added 5 mmol of the sulfone, 3.0 mL (15 mmol) of anisole, and 0.88 mL (7.5 mmol) of triflic acid. The reaction mixture was stirred at 150 °C for 4 h, allowed to cool to room temperature, and poured over 50 g of ice. The mixture was extracted with chloroform and the chloroform extract was washed sequentially with 40 mL of water, 40 mL of saturated $NaHCO_3$, and 40 mL of water and then dried over $CaCl_2$. The dry chloroform extract was then subjected to quantitative GC/MS analysis. This procedure was repeated as above except that the reaction mixture was separated by column chromatography using silica gel in a 50 cm × 2 cm column. The product sulfone was eluted using a diethyl ether-chloroform (v:v 2:8) mixture. Evaporation of the solvents gave methyl *p*-anisyl sulfone [mp 120–121 °C;[12] mass spectrum, *m/e* 186 (M^+), 171, 123, 107, 94, 77] and phenyl *p*-anisyl sulfone [mp 90–91 °C;[13] mass spectrum, *m/e* 248 (M^+), 177, 123, 107, 77].

General Procedure for the Reaction of Sulfones with Diphenyl Ether. The procedure was exactly as described above except that diphenyl ether was used in place of anisole. Methyl *p*-phenoxyphenyl sulfone [mp 85–86 °C;[14] mass spectrum, *m/e* 248 (M^+), 233, 185, 169, 141, 77] and phenyl *p*-phenoxyphenyl sulfone [mp 92–93 °C;[15] mass spectrum *m/e* 310 (M^+), 233, 217, 185, 169, 77] were obtained as transsulfonylation products. The identity of these known products was confirmed by NMR as well as by melting point and MS.

General Procedure for the Reaction of Methyl Mesityl Sulfone with Various Arenes. The procedure was as described above except that various arenes (15 mmol) were used in reaction with methyl mesityl sulfone (5 mmol) and triflic acid (7.5 mmol). Analyses by GC/MS and column chromatography were carried out as before. The results are presented in Table I. The product sulfones formed by transsulfonylation in experiments 2 and 3 were the same ones used as starting materials in some of the experiments described above. The fact that the retention time in the capillary GC of the product of experiment 2, Table I, was the same as that of the pure methyl *p*-tolyl sulfone used as starting material previously indicated that the product sulfone was indeed the para isomer; there was no indication of more than a trace of other isomers formed in the transsulfonylation. The product sulfones formed by transsulfonylation in experiments 4 and 6, Table I, were the same ones produced in previous experiments. The product sulfone of experiment 5, Table I, ethyl *p*-ethoxyphenyl sulfone, had mp 89–90 °C,[16] mass spectrum, *m/e* 200 (M^+), 185, 137, 121, 77.

Tests for Desulfonylation in the Absence of a Nucleophilic Arene. Each of the seven aryl sulfones was stirred with triflic acid (7.5 mmol) at 150 °C for 3 h and the reaction mixture was worked up as before. Each of the starting sulfones was recovered in almost quantitative yield by evaporation of the chloroform solution.

Acknowledgment. Support for this work by the Robert A. Welch Foundation is gratefully acknowledged.

Registry No. **5**, 97416-12-1; **6**, 6462-31-3; **7**, 3112-82-1; 4-$MeSO_2C_6H_4OMe$, 3517-90-6; 4-$PhSO_2C_6H_4OMe$, 3112-84-3; 4-$MeSO_2C_6H_4OPh$, 21134-15-6; 4-$PhSO_2C_6H_4OPh$, 47189-05-9; 4-$EtSO_2C_6H_4OEt$, 82961-62-4; 4-$MeSO_2C_6H_4Me$, 3185-99-7; anisole, 100-66-3; diphenyl ether, 101-84-8; toluene, 108-88-3; *m*-xylene, 108-38-3; phenetole, 103-73-1; isodurene, 527-53-7; methyl isoduryl sulfone, 97416-13-2.

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Catalysis of Sulfonate Ester Hydrolysis by Intramolecular Amide Group Assistance

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Kinetics of the alkaline hydrolysis of aryl 2-(acylamino)benzenesulfonates (**1**, X = OAr) obey the equation

$$k_{obsd} = (k_a + k_b[OH^-])/(1 + [H^+]/K_a)$$

Hammett equations correlate the parameters k_a, k_b, and K_a for variation in both amido and leaving phenolate substituents. The values and sign of the ρ values together with entropy of activation data, reactivity, trapping, and oxygen-18 incorporation are consistent with the formation of an intermediate benzoxathiazine *S,S*-dioxide (**2**). The k_a term involves intramolecular attack of the amido anion. The k_b term is consistent with a specific anion effect on k_a. Regular bimolecular $B_{Ac}2$ mechanisms for k_a and k_b are not consistent with the high observed reactivity of these parameters.

