloroform. The NMR spectrum of the product mixture showed a 1:1 ratio of amide to 4-nitrophenol as judged from the doublet of doublets of the AB 4-nitrophenol system and the methylene peak of the sulfonamide.

Deuterium Isotope Effects. Solvent deuterium oxide and primary deuterium isotope effects for 2,6-dinitrophenyl, 2,4-dinitrophenyl, and 3-nitrophenyl phenylmethanesulfonates, and phenylmethanesulfonyl fluoride are recorded in Table V together with the conditions of measurement.

4-Nitrophenyl phenylmethanesulfonate gave complicated kinetics for the isotopic studies: examples of the progress curves for α-deuterated ester hydrolysis in H_2O buffers and the protio ester in D_2O buffers are shown in Figures 4 and 5. The latter hydrolysis involves essentially a "burst" of 4-nitrophenol lib-

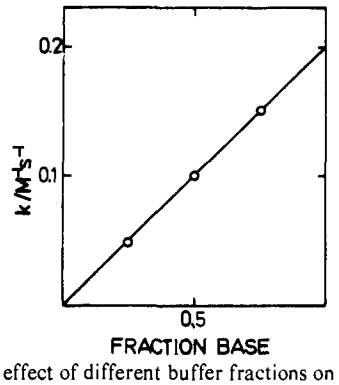


Figure 3. The effect of different buffer fractions on the catalytic power of tris(hydroxymethyl)aminomethane on the release of 2,4-dinitrophenol from 2,4-dinitrophenyl phenylmethanesulfonate. Conditions: ionic strength made up to 1 M with NaCl, 25 °C; line is drawn from data in Table IV assuming no general acid catalysis.

Table IV. General-Base-Catalyzed Hydrolysis of 2,4-Dinitrophenyl Phenylmethanesulfonate

Base	Abbreviation	pK_a[c]	k_1, M^{-1} s^{-1} [b,g]
Hydroxide	(OH)	16.5[d]	3800 (10)
Tris[a]	(TRIS)	8.23[e]	9.2 (12)
Imidazole	(IM)	7.06	0.13 (5)
Methylglycinate	(MGLY)	7.58	0.11 (4)
Pyridine	(PYR)	5.27	0.0023 (4)
4-Picoline	(PIC)	5.90	0.0080 (3)
Piperidine	(PIP)	11.22[f]	121 (5)
β-Alanine	(BA)	10.19[f]	3.7 (3)
Ethylamine	(ET)	10.63[f]	7.8 (4)
Ethyl β-alaninate	(EBA)	8.64[f]	0.66 (3)
Aniline	(AN)	4.70	0.0040 (4)
Morpholine	(MOR)	8.72	3.1 (3)
Phosphate dianion	(P_i^{2-})	6.68	0.0049 (4)

[a] Tris(hydroxymethyl)aminomethane. [b] At 25 °C, 1 M ionic strength made up with NaCl; aqueous buffers. [c] See footnote *b* of Table III. [d] C. K. Sauers, W. P. Jencks, and S. Groh, *J. Am. Chem. Soc.*, **97**, 5546 (1975); A. R. Fersht and W. P. Jencks, *ibid.*, **92**, 5442 (1970); A. R. Fersht, *ibid.*, **93**, 3504 (1971). [e] A. Williams and W. P. Jencks, *J. Chem. Soc., Perkin Trans. 2*, 1753 (1974). [f] Buffer species utilized was Tris, 0.1 M at pH 8.2. [g] Number in parentheses is the number of kinetic runs used to determine k_1; the error on k_1 is no greater than 10%.

eration, while the former involves an induction period. We analyze these phenomena in terms of an exchange process and the hydrolytic reaction:

$$C_6H_5\bar{C}HSO_2OpNp \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} C_6H_5CH_2SO_2OpNp \xrightarrow{-OpNp} C_6H_5CHSO_2 \quad (5)$$

The exchange rate may be estimated from the rate of attainment of the final rate of hydrolysis as one species is converted into its isotopically labeled form. The rate of approach of the initial curve to the final linear correlation (Δ) is plotted vs. time as indicated in the figures; the value of Δ was obtained graphically from larger scale plots than those illustrated.

As a check on the method protio and deuterio esters were found to give good first-order kinetics in the protio and deuterio buffers, respectively, the rate constants being identical with those from the linear final portions of the plots similar to those in Figures 4 and 5, respectively.

The rate constants obtained from the induction period and burst phase, identified as proton or deuteron exchange, are proportional to hydroxide or deuterioxide ion concentration, respectively, but no dependence on buffer concentration was noticed in the range 0.04-0.1 M (carbonate-bicarbonate).

Table V. Isotope Effects on the Hydrolysis of Phenylmethanesulfonic Acid Derivatives[a]

Derivative	k, M^{-1} s^{-1} [b,g,i]		k^H/k^D
Fluoride[d]	$k_{OH}{}^D$, 995(4)	$k_{OH}{}^H$, 5800 (8)	6.0
2,6-Dinitrophenyl[e]	$k_{OD}{}^H$, 24 000 (3)	$k_{OH}{}^H$, 10 000 (9)	0.42
2,4-Dinitrophenyl[e]	$k_{OH}{}^D$, 957 (3)	$k_{OH}{}^H$, 3800 (10)	4.0
3-Nitrophenyl[c]	$k_{OH}{}^H$, 0.23 (5)	$k_{OD}{}^H$, 0.29 (3)	0.80
4-Nitrophenyl[f]			
Reaction	$k_{OD}{}^D$, 33 (9)	$k_{OH}{}^h$, 21 (8)[h]	0.64
Exchange	$k_{OD}{}^H$, 990 (9)	$k_{OH}{}^D$, 61 (8)	16.2[j]

[a] At 25 °C, ionic strength made up to 1 M with NaCl; aqueous buffers. [b] Superscripts refer to the isotopic labeling of the α-carbon and subscripts to the solvent nucleophile. [c] Piperidine buffer (rate constants are buffer independent). [d] pH stat method employed. [e] Tris(hydroxymethyl)aminomethane buffer (rate constants are for zero buffer concentration). [f] Bicarbonate buffers. [g] Number in parentheses is the number of kinetic runs contributing to the rate constant. [h] This value agrees well with that from experiments with other buffers (see Table III). [i] Except for the 3-nitrophenyl case these results are obtained by extrapolation to zero buffer concentration. [j] We estimate $k_{OH}{}^H$ for exchange to be 415 M^{-1} s^{-1} using $k_{OD}{}^H$ for exchange and the ratio of hydroxide to deuterioxide rates for proton transfer from the 2,6-dinitrophenyl ester (0.42); this gives rise to a ratio $k_{OH}{}^H/k_{OD}{}^D$ = 6.8 for the exchange process.

