Mechanisms of Decomposition of Aryl *N*-(Methoxycarbonyl)sulfamates in Aqueous Media

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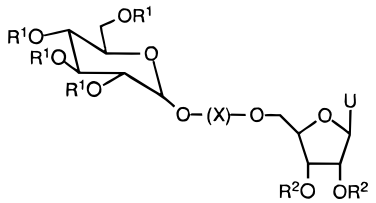
Abstract: Rate constants and products are reported for the decomposition of aryl *N*-(methoxycarbonyl)sulfamates **1a**−**h** (range) in aqueous solutions (pH 0−14) at 50 °C. The pK_a values at 25 °C of **1a**−**h** are 0.46−2.40. The pH-rate profiles of **1** indicate a rate law that includes three terms: two pH independent terms, k_a in acid and k_p around neutral pH, with $k_a > k_p$, and a hydroxide ion dependent term, k_{OH}. In acid, product analysis reveals that both S−O (k_{SO2}) and C−O (k_{CO}) bond cleavage reactions are involved