The amide group is a well-known intramolecular nucleophilic catalyst for many ester hydrolyses,[1] where it can act in its neutral or conjugate base forms. Previous work from these laboratories has indicated that a neighboring oxyanion is a powerful nucleophile in sulfonyl group transfer.[2,3] We are interested in the amido anion as a potential neighboring group for sulfonyl transfer where the reacting nucleophile is the oxyanion function. Aberlin and Bunton[4] showed that the hydrolysis of 2-acetamido-

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(1) (a) Cremin, D. J.; Hegarty, A. F. *Tetrahedron* **1977**, *33*, 1823. (b) de Jersy, J.; Willasden, P.; Zerner, B. *Biochemistry* **1969**, *8*, 1959. (c) Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1975**, 947. (d) Hegarty, A. F.; Frost, L. N.; Coy, J. H. *J. Org. Chem.* **1974**, *39*, 1089. (e) Morawetz, H.; Shafer, J. A. *Ibid.* **1963**, *28*, 1899.
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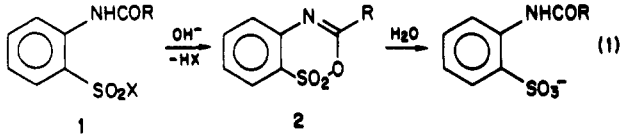
benzenesulfonyl fluoride (1, R = CH_3; X = F) probably



(1)

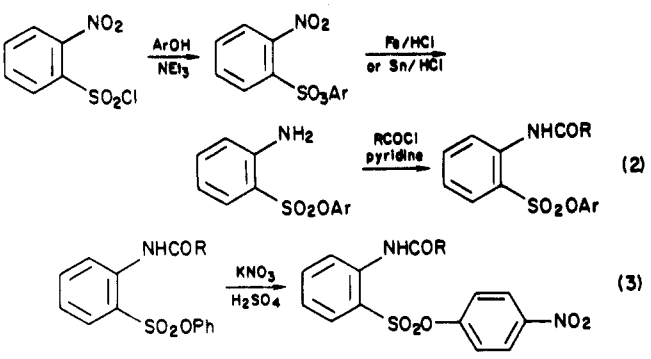
1 2

involved neighboring group participation by the amido base to form benzoxathiazine-*S*,*S*-dioxide (2, R = CH_3). Duchek[5] synthesized this species and showed that it was very reactive toward nucleophiles, consistent with its being an intermediate in the fluoride hydrolysis.

We examine the alkaline hydrolysis of aryl sulfonate esters (1; X = OAr) using oxygen-18 incorporation and structure–reactivity relationships to indicate that the species 2 is a probable intermediate.

Experimental Section

Materials. Substrates were prepared by standard chemical techniques according to pathways given in eq 2 and 3 for the 2-(acylaminobenzenesulfonates. Examples of the preparations



(2)

(3)

are given below for the synthesis of 4-nitrophenyl 2-acetamidobenzenesulfonate. Phenyl 2-nitrobenzenesulfonate was prepared by adding a dichloromethane solution of 2-nitrobenzenesulfonyl chloride (3.5 g, 15.8 mmol; prepared by the method of Vogel[6]) to an ice-cold solution of phenol (1.49 g, 15.8 mmol in 20 mL of dichloromethane. The mixture was stirred overnight and then worked up with diluted HCl (4%), and the dichloromethane phase was dried and evaporated. The residue was recrystallized from ethanol and melted at 55–57 °C. Reduction of the nitro group was carried out as follows. The ester (5.6 g, 20 mmol), concentrated HCl (10 mL), ethanol (8.5 mL), and dioxan (12 mL) for solubilization of the phenyl ester were maintained at 60 °C and stirred while granulated tin (4.5 g, 38 mmol) was added. The rate of addition was controlled to maintain the temperature at 60 °C. The mixture was stirred for an hour after all the tin had been added and then poured into an ice–water mixture. A solid separated, which was dissolved on addition of NaOH (2 N), the alkaline solution was extracted with ether, and the ether layer was dried and evaporated. The residue, after evaporation, was recrystallized from aqueous ethanol and had mp 72–37 °C (yield 85%). The 2-amino function was acetylated by standard procedures with acetic anhydride. The crude product was used directly to prepare the 4-nitrophenyl ester. Phenyl 2-acetamidobenzenesulfonate (0.17 g, 0.58 mmol) was dissolved in H_2SO_4 (3.16 g) and cooled in ice. A mixture of KNO_3 (0.059 g, 0.58 mmol) in H_2SO_4 (2.7 g) was added dropwise to the above solution, which was then kept at room temperature overnight with stirring. The mixture was then added to ice and extracted with chloroform, and the dried organic phase was evaporated. The residue, after recrystallization from ethanol, had mp 72–73 °C.

4-Benzamidobenzenesulfonyl chloride was prepared by the method of Bere and Smiles[7] and used without purification to prepare the corresponding 4-nitrophenyl ester.

Phenyl 2-(*N*-methylacetamido)benzenesulfonate was prepared by adding methyl iodide (0.36 g, 2.5 mmol) to a boiling solution of phenyl 2-acetamidobenzenesulfonate (0.5 g, 1.7 mmol) containing finely powdered KOH (0.17 g, 3 mmol) in anhydrous acetone (7 mL). A white precipitate formed immediately, the mixture was refluxed a further 5 min, and then the solvent was evaporated. The residue (0.45 g) was washed with water and used directly after drying. TLC analysis indicated the absence of byproducts in the reaction. Standard nitration with KNO_3/H_2SO_4 gave the 4-nitrophenyl 2-(*N*-methylacetamido)benzenesulfonate.