Reaction of α-Chymotrypsin with Phenylmethanesulfonyl Fluoride. The release of dye from the chymotrypsin-Biebrich scarlet complex by phenylmethanesulfonyl fluoride was accurately first order up to about 90% of the reaction. The pseudo-first-order rate constants increase with increasing sulfonyl fluoride concentration, but the relationship is not linear. The initial slope of this relationship is essentially the ratio k_r/K_i (eq 6, CT = chymotrypsin):

$$CT + I \overset{K_i}{\rightleftharpoons} CT \cdot I \xrightarrow{k_r} \text{inhibited enzyme} \quad (6)$$

The value for k_r/K_i obtained agrees as well as can be expected for this type of measurement with those obtained by a different method (248 M^{-1} s^{-1}, 25 °C).[13a] The results are recorded in Table VI.

Discussion

Evidence for an E1cB Mechanism. It is proposed that the hydrolysis and aminolysis of aryl phenylmethanesulfonates involves a stepwise elimination-addition mechanism (E-A, eq 3). The simplest evidence that the normal addition-elimination (A-E) process is not operating is that the hydroxide rate constant for hydrolysis of 4-nitrophenyl phenylmethanesulfonate is some 1000-fold greater than that for the corresponding benzene- and methanesulfonate esters, which possess an A-E pathway.[8] The latter esters have similar rate constants for reaction with hydroxide ion and the benzenesulfonate presumably cannot involve a sulfene intermediate. Vizgert's data[8] indicate that the sensitivity of the reaction to substituent change on the sulfur is similar to that for carboxylate esters, where the reactivity is in a similar ratio $C_6H_5 < CH_3$.[19a] We therefore conclude that the 4-nitrophenyl methanesulfonate alkaline hydrolysis does not possess an elimination-addition mechanism.

The very high selectivity to Hammett's σ^- (5.4) and the large Brønsted-type β_{LG} (−2.4) are consistent with phenolate ion character in the transition state of the rate-limiting step; alkaline hydrolysis of substituted phenyl benzenesulfonates has a Hammett selectivity of 2.5[8] and is vs. σ. That such high

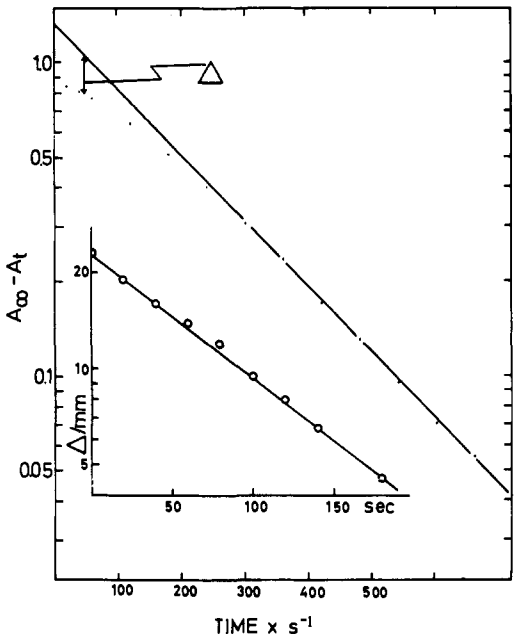


Figure 4. Release of 4-nitrophenol from 4-nitrophenyl α,α-dideuteriophenylmethanesulfonate in bicarbonate buffers in ^1H_2O. Absorbance difference at 400 nm ($A_\infty - A_t$) is only linear after all the deuterium has exchanged and the rate of exchange is a first-order process (inset). Conditions: pH 10.17, buffer concentration = 0.04 M, fraction base = 0.5.

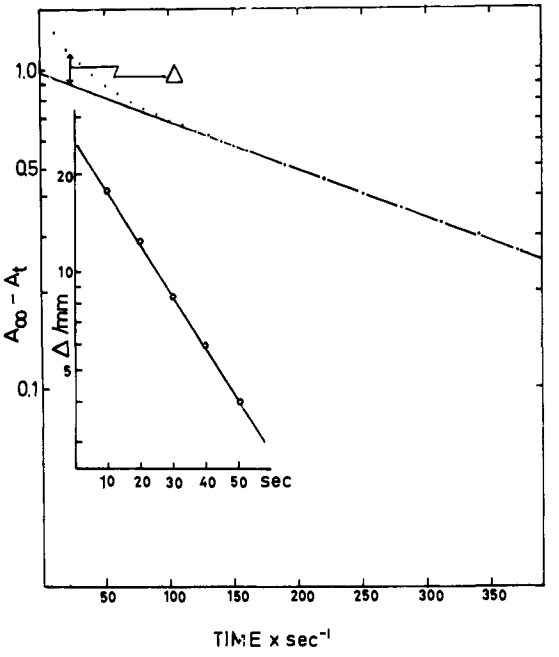


Figure 5. Release of 4-nitrophenol from 4-nitrophenyl phenylmethanesulfonate in bicarbonate buffers in D_2O. Absorbance difference at 400 nm ($A_\infty - A_t$) is only first order after the ^1H has exchanged; rate of exchange is a first-order process (inset). In the inset the point at zero time is not estimated, since the process is a deceleration (in Figure 4, the release of D from the α,α-dideutero compound, a zero point is easily estimated because the process is an acceleration). Conditions: pD = 10.54 (estimated from pD = measured pH + 0.37, see A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 947 (1975)), buffer concentration = 0.04 M, fraction base = 0.5.