2-Acetamidobenzenesulfonic acid (sodium salt) was prepared from sodium orthanilate by using acetic anhydride. The product was recrystallized from 95% ethanol and had mp *ca.* 290 °C.[8]

Materials used for kinetics either were of analytical reagent grade or were recrystallized or redistilled from bench grade materials. Water used throughout was glass-distilled deionized material. Dioxan was purified by percolation of the AR grade material through activated alumina; the absence of peroxide impurities was checked with KI. ^{18}O-Enriched water was purchased from Prochem Ltd.

The substrates were routinely checked for purity by TLC on Merck silica gel precoated plates, generally by using CH_2Cl_2 or CH_2Cl_2/ethyl ether mixtures for elution, and structures were confirmed by IR and NMR spectroscopy. Satisfactory analyses were obtained for new species (microanalyses were carried out by the Institute of Pharmaceutical Chemistry at Genoa). Analytical and spectroscopic data are reported in Table S1 (supplementary material) for the new species.

Methods. 20% Aqueous dioxan (v/v) was used as solvent for kinetic and pK_a measurements because of the low solubility of the substrates in water. Values of pK_w for this solvent were obtained from literature.[9] Kinetics were measured spectrophotometrically with either a Perkin-Elmer 554 or a Gilford 2400 S instrument coupled with potentiometric recorders and fitted with thermostatically controlled cell holders. A typical experiment involved adding an aliquot of substrate (25 μL) dissolved in dioxan to 2.5 mL of buffer in a silica cell in the cell compartment of the spectrophotometer. The absorbance was then measured against time at a fixed wavelength previously determined from a separate spectral scan of the reaction. The pH of the buffer in the silica cell was measured before and after the reaction with a Radiometer PHM 62 pH meter calibrated with Merck standard buffers to ±0.02 pH unit. In some cases the pH of the solution in the cell was maintained constant by the use of a pH-stat apparatus similar to the one described previously.[10] The pseudo-first-order rate constants were obtained from plots of $A_\infty - A_t$ against time using two-cycle semilogarithmic graph paper. Reactions were normally followed to about seven half-lives.

Ionization constants were obtained for substrates by measuring the UV spectra as a function of pH and the pK_a determined from a plot of pH vs. log FA/FB (eq 4) where FA and FB are the

$$pH = pK_a - \log FA/FB \quad (4)$$

fraction of acid and base species, respectively, as determined from the absorbance measurements at an appropriate wavelength in the spectrum.

Product analysis was carried out on the hydrolysis of 4-nitrophenyl 2-benzamidobenzenesulfonate. The ester (0.2 g) dissolved in peroxide-free dioxane (5 mL) was added to an aqueous solution of KOH (0.2 M, 5 mL). The solution was stirred until TLC analysis indicated that the reaction was complete. The mixture was acidified to pH 4 and extracted with ether (3 × 15 mL), and the aqueous phase was evaporated under reduced pressure. The product was treated with the nitrous acid/2-naphthol test[11] and shown to contain no aromatic amine. NMR spectroscopy in D_2O indicated 2-benzamidobenzenesulfonic acid (potassium salt) as the only product other than 4-nitrophenol. An identical experiment was carried out with the 2-acetamido ester. In this case 2-acetamidobenzenesulfonic acid potassium salt prepared separately was used as a standard in the TLC analysis.

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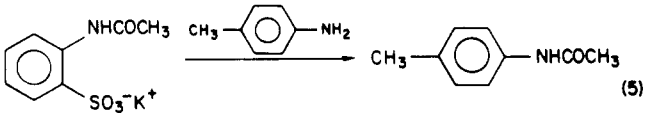
(11) Schetty, G. *Helv. Chim. Acta* **1966**, *49*, 461.

Table I. Physical and Ionization Constants for the Substrates at 25 °C[f]

substrate 1							
R	X	μ/M[a]	λ/nm[b]	pK_a^{spectr}	N[c]	pK_a^{kin}[d]	mp/°C[e]
C_6H_5	4-$NO_2C_6H_4O$	0.2	330	12.26	8	12.35	116-116.5
C_6H_5	4-$NO_2C_6H_4O$	1.0				12.39	
C_6H_5	4-CNC_6H_4O	1.0	330	12.35	8		96-97
C_6H_5	3-ClC_6H_4O	0.2	330	12.35	8	12.37	96-97
C_6H_5	3-BrC_6H_4O	0.2	330	12.52	8	12.65	115-116
C_6H_5	3-BrC_6H_4O	1.0				12.60	
C_6H_5	3-CNC_6H_4O	1.0	330	12.35	12		107.5-109
C_6H_5	C_6H_5O	1.0	330	12.65	7		100-101
4-$CH_3C_6H_4$	4-$NO_2C_6H_4$	1.0	330	12.65	7	12.62	131-132
3-ClC_6H_4	4-$NO_2C_6H_4$	1.0	330	11.52	8	11.62	124-125
3-$NO_2C_6H_4$	4-$NO_2C_6H_4O$	1.0				10.87	179-181
CH_3	4-$NO_2C_6H_4O$	0.2	310	13.09	7	12.92	72-73
CH_3	4-$NO_2C_6H_4O$	1.0	310	13.02	9	13.01	
other substrate							
C_6H_5CONH—(C$_6$H$_4$)—$SO_2OC_6H_4$-4-NO_2		1.0	320	13.28	9		190-191