selectivity and the σ^- dependence are not due to Ar–O cleavage is demonstrated by the absence of ^{18}O incorporation from enriched water into the product phenol. As the pK_a of the leaving phenol is reduced the high selectivity changes abruptly to a line of low slope (Figure 1) and this is consistent with a change in rate determining step pointing to the existence of an intermediate. The high slope is presumably due to the rate-limiting departure of the leaving group (where rate will be very sensitive to phenol structure), while the low slope is due to the proton transfer step, which is remote from the influence of the phenol substituent. The kinetic rate law for mechanism 3 is given in the equation

$$k = k_1[B]k_2/(k_{-1}[HB] + k_2) \qquad (7)$$

and the break in the Brønsted relationship (Figure 1) is due to the variation of k_2 (B and HB are in this case OH^- and H_2O, respectively) and k_1 will be relatively invariant; k_{-1} is a diffusion-controlled rate constant and is therefore not dependent on phenol substituent. Increasing buffer concentration will also cause a change in the rate-limiting step, as evidenced by nonlinear buffer–rate plots (e.g., Figure 2). However, these nonlinear plots only occur for those esters near the break point in the Brønsted relationship; esters with phenols of low pK_a (numbers 8, 10, 11, 17 in Table III) show only general base catalysis because the base concentration necessary for a change in rate-limiting step would need to be greater than unity. These experiments eliminate the concerted and stepwise A-E mechanism (eq 1) and are, moreover, not consistent with proton transfer concerted with leaving group departure (eq 4), where the C–H and S–OAr bond cleavages are equally advanced in the transition states.

The work of King and Beatson[1] shows that (for a D_2O–DME (1,2-dimethoxyethane) solution) the triethylamine catalyzed proton exchange is related to the release of phenoxide ion via a linear free energy relationship for esters of weakly acidic phenols up to those of strongly acidic phenols, but with *no* breakpoint. This is consistent with our observation of a break in the Brønsted-type relationship (Figure 1) because in the former relationship the results are all for the condition where proton transfer is rate limiting.

Table VI. Inhibition of α-Chymotrypsin with Phenylmethanesulfonyl Fluoride[a]

Inhibitor	k_r/K_i, $M^{-1}\,s^{-1}$ [b]	[I] M × 10^4
α,α-Dideutero	65	2.5–10
α,α-Diprotio	57	2.5–10

[a] 25 °C, pH 6.60, phosphate buffer 0.02 M, 0.1 M ionic strength made up with NaCl; aqueous buffers. [b] The rate constant is proportional to inhibitor concentration in the range 0–5 × 10^{-4} M inhibitor; a slight negative deviation from linearity was observed at higher concentrations, but a $K_i > 1$ mM was indicated by the absence of *initial* dye expulsion from the enzyme-inhibitor complex on adding inhibitor to concentration 1 mM.

Trapping experiments with amines in the region where rate is buffer independent are consistent with a rate-limiting step prior to reaction with the amine trapping agent. King and his co-workers[1,19b] were also able to trap the sulfene with an enamine via a cycloaddition reaction, and ynamine adducts have also been observed.[19c] Both trapping approaches specifically point to phenylsulfene as the intermediate. It is very unlikely that the carbanion intermediate could be the trapped species in either amine or enamine trapping experiments. Kinetic experiments demonstrate the independence of the rate of phenol release on amine concentration (see Results), thus removing the possibility of direct attack on the neutral substrate.

Deuterium isotope effects (Table V) are also consistent with the elimination–addition mechanism of eq 3. Large primary deuterium isotope effects exist for esters to the left of the break in the Brønsted plot of Figure 1, in agreement with rate-limiting proton transfer. No effect is seen with esters of the less acidic phenols presumably because rapid exchange takes place

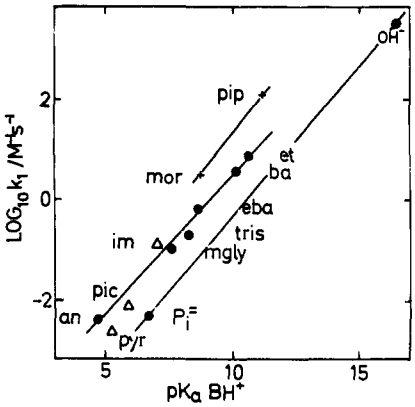


Figure 6. Brønsted relationship between log k_1 and the pK_a of the conjugate acid of the base catalyzing the release of 2,4-dinitrophenol from 2,4-dinitrophenyl phenylmethanesulfonate. Data and nomenclature are from Table IV and the lines are arbitrary.

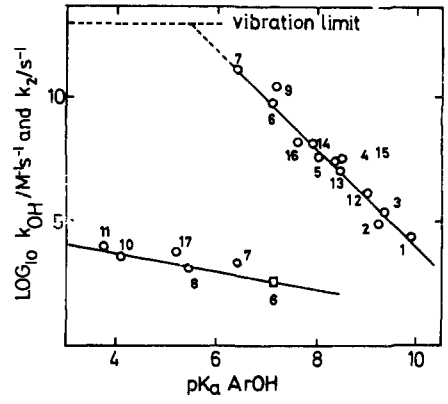


Figure 7. Brønsted-type relationship for k_{OH} (measured at zero buffer concentration and essentially a proton transfer to hydroxide) and k_2, the decomposition of the conjugate carbanionic base in the hydrolysis of substituted phenyl phenylmethanesulfonates. Substrates are identified by numbers from Table III, which also supplies the data. Since deprotonation by OH^- is not rate limiting for the 4-nitrophenyl ester (point 6), the proton exchange rate constant is used for this substrate. The vibration limit is the rate constant derived from the half-life for a vibration of the S-O bond; lines are derived from equations in footnote i of Table III.

at the α-carbon atom. Solvent deuterium oxide isotope effects, while consistent with the E-A process, are not diagnostic.[20a]

The action of bases on the cleavage of 2,4-dinitrophenyl phenylmethanesulfonate yields a Brønsted relationship (Figure 6), where bases of similar structure fall on separate lines, but the sensitivity is approximately constant (0.55-0.65). Nucleophilic attack by the base species is not consistent with the relatively high reactivity observed compared with the known low efficiency of sulfonates to nucleophiles other than hydroxide.[19d]

The large observed β_{LG} for the second-order rate constant k_{OH} for the esters of the least acidic phenols could result from rate-determining diffusion apart of the phenolate anion from the sulfene

$$C_6H_5CH_2SO_2OAr \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_6H_5C\overline{H}SO_2OAr \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C_6H_5CH{=}SO_2 \cdot \overline{O}Ar \xrightarrow{\text{d.c}} \quad (8)$$

or from rate determining S-OAr cleavage, where the fission is far advanced in the transition state. The former explanation could be advanced for other E-A acyl transfer reactions (aryl carbamate,[20a] aryl methylaminosulfonate[20b]) which exhibit high β_{LG} values; a similar possibility has been argued for attack of amines on *N*-acetylimidazole, which possesses a very high β_{Nuc}.[20c] The rate-limiting step for the hydrolysis of esters of the acidic phenols is clearly proton transfer because of the very low β_{LG} and presumably in the region of the pK_a of 4-nitrophenol two changes are occurring in rate limiting step (from diffusion apart, d.c, to return from sulfene, k_-, to proton transfer).

The mechanism involving direct formation of sulfene via a nonstepwise process could explain most of the kinetic results, the changeover in rate-limiting step being from formation to decomposition of sulfene.

$$C_6H_5CH_2SO_2OAr \underset{H_2O}{\overset{OH^-}{\rightleftharpoons}} C_6H_5CH{=}SO_2 + \overline{O}Ar \xrightarrow{H_2O \text{ or } N\equiv} \text{products} \quad (9)$$

Deuterium exchange via sulfene reversal on this mechanism may account for results of experiments carried out with large quantities of materials (e.g., gram amounts). The process is not consistent with our results, however, which are for experiments with very low concentrations of substrate where the back reaction (a bimolecular one) would not occur except with very large quantities of phenol. Moreover, King and Beatson[1] found that even with added phenols the exchange rate was not enhanced. It is difficult to see how the phenolate produced in our experiments at ca. 0.1 mM could react with the sulfene faster than water at 55.5 M or diethylamine buffer at 1 M (the maximal concentration of buffers), in order to ensure the sulfene formation was not rate limiting for the esters of least acidic phenols. In the case of the acidic phenols, where presumably sulfene formation is rate determining for this mechanism, the Brønsted type β_{LG} is inordinately low for S-OAr cleavage in the transition state.

An ion pair mechanism of the type

$$C_6H_5CH_2SO_2OAr \rightleftarrows C_6H_5CH_2SO_2^+ \cdot \overline{O}Ar \xrightarrow[\text{slow}]{OH^-} \text{products} \quad (10)$$

could be an alternative to the one proposed; the changeover in rate-limiting step should involve proton transfer rate limiting for the esters of the more basic phenolates, since for these the reversal of the ion pair (to give ester) would be fastest. This is contrary to the observed absence of a primary deuterium isotope effect for these esters and the absence of general base catalysis. The mechanism is also not consistent with the low β_{LG} observed for the esters of the acidic phenols: since an S-OAr bond is breaking, we should expect here a large selectivity to the pK_a of the departing phenol.

Acidity of the α-Proton. The proton exchange rate constant provides us with data to estimate the pK_a of the α-proton in the aryl phenylmethanesulfonates. The proton exchange rate for the 4-nitrophenyl ester may be determined for D_2O solvent (Table V) and comparison with the hydrolysis rate constant ratio for 2,6-dinitrophenyl phenylmethanesulfonate in H_2O and in D_2O (this is essentially a proton transfer rate) allows us to estimate the proton exchange rate for the 4-nitrophenyl ester in H_2O. This value, with the hydroxide rate constants (k_1) for hydrolysis of esters 8, 10, 11, and 17 (k_1 is the bimolecular rate constant for abstraction of a proton from the substrate by hydroxide ion or general base and for these esters the hydroxide term is identical with the rate constant for ester hydrolysis by hydroxide ion) yields a Brønsted-type correlation (Figure 7) for the proton transfer step. If we may assume that the protonation step (by water) is diffusion controlled[21] ($k_{-1} = 2 \times 10^{10}\ s^{-1}$) we are then able to calculate k_2 from the equation

$$k_{OH} = (k_1/k_{-1})k_2 \quad (11)$$

for the less reactive esters where k_2 is rate limiting; we also

assume that the extrapolation of the k_1 vs. pK_a Brønsted relationship holds for the least reactive esters and the similarity in structure would seem to support this. This latter assumption is given support by King and Beatson's[1] observation that the triethylamine-induced proton transfer is linearly dependent on Hammett's σ from 4-methoxyl to 2,4-dinitrophenyl esters. The correlation between k_2 and the pK_a of the leaving phenol is also illustrated in Figure 7.

The value for k_2 for the 4-nitrophenyl ester may also be estimated from the data for the nonlinear buffer plots. Taking the data from Figure 2 the concentration of diethylammonium ion for half maximal *change* in rate constant is approximately 0.05 M and thus $k_2 = 0.05\ k_{-1} = 10^9\ s^{-1}$, assuming diffusion-controlled protonation by the ammonium ion; this is a distinctly more reasonable assumption than that for protonation by water, and yet the rate constant comes within an order of magnitude of that calculated from hydroxide-induced transfer (Table III: $5 \times 10^9\ s^{-1}$). A value of $2 \times 10^9\ s^{-1}$ may also be estimated for the k_2 step for the 4-nitrophenyl ester from data at fraction base = 0.5 for carbonate-bicarbonate buffers.