[a] Ionic strength made up with KCl. [b] Wavelength for spectroscopic determination of pK_a. [c] Number of points for spectroscopic determination of pK_a (not including duplicates). [d] This value is derived from the kinetic data (for conditions, see Table II). [e] Solvent used for recrystallization is ethanol except for the 3-chlorobenzamido ester for which methanol was used. [f] Value of pK_w for these conditions is 14.62.[9]

4-Nitrophenyl 2-acetamidobenzenesulfonate was hydrolyzed in ^{18}O-enriched water to check the position of any labeling in the acetyl function as shown in eq 5. The ester (0.17 g) in dioxan



(5)

(5 mL) was added to aqueous KOH (0.2 N, 5 mL; containing enriched water at 4.64% ^{18}O enrichment). The mixture was stirred at room temperature for 20 min until TLC analysis indicated that hydrolysis was complete. It was then acidified to pH 4 with condentrated HCl and extracted with ether, and the aqueous phase was evaporated under reduced pressure. The white solid (0.5 g), containing mostly KCl and potassium *N*-acetylorthanilate (checked by NMR spectroscopy), was added to 4-toluidine (1.13 g), and the mixture was refluxed under argon for 2 h (oil bath at 220 °C (eq 5)). Water was added to the cooled mixture, and then concentrated HCl was added in order to neutralize the excess amine. The solution was finally extracted with ether to give the product *N*-acetyl-4-toluidine, which contained only traces of impurities as judged from TLC analysis. An analytical sample obtained by recrystallization from ethanol (mp 148–149 °C, lit.[12] mp 146 °C) was subjected to mass spectral analysis (AEI MS 902 high-resolution mass spectrograph) under the supervision of Dr. J. F. J. Todd.

Trapping with ammonia was carried out as summarized in Table V by allowing 4-nitrophenyl 2-benzamidobenzenesulfonate to react in buffers with increasing ammonia concentration. Reaction rates were measured, and the UV spectra were recorded after completion of the reactions and used to analyze for trapped products. The 4-nitrophenol peak at 400 nm provided an excellent internal check on stoichiometry. It proved difficult to study the trapping reaction by TLC analysis although this was attempted by using benzyl amine as the trapping agent instead of ammonia.

Reaction rates were measured at different temperatures for the hydrolysis of the 4-nitrophenyl benzamidobenzenesulfonates under different conditions in order to obtain values of the activation parameters. The relevant rate data are reported in Table S2 (supplementary material).

Results

Product analysis under the conditions of the hydrolytic kinetics at high pH revealed that only the sulfonate ester link is cleaved in the case of the 4-nitrophenyl esters of the 2-acetamido and 2-benzamidosulfonic acids. The very sensitive diazonium salt/2-naphthol test indicated no free amino group production. These results contrast with those found with the fluoride derivative.[4]

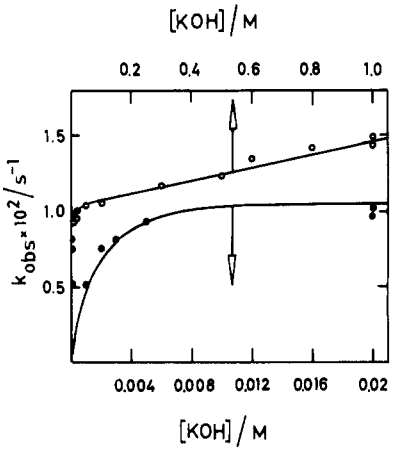


Figure 1. Dependence on hydroxide ion concentration of the pseudo-first-order rate constant for hydrolysis of 4-nitrophenyl 2-(3-chlorobenzamido)benzenesulfonate at 25 °C. Ionic strength maintained at 1 M with KCl. Points for very low concentrations (●) are on the expanded scale. The lines are calculated from eq 6 with parameters given in Table I and II.

The rate of hydrolysis obeyed excellent pseudo-first-order kinetics up to 90% of the total reaction. The pseudo-first-order rate constants varied with hydroxide ion concentration according to eq 6

$$k_{obsd} = (k_a + k_b[OH^-])/(1 + [H^+]/K_a) \quad (6)$$

except when there was no ionizable NH group. In the latter cases the rate constants were overall second order, i.e., first order in both substrate and hydroxide ion concentration. The data for the ionization constants (K_a) and rate parameters are collected in Tables I and II, and an example of the hydroxide ion concentration dependence is illustrated in Figure 1. Some ionization constants (K_a) were obtained spectrophotometrically as well as kinetically, and Table I indicates excellent agreement between the results of the two methods. A typical plot of absorbance vs. pH used for the spectrophotometric determination of pK_a is shown in Figure 2. The values of k_a, k_b, and K_a

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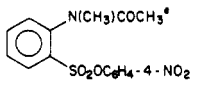
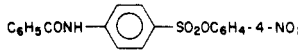
Table II. Rate Parameters for the Hydrolysis of the Substrates at 25 °C

substrate 1 R	substrate 1 X	μ/M [b]	λ^kin/ nm	N [c]	[OH⁻] range, M	10⁴k_a/ s⁻¹ [d]	10⁴k_b/ s⁻¹ [d]	10²(k_aK_a/K_w)/ M⁻¹ s⁻¹
C_6H_5	4-$NO_2C_6H_4O$	0.2	400	8	0.005-0.1	300		687
C_6H_5	4-$NO_2C_6H_4O$	1.0	400	10	0.005-1.0	364	119	618
C_6H_5	4-CNC_6H_4O	1.0	275	11	0.01-0.2	67.5	22.5	126
C_6H_5	3-ClC_6H_4O	0.2	275	8	0.001-0.2	1.52		
C_6H_5	3-BrC_6H_4O	0.2	275	6	0.005-0.2	1.97		
C_6H_5	3-BrC_6H_4O	1.0	275	8	0.005-1.0	2.15	0.46	2.25
C_6H_5	3-CNC_6H_4O	1.0	248	10	0.005-1.0	12.1	5.36	22.5
C_6H_5	C_6H_5O	1.0	320	4	0.005-1.0	0.114	0.021	0.106
4-$CH_3C_6H_4$	4-$NO_2C_6H_4O$	1.0	400	16	0.005-1.0	537	166	501
3-ClC_6H_4	4-$NO_2C_6H_4O$	1.0	400	14	0.001-1.0	103	43.5	1300
3-$NO_2C_6H_4$	4-$NO_2C_6H_4O$	1.0	400	15	0.00012-1.0	36.6	13.8	2060
CH_3	4-$NO_2C_6H_4O$	0.2	400	6	0.005-0.2	245		
CH_3	4-$NO_2C_6H_4O$	1.0	400	10	0.005-1.0	293	127	117
other substrates								
		1.0	400	6	0.02-1.0			2.85 [a]
		1.0	400	6	0.02-0.75	2.8	7.2	0.613
$C_6H_5SO_2OC_6H_4$-4-NO_2		0.2	400	4	0.02-0.2	2.6	3.5	1.6 [a,f]

[a] These rate constants are unambiguously bimolecular. [b] Ionic strength made up with KCl. [c] Number of points not including duplicates. [d] Errors on these values are not greater than 5%. [e] Mp 123.5-124.5 °C. [f] Davy, M. B.; Douglas, K. T.; Loran, J. S.; Steltner, A.; Williams, A. *J. Am. Chem. Soc.* **1977**, *99*, 1196.

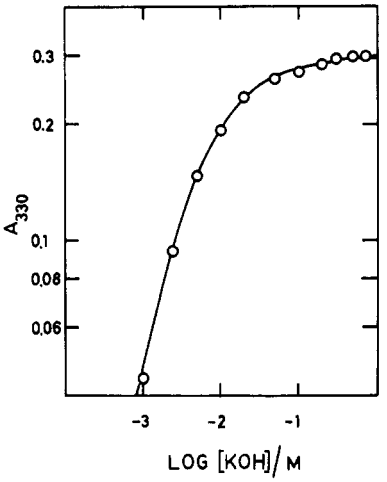


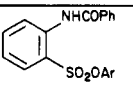
Figure 2. The pH dependence of the absorption at 330 nm of 3-cyanophenyl 2-benzamidobenzenesulfonate at 25 °C. Ionic strength maintained at 1 M with KCl. The line is calculated from the pK_a parameters in Table I.

fitted Hammett relationships satisfactorily. The relationships for k_a and k_b for variation of the leaving phenolate ion are slightly better with σ^- whereas Hammett σ fits K_a and the parameters k_a and k_b for variation in the amido side chain. The values are recorded in Table III.

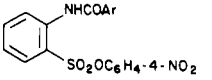
Trapping with ^{18}O-labeled water (4.64% ^{18}O enrichment) of the hydrolysis of 4-nitrophenyl 2-acetamidobenzenesulfonate, followed by treatment of the solfonate product with 4-toluidine, gave *N*-acetyl-4-toluidine, which had 4.97% ^{18}O labeling. The product from naturally occurring water has 0.664% ^{18}O labeling (derived from the small natural ^{18}O abundance). The label was thus incorporated to the extent of [(4.97 − 0.664)/4.64] 100% = 92.8%. The 7.2% difference from 100% may be due to part of the reaction not giving rise to the labeled product or, most likely, to error. Acetanilides, under the same conditions of time and temperature, are not expected to incorporate ^{18}O from water in significant amounts.

Thermodynamic activation parameters for the hydrolysis of the 4-nitrophenyl benzamidobenzenesulfonates were

Table III. Correlation of Kinetic and Equilibrium Parameters with Hammett's σ and σ^-



$\log k_a = (2.86 \pm 0.18)\sigma^- - (4.81 \pm 0.14)$ $r = 0.994$ [c]
$\log k_b = (3.08 \pm 0.30)\sigma^- - (5.49 \pm 0.22)$ $r = 0.986$ [c]
pK_a [b] $= (-0.46 \pm 0.11)\sigma + (12.68 \pm 0.06)$ $r = 0.809$



$\log k_a = -(1.35 \pm 0.05)\sigma - (1.48 \pm 0.02)$ $r = 0.999$
$\log k_b = -(1.24 \pm 0.08)\sigma - (1.95 \pm 0.03)$ $r = 0.996$
$pK_a = -(2.02 \pm 0.12)\sigma + (12.31 \pm 0.02)$ $r = 0.997$

[a] 1 M ionic strength made up with KCl, 25 °C. [b] Values of pK_a for 0.2 M ionic strength are included as there does not appear to be a marked salt dependence of pK_a here. [c] The σ^- correlation is marginally superior to the σ correlation (r = 0.974 for k_a and 0.983 for k_b).