We can also check the method using the buffer-catalyzed hydrolysis of the 2,4-dinitrophenyl phenylmethanesulfonate. No buffer curvature is possible with this ester, since the value of k_{OH} for the condition where reaction is buffer independent (k_{-1} [HB] > k_2) is some six orders of magnitude greater than k_{OH} at zero buffer concentration (see Figure 1). We should add here that the rate constant at zero buffer concentration is proportional to hydroxide ion concentration, as is the rate constant which is independent of buffer concentration; both of these rate constants are designated k_{OH}. We may calculate the former k_{OH} from the equation of footnote *j* of Table III to be $2.7 \times 10^9\ M^{-1}\ s^{-1}$ and the concentration of $TrisH^+$ required to reach half of this value is approximately 10^4 M; it is obtained from the general base term for Tris (Table IV) for the reaction of the 2,4-dinitrophenyl ester at fraction base = 0.5 and is simply the hypothetical concentration of Tris required to bring the rate constant to that for $k_{OH} = 2.7 \times 10^9\ M^{-1}\ s^{-1}$ at this pH. This value is a lower limit because presumably buffer curvature sets in as the concentration is raised; thus $k_2 \geq k_{-1}[TrisH^+] \geq 2 \times 10^{14}\ s^{-1}$, which is in good agreement with the value of k_2 (hypothetical) estimated from the equation in footnote *k* of Table III ($6 \times 10^{15}\ s^{-1}$).[2] These calculations ignore the fact that diffusion rather than S-OAr bond cleavage will limit the breakdown of the reaction complex, so that curvature would in actuality set in at a much lower level of buffer concentration. At lower buffer concentration, however, the deprotonation step is rate limiting; the value calculated for k_2 from this condition is that for a hypothetical case where diffusion never limits the S-OAr cleavage step and should therefore be predictable from eq *k* of Table III.

The question of whether k_{-1} is diffusion controlled when the donor acid is water is crucial and has been discussed in depth.[21a-d] It would appear that our results are internally consistent, as essentially the same k_2 is estimated using general acids of widely differing pK_a; however, the pK_{SH} values ought to be consistent with values in the literature. It is difficult to estimate or measure the pK_{SH} for the 4-nitrophenyl phenylmethanesulfonate, but comparing the pK_{SH} values of acetylacetone and 4-nitrophenyl acetoacetate ($CH_3COCH_2COCH_3$, 9.3,[21e] and $CH_3COCH_2COOpNp$, 8.5[21f]) and ethyl acetoacetate and 4-nitrophenyl ethyl malonate ($C_2H_5OCOCH_2COC_2H_5$, 10.5,[21e] and $C_2H_5OCOCH_2COOpNp$, 10.4[21f]) would suggest that there is little difference between alkyl and 4-nitrophenoxy substituents; thus the value of 21.7 (water) for the pK_{SH} of 4-nitrophenyl phenylmethanesulfonate is probably quite reasonable compared with that for $C_6H_5CH_2SO_2CH_3$ (25.6).[21g] By the same token the value of about 30 for the pK_{SH} of 4-nitrophenyl methanesulfonate (see later and Table VII) is a reasonable estimate. At least for the disulfones which have a low pK_{SH}[21g,h] there is only about a difference of two between the pK values in water and Me_2SO.[26]

Table VII. Decomposition of Sulfonate Conjugate Bases

	Conjugate base[a]	pK_{SH}	k_2, s^{-1}	k_{OH},[b] $M^{-1}\ s^{-1}$
24	$S\bar{O}_3OpNp$ [e]	<2[g]	1.6×10^{-8} [d]	1.6×10^4 [d]
23	$CH_3\bar{N}SO_2OpNp$	8.88	8.0×10^{-3} [c]	1.1×10^3 [c]
6	$C_6H_5\bar{C}HSO_2OpNp$	21.66	5.0×10^9 [c]	110
22	CH_3SO_2OpNp	30[f]		4×10^{-2}

[a] pNp represents the 4-nitrophenyl group. [b] Equivalent second-order rate constant for reaction of hydroxide with neutral ester ($k_2 \equiv k_{OH}(K_w/K_{SH})$). [c] 25 °C. [d] 35 °C. [e] Data from S. J. Benkovic and P. A. Benkovic, *J. Am. Chem. Soc.*, **88**, 5504 (1966). [f] This pK_{SH} is estimated to be close to that of $CH_3SO_2CH_3$ and $CH_3SO_2C_6H_5$ (31 and 29, respectively, from data kindly supplied from unpublished work by Professor F. G. Bordwell for Me_2SO solvent). [g] pK_a estimated to be approximately 2 from references in footnote *b* of Table III.

Since the esters studied here are carbon acids, it is possible that despite the large difference between the pK_a of water or acid and the pK_{SH} of the carbon acid the return rate constant k_{-1} might not be diffusion controlled. Davies, Keefe, and Robinson[21h] indicate that abnormal carbon acids are carbonyls and nitroalkanes, but that nitriles, sulfones, acetylenes, and chloroform are almost normal. Hibbert[21i] has shown that acid-catalyzed return for disulfones is diffusion controlled (pK_{SH} of the disulfones ~ 11-15) and Bell and Cox[21j] observe that proton transfer from an acid of $pK_a \sim 9$ to the carbanion of a disulfone of $pK_{SH} \sim 15$ is close to the diffusion limit.

Restructuring of solvent shells has been proposed as an explanation of a protonation rate constant slightly less than the normal diffusion-controlled rate constant for cyanocarbon acids,[21k] and a similar lower rate was observed for disulfones.[21j] Assuming this to be the case for our sulfonates the k_2 values will be uniformly lower by about an order of magnitude than those quoted in Table III; the pK_{SH} values will also differ. These considerations, however, do not alter the main conclusions of this paper.