Table IV. Thermodynamic Activation Parameters for the Hydrolysis of 4-Nitrophenyl Benzamidobenzenesulfonates

substrate		$\Delta H^{\ddagger}$/kcal mol⁻¹	$-\Delta S^{\ddagger}$/eu mol⁻¹ [a]
ortho ester	k_a	18.1 ± 0.3	4.0 ± 1.0
	k_b	18.3 ± 0.4	6.3 ± 1.4
	k_aK_a/K_w [b]	13.9 ± 0.1	6.9 ± 0.5
para ester	k_aK_a/K_w [c]	14.1 ± 0.7	21.3 ± 2.9

[a] At 25 °C. [b] From $k_{obsd}/[OH^-]$ at pH 10.2 (carbonate buffer 0.01 M). [c] From $k_{obsd}/[OH^-]$ at pH 11.8 (KOH buffer 0.0025 M).

calculated for both the ortho and the para ester and are shown in Table IV. In the para case, the term measured is k_aK_a/K_w, since calculations for 25 °C show that the ester is almost completely undissociated in the conditions used, and the contribution from k_b to the overall rate is negligible. In the case of the ortho ester, activation parameters were obtained for k_a, k_b, and k_aK_a/K_w.

The results of trapping experiments with ammonia are given in Table V. The hydrolysis of 4-nitrophenyl 2-benzamidobenzenesulfonate at pH 10.25 in the absence of ammonia buffer yields a UV spectrum with a peak at 400

Table V. Ammonia Trapping of the Intermediate in the Hydrolysis of 4-Nitrophenyl 2-Benzamidobenzenesulfonate[a]

$[NH_3]$	pH	10^4k_{obsd}	A_{264}	A_{400}
0	10.25	4.54	0.60	0.73
0.02	10.21	4.49	0.49	0.73
0.1	10.23	4.39	0.43	0.79
0.2	10.25	4.49	0.38	0.75
0.4	10.25	4.62	0.34	0.75

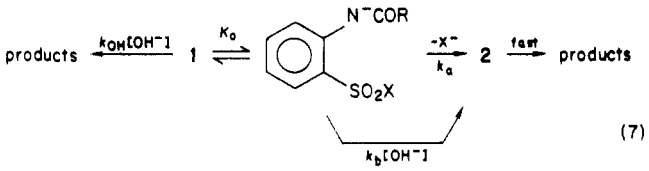
[a] 5.05×10^{-5} M ester; 0.008 M carbonate buffer, temperature 25 °C, ionic strength maintained at 1 M with KCl.

nm corresponding to the 4-nitrophenolate ion and a maximum at 264 nm attributable to the 2-benzamidobenzenesulfonic acid anion. As the ammonia concentration is increased there is a decrease in the benzamidobenzenesulfonate product as deduced from the decrease in the absorbance at 264 nm. At 0.4 M ammonia the product spectrum shows only a slight shoulder in the 264-nm region. It proved impossible for us to prepare the benzamidobenzenesulfonate product by a different route to compare authentic spectra, but benzanilide has an absorption maximum in a similar region with a similar strength (log ϵ 4.2 at 267 nm).[13] No change in the rate constant for release of the 4-nitrophenol from the 2-benzamidobenzenesulfonate ester was observed on using benzylamine buffers up to 0.4 M in 50% aqueous dioxan at pH 10.15 either. These experiments show that the products of trapping vary with the concentration of trapping agent while the rate constant is unaltered.

Hydrolysis of the 4-nitrophenyl ester of 2-benzamidobenzenesulfonic acid for 2 days at 70 °C in the presence of 0.1 M KF (phosphate buffer at pH 7) gave no indication of orthanilic acid liberation, as judged by the very sensitive HNO_2/2-naphthol test.[11]

Discussion

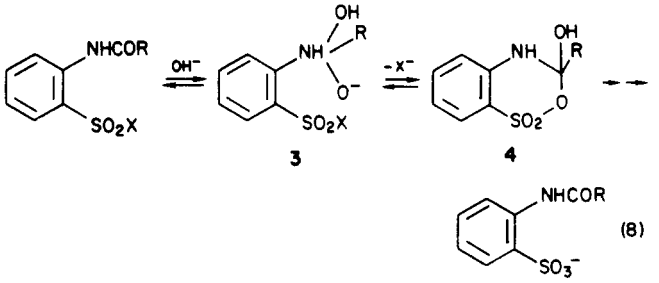
The kinetic law for the ortho sulfonate ester hydrolysis suggests that two different mechanisms represented by the parameters k_a and k_b could account for the reaction. We propose that the k_a term comes from the mechanism shown in eq 7, where the amido group ionizes (K_a) to give an anion



(7)

which expels the leaving group X^- in a unimolecular step k_a to give the intermediate. Comparison of the reactivity of HO^- toward the ortho and para isomers of 4′-nitrophenyl benzamidobenzenesulfonate reveals a ca. 1000-fold ratio between the second-order rate constants. The mechanism for the para ester can only be of the B_{Ac} 2-type (equivalent to k_{OH} in eq 7), and the rate constant for this isomer (6.13 10^{-3} M^{-1} s^{-1}) comes close to that for the 4-nitrophenyl benzenesulfonate (Table II). The term k_{OH} in the above mechanism provides only a minor contribution to the reaction flux for the ortho ester.

Oxygen-18 labeling studies are consistent with the intervention of an intermediate (**2**, R = CH_3) in the hydrolysis of the 2-acetamidobenzenesulfonate. The amido oxygen in the product from the reaction in ^{18}O-enriched water is, within the limits of the experimental error, completely labeled. Oxygen exchange at the amide will be very slow under the conditions of the experiment. Acetanilide has a half-life of about 6 h,[14] whereas the hydrolysis was carried out in 20 min and had a half-life of less than 28 s. Labeling at the amide oxygen must therefore arise through the intervention of an intermediate such as **2**. It would be difficult to explain incorporation *either* by adventitious labeling while a normal $B_{Ac}2$ mechanism occurs at the sulfur *or* by formation of a tetrahedral intermediate followed by intramolecular participation as in eq 8. The

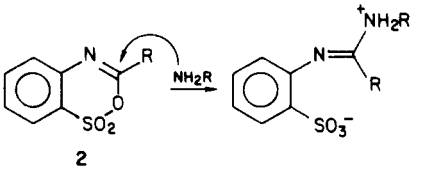


(8)

latter mechanism can also be excluded since the putative bimolecular rate constant (k_aK_a/K_w) of 1.17 M^{-1} s^{-1} for the 4-nitrophenyl 2-acetamidobenzenesulfonate is about 16 000-fold faster than the rate constant for addition of hydroxide ion to acetanilide (7.10×10^{-5} M^{-1} s^{-1} at 25 °C).[14] The second-order rate constant (k_aK_a/K_w) for the hydrolysis of 4-nitrophenyl 2-acetamidobenzenesulfonate is some 40-fold larger than that of the N-methylated analogue [1.17 as opposed to 2.85×10^{-2} M^{-1} s^{-1} (see Table II)]. While this is by no means conclusive evidence, because of the extra steric requirements of the alkylated ester, it is certainly consistent with the proposed scheme (eq 7).

Temperature coefficients for the hydrolysis of 4′-nitrophenyl bezamidobenzenesulfonates carried out in the pH region where k_a prevails provide strong support to the mechanisms proposed for the two esters.[15]

Experiments with ammonia as the trapping agent indicate that while the rate constant for release of the phenol is unchanged with increasing amine concentration, the product composition is markedly altered. The results summarized in Table V suggest that the rate-limiting step (phenol release) precedes a subsequent product forming stage. The site of attack of the nucleophile must be at the imino function in **2**, otherwise the strong absorbance of the benzanilide would not be destroyed. This site must be



(9)

that attacked in the trapping by water, otherwise ^{18}O would not be incorporated into the amide group. These results are substantially the same as those obtained by Duchek[5] on his isolated intermediate. Aberlin and Bunton[4] found that the amide group was cleaved in the hydrolysis of the 2-acetamidobenzenesulfonyl fluoride. This cannot be due to attack of the fluoride ion (from the early stage of the reaction) on the intermediate (**2**, R = CH_3) at the imino group (eq 10). Duchek[5] observed that the imino fluoride **5** readily hydrolyzed to the acetanilide (as did the intermediate **2** itself) when exposed to moisture. We find that the hydrolysis of 4-nitrophenyl 2-benzamidobenzene-

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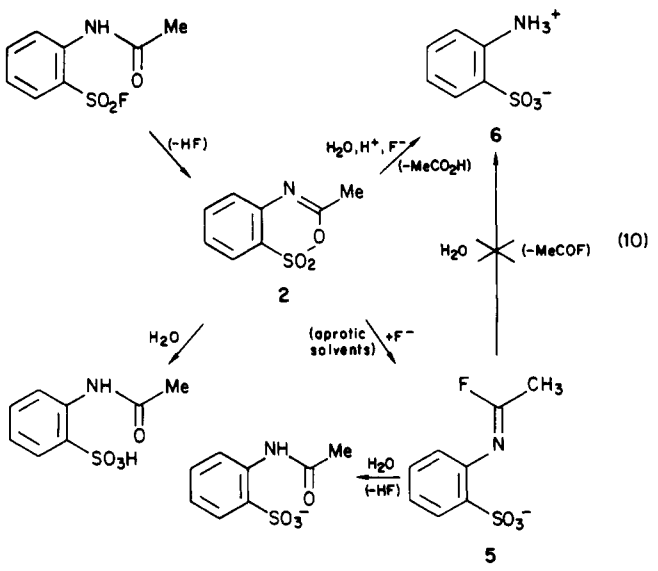
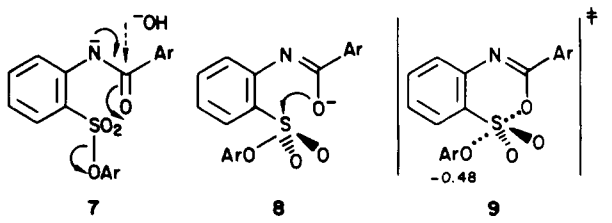