Concerted Mechanism of Sulfene Formation. The linear free energy relationship for k_2 (Figure 7) predicts a lifetime for the conjugate base equivalent to the vibration time for the S-O bond (~10^{-13} s) for esters of phenols with pK_a 5-6. For esters of phenols of higher acidity (8, 10, 11, 17) the intermediate conjugate base (a carbanion) cannot exist as a discrete species (provided the linear free energy relationship holds) and the sulfene is formed directly via a concerted mechanism.[22]

The linear free energy relationship for k_2 (see Figure 7) extends over approximately six orders of magnitude in reactivity and we might ask whether we may make such a straight line extrapolation to the vibration limit. Conventional structure-reactivity arguments might suggest that as the reaction becomes faster the transition state comes to resemble starting material with less and less buildup of negative charge on the aryl oxygen, and hence a smaller dependence on the pK_a of the leaving group. The extrapolation, however, involves only two to three powers of ten (see Figure 7) from a linear free energy relationship which extends over some seven orders of magnitude, and there is thus little to suppose that the extrapolation is not valid. There are well-known examples, such as the base-catalyzed decomposition of benzisoxazoles,[23a] where linearity is retained over many more orders of magnitude. We are not proposing that the correlation for k_2 is linear up to and beyond the vibration limit; clearly, curvature will occur as this limit is approached because rate constants cannot exceed a value equivalent to $10^{13}\ s^{-1}$, as the half life would then be faster than a vibration time. When this limit is approached in the last step of a two-step reaction the mechanism must change to a

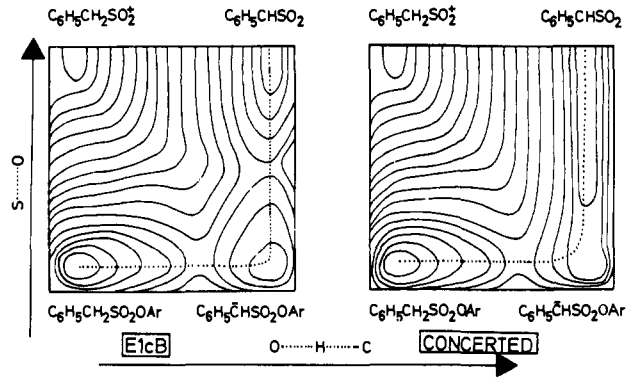


Figure 8. Three-dimensional free energy diagrams for the formation of sulfene from phenyl phenylmethanesulfonates with hydroxide ion. We use as coordinates the S-O fission and the proton transfer O···H···C and it is assumed that other interatomic distances which are not explicity indicated in the reaction coordinates will adjust to their most stable values. The dotted lines refer to the reaction paths of least free energy; in both mechanisms the $C_6H_5CH_2SO_2^+$ position involves a small well at the top of a high *maximum* so that the diagrams are highly distorted to force the reaction via the bottom and right hand coordinates. Although the free energy difference for the bottom coordinate is known, it is not possible as yet to estimate energies (except possibly gas phase using, e.g., CNDO calculations) for the sulfene or the $C_6H_5CH_2SO_2^+$ cation in solution, although the latter is presumably very high.

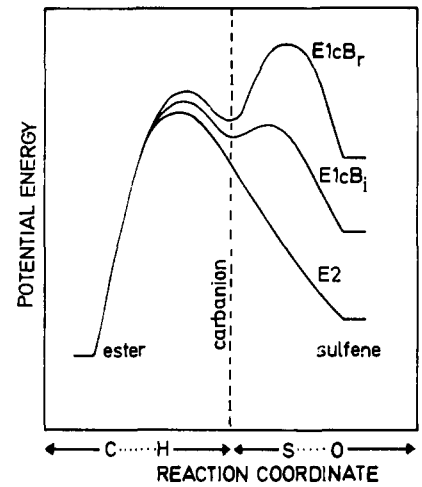


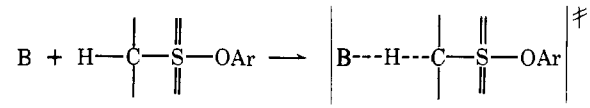
Figure 9. Two-dimensional free energy diagram for the formation of sulfene from substituted phenyl phenylmethanesulfonates with hydroxide ion. The $E1cB_i$ and $E1cB_r$ mechanisms represent E1cB paths with decomposition of carbanion not rate limiting and rate limiting, respectively. The E2 path has unsymmetrical timing and the dotted line represents the position on the reaction coordinate corresponding to carbanion structure and to the left involves proton transfer, while to the right is S-OAr cleavage.

concerted one because the intermediate can have no discrete existence. Although we may not compare the azide and halides with the phenyl esters, these may be undergoing a concerted elimination for the same reason as the esters of acidic phenols. Before the rate constant k_2, estimated from the linear free energy relationship, exceeds 10^{13} s^{-1} there will be a region in which there is essentially a preassociation mechanism, where the intermediate anion will decompose before water diffuses away from the carbanion. If it were possible to measure the decomposition of the carbanionic conjugate base, the rate constant would level off at ca. 10^{10} s^{-1} as the pK_a of the leaving phenol was increased, owing to a changeover in rate-limiting step from decomposition to diffusion of the product sulfene and phenol from the reaction complex (see later). This consideration has no effect on the transition from stepwise to concerted paths for the elimination.

Both large primary deuterium isotope effects (on the hydrolysis of the fluoride and 2,4-dinitrophenyl ester) and the high Brønsted β for the action of general bases on the hydrolysis of 2,4-dinitrophenyl phenylmethanesulfonate are in accord with a transition state with the proton approximately half transferred (consequence B of Bunnett's review on elimination mechanisms),[23b] and this would be expected if the mechanism were derived in a smooth transition from an E1cB process; in our opinion the transition state is intermediate between neutral and carbanionic species and, although the reaction coordinate we believe does go through the carbanion structure, this does not represent a minimum on the potential energy surface for esters of phenols with pK_a below about 6.