sulfonate in phosphate buffer at pH 7 in the presence of 0.1 M KF at 70 °C for 2 days gives no orthanilic acid. During the hydrolysis of the *o*-sulfonyl fluoride[4] the medium should rapidly become acidic, owing to the absence of buffer. A reasonable hypothesis about the amido fission observed by Aberlin and Bunton[4] is that the fluoride ion attacks the intermediate (**2**, R = CH_3) to give a species which breaks down in acid solution to give the amine **6** (eq 10). Under these conditions, the reaction would not proceed via the imidoyl fluoride **5**.

Simple attack of HO^- on the sulfonate group of the anionic ester is most probably the mechanism giving rise to k_b in the hydrolysis of 4-nitrophenyl 4-benzamidobenzenesulfonate. It cannot hold for the hydrolysis of aryl 2-acylamidobenzenesulfonates, though. Indeed, the Hammett ρ value for variation of the aryl amide group is negative (−1.24) by an amount that cannot be explained simply on the grounds that the equilibrium used to obtain ρ is not appropriate as a standard model.

However, the k_b term gives only a minor contribution to the overall reaction flux, even at high KOH concentration. The Hammett ρ values for variation of the leaving phenol or of the aryl amide group are very much like the corresponding ones derived from k_a. Furthermore, the activation entropy is only moderately negative (−6.3 eu mol^{-1}) and identical in value (within the limits of the experimental error) with that derived from k_aK_a/K_w (−6.9 eu mol^{-1}). The simplest explanation is that the k_b term arises from a specific anion effect, which becomes detectable when a substantial part of the chloride ions is substituted by hydroxide ions. This could be tentatively envisaged as a weak interaction of the type **7** between HO^- and the ester anion which would give rise to the enhancement of the nucleophilicity of the acylamido anion.

Substituent Effects. The substituent effect on pK_a is quite marked (ρ = −2.02) for variation in the amido function as might have been predicted. It is a little more negative than that found for the ionization of other anilides substituted on the carbonyl function.[16] The effect of



leaving group substituents on the pK_a (ρ = −0.46) seems too negative for transmission of the substituent effect through the OSC=CH system. This may be due to an interaction of the type **8**.

The large negative ρ value for leaving group variation for k_a indicates considerable change in effective charge (−1.28) on the leaving oxygen from ground to transition state. This is similar to that derived from the work of Vizgert for hydroxide ion attack on the aryl esters of benzenesulfonic acid.[17] The change of about −1.3 in a total of −1.8 is consistent with extensive S–O bond fission in the transition state **9**.[18]

The value of ρ for k_a for variation in the amido function suggests that extensive S–O bond formation could occur in the transition state. The data seem to fit a concerted process at the sulfur atom, involving passage through a transition structure lying on the product side of the reaction.[19]

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Registry No. 1 (R = CH_3, X = C_6H_5O), 97042-32-5; 1 (R = CH_3, X = 4-$NO_2C_6H_4O$), 97042-33-6; 1 (R = C_6H_5, X = 4-$NO_2C_6H_4O$), 97042-36-9; 1 (R = C_6H_5, X = 4-CNC_6H_4O), 97042-37-0; 1 (R = C_6H_5, X = 3-ClC_6H_4O), 97042-38-1; 1 (R = C_6H_5, X = 3-BrC_6H_4O), 97042-39-2; 1 (R = C_6H_5, X = 3-CNC_6H_4O), 97042-40-5; 1 (R = C_6H_5, X = C_6H_5O), 97042-41-6; 1 (R = 4-$CH_3C_6H_4$, X = 4-$NO_2C_6H_4$), 97042-42-7; 1 (R = 3-ClC_6H_4, X = 4-$NO_2C_6H_4$), 97042-43-8; 1 (R = 3-$NO_2C_6H_4$, X = 4-$NO_2C_6H_4O$), 97042-44-9; 4-$C_6H_5CONHC_6H_4SO_2OC_6H_4$-4-$NO_2$, 97042-45-0; $C_6H_5SO_2OC_6H_4$-4-NO_2, 3313-84-6; 2-nitrobenzenesulfonyl chloride, 1694-92-4; phenyl 2-nitrobenzenesulfonate, 41480-05-1; phenyl 2-aminobenzenesulfonate, 68227-69-0; phenyl 2-(*N*-methylacetamido)benzenesulfonate, 97042-34-7; 4-nitrophenyl 2-(*N*-methylacetamido)benzenesulfonate, 97042-35-8; phenol, 108-95-2.

Supplementary Material Available: Analytical and spectroscopic data (Table S1) and rate data for different temperatures used to calculate activation parameters (Table S2) (3 pages). Ordering information is given on any current masthead page.

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