The change to a concerted mechanism is illustrated in Figure 8, where the fission of C-H and S-O bonds is represented by the coordinates of a three-dimensional potential energy diagram. The dotted lines in the figure represent possible reaction coordinates; since the position of the transition state will not differ very much in the concerted mechansim from that for the rate-limiting step in the E1cB proton transfer, it is doubtful whether any physical measurements (such as heavy atom isotope effect on the leaving atom) would provide a distinction.

The mechanism for base-catalyzed hydrolysis of 2,4-dinitrophenyl phenylmethanesulfonate and those esters of greater acidity is a concerted one in that it involves *no intermediates*, but the timing of the C-H bond-breaking process is well advanced with respect to the S-O cleavage. The transition state may be pictured as in eq 12. Breakdown of the transition state



⟶ sulfene (12)

follows a structure similar to that for the carbanion, but as we have shown for these esters this species cannot exist, as it decomposes with a half life less than a vibration time. We must therefore view the mechanism as a concerted E2 process with "unsymmetrical" or "skewed" timing for bond cleavage. The transition state is not carbanion-like, as this would involve complete proton transfer in the transition state and result in a low primary deuterium isotope effect and high Brønsted β value for reactions were proton transfer were rate limiting. As an alternative to Figure 8 one might picture a two-dimensional potential energy diagram (Figure 9) connecting the two mechanisms being proposed.

A further result of the reactivity in the decomposition of the carbanionic conjugate base passing through 10^{10} s^{-1} is that rotational equilibrium of the base is probably not attained in the E1cB mechanism just prior to its merging into a concerted process. A reasonable barrier to rotation (~3 kcal/mol)[24] is equivalent to a rate constant of approximately 10^{11} s^{-1}.

Addition-Elimination Mechanism. The 1000-fold difference between 4-nitrophenyl methanesulfonate and phenyl methanesulfonate hydrolysis, while diagnostic for an E-A mechanism in the latter ester, is relatively small; conditions are conceivable where the $S_N2(S)$ process might prevail, such as decreasing leaving group ability or intramolecular attack by a nucleophile. Since it is known that only small advantages are to be gained from proton abstraction by an intramolecular base and enormous advantage from intramolecular nucleophilic attack,[25] it it not surprising that our experiments discount the E-A mechanism

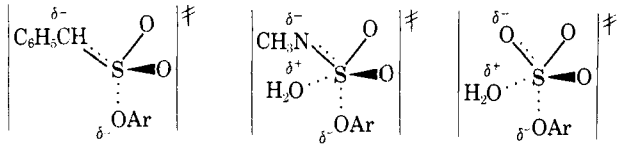
$$C_6H_5CH_2SO_2F \cdot CTOH \overset{-HF}{\rightleftarrows} C_6H_5CH{=}SO_2 \cdot CTOH$$

enzyme—inhibitor complex

$$\rightarrow C_6H_5CH_2SO_2OCT \quad (13)$$

for inhibition of α-chymotrypsin (CTOH) by phenylmethanesulfonyl fluoride. We observe that the α,α-dideuterio fluoride has approximately the same rate of inhibition of chymotrypsin as the protio species. A mechanism involving a fast preequilibrium exchange of the protons followed by the E1cB process is unlikely, as there is a difference in the rate parameters between the deuterio and protio forms which is outside the limits of the experimental error.

Internal Nucleophilicity.[7f,10] Participation by solvent in the elimination of phenolate anion from the conjugate base of the substrate is only necessary when the internal nucleophile is not very powerful, as for example in 4-nitrophenyl sulfate. Leaving group release from the conjugate base is independent of amine concentration (at high concentration), indicating no N-S bonding in the transition state of the rate-limiting step (I). This is understandable because the highly unstable carbanion should provide a large driving force (internal nucleophilicity) for the expulsion of the leaving group. The aminosulfonate analogue does not require any assistance for the expulsion of acidic phenols from the conjugate base;[20] for poor leaving phenols such as the 4-methoxyphenol, water assistance is necessary (II), as is evidenced by a break in the linear free energy rela-



I II III

tionship between decomposition and phenol pK_a.[20] The aminolysis and presumably also the hydrolysis of aryl sulfates requires assistance for the departure of even the 4-nitrophenolate anion (III) because the conjugate base of the ester has only a weak internal nucleophile (the oxyanion of $pK_a \sim 2$). An interesting linear free energy relationship (Figure 10) holds between pK_{SH}, the acidity of the neutral substrate, and the decomposition of the conjugate base (k_2) for carbon acid, aminosulfonate, and sulfonate:

$$\log (k_2/s^{-1}) = 0.9pK_{SH} - 10.5 \qquad (14)$$

If we consider the condition that k_2 is rate limiting, then the overall rate constant for alkaline hydrolysis is given by

$$K_{OH} = K_{SH}k_2/K_w \qquad (15)$$

and the selectivity (a Brønsted-type "β" value) of k_{OH} toward the pK_{SH} for the α-proton is −0.1; in other words, the increased internal nucleophilicity is largely offset by the decreased concentration of the conjugate base, so that the overall rate is relatively invariant (Figure 9). When the conjugate base becomes more basic than those of phenylmethanesulfonates, its decomposition will exceed the rate at which products can diffuse away from the reaction complex and hence the linear free energy relationship (Figure 10) for both k_2 and k_{OH} will suffer a break and the latter overall rate constant will decrease (with a selectivity −0.9 vs. pK_{SH}). It is for esters in this region of pK_{SH} (CH_3SO_2OpNp is estimated to have a pK_{SH} close to 30—see Table VII) that a change in mechanism to A-E will occur. 4-Nitrophenyl methanesulfonate has an alkaline hydrolysis rate constant some five orders of magnitude above the value expected for its E1cB mechanism. It should be emphasized, however, that the pK_{SH} of ~30 for the 4-nitrophenyl methanesulfonate is only an approximation for Me_2SO solvent and another estimate (private communication from Professor J. F. King) is 26. The value of k_{OH} for this ester must fall above the line, as there is good evidence that the hydrolysis involves a pathway other than E1cB (see earlier). It may be, however, that this ester lies close to the borderline between addition-elimination and elimination-addition mechanisms for hydrolysis, and this would be borne out by the closeness of the rate constant to that predicted from the free energy relationship of Figure 10 if the pK_{SH} of 26 is chosen.

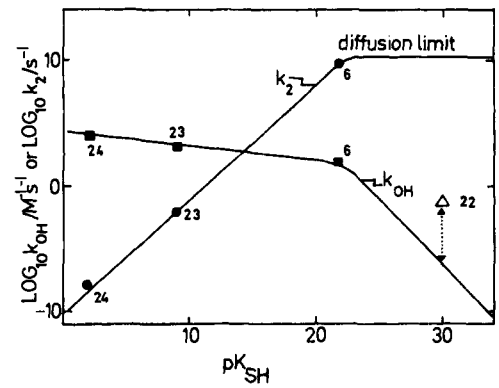


Figure 10. Brønsted type plot of k_{OH} (buffer independent) and k_2, the decomposition rate of the conjugate base vs. the pK_{SH} of the conjugate acid for the nitrophenyl esters $HXSO_2OpNp$; data and the numbering system for substrate identification are taken from Table VII.

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(26) From the pK_{SH} values for $C_6H_5CH_2SO_2CH_3$ (25.6), $C_6H_5CH_2SO_2C_6H_5$ (20.3), and $C_6H_5CH_2SO_2CF_3$ (14.6)[21g] in Me_2SO it might appear that applying Charton's σ_I values that the phenyl ester might have a low $pK_{SH} \sim 17$; however, the σ_I values ignore the considerable electron donating resonance interactions which could occur between the oxygen and the sulfone group. Evidence for this interaction in the sulfone series is the similarity in reactivity to hydroxide ion in the pair of esters: catechol sulfate and 2-hydroxyphenylmethanesulfonic acid sultone (E. T. Kaiser, I. R. Katz, and T. F.

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Nonenforced Catalysis of the Bisulfite Carbonyl Addition Reaction by Hydrogen Bonding[1]

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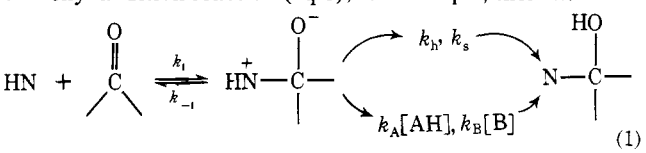
Contribution No. 1129 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154. *Received July 26, 1976*

Abstract. The rates of dissociation of the bisulfite adducts of *p*-methoxyacetophenone and *p*-methoxy-, *p*-chloro-, and *p*-nitrobenzaldehyde have been measured spectrophotometrically in aqueous solution at 25 °C, ionic strength 1.0 with KCl or Me_4NCl. The reaction is catalyzed by oxygen and nitrogen bases with a Bronsted β of 0.94 ± 0.05 for both *p*-methoxyacetophenone and *p*-methoxybenzaldehyde. The reaction is also accelerated by mono- and divalent cations. The observed rate enhancements are correlated with the association constants for ion pair formation between these cations and sulfite dianion. A mechanism is suggested in which transition-state stabilization occurs through hydrogen bonding of the buffer acid with the dianionic transition state. Proton transfer from solvent to trap the initially formed dianionic addition compound is fast, so that catalysis is not enforced by a short lifetime of this intermediate. This reaction therefore provides an example of catalysis by hydrogen bonding in which the catalysis is not required or facilitated by the lifetime of unstable intermediates.

It would be helpful to our understanding of the mechanism of catalysis of carbonyl and acyl group reactions if we knew why some of these reactions are subject to general acid–base catalysis while others are not. There is a tendency for general acid catalysis of carbonyl addition reactions to become significant and to exhibit progressively increasing Bronsted α coefficients as the nucleophile becomes weaker and less basic, and this tendency has been rationalized in terms of "Hammond postulate" and related effects or generalizations such as "catalysis occurs when it is most needed".[3] However, Sayer et al. have pointed out that the appearance of general acid catalysis in this series of reactions corresponds to changes in the rate-determining step and mechanism rather than to a change in the structure of a common transition state as the nucleophile becomes weaker,[4] and it is now becoming apparent that the mechanism of catalysis for many, and perhaps most, reactions of this kind is *enforced* by the lifetime and acid–base properties of the initially formed intermediate.[5] In a simple carbonyl addition reaction (eq 1), for example, there *must* be



(1)

catalysis of product formation through trapping of the addition intermediate by proton transfer after encounter with a molecule of buffer acid or base (k_A or k_B) whenever the intermediate breaks down to expel the nucleophile NH and regenerate reactants faster than it is trapped by proton transfer involving the solvent, i.e., when $k_{-1} > (k_h + k_s)$, in which k_h and k_s are the rate constants for proton transfer to or from solvent and through one or more solvent molecules, respectively. If the lifetime is so short that the intermediate breaks down faster than it separates from the catalyst, the intermediate *must* be formed within an encounter complex and exhibit catalysis by a "preassociation" mechanism, and if it is still shorter the intermediate cannot exist and the catalyzed reaction *must* be concerted. Since the catalyst is correctly located for subsequent proton transfer in a preassociation mechanism, there *must* be an opportunity for hydrogen bonding of the catalyst to the transition state[5] and for stabilization of the transition state by this hydrogen bonding.

In general, catalysis by hydrogen bonding is more likely to be significant when the intermediate has a short lifetime (large k_{-1}). When nucleophile attack, k_1, is rate determining, a rate constant k_{HA}' for catalysis by hydrogen bonding to the transition state must be comparable with k_1 to be experimentally significant, whereas when trapping is rate determining k_{HA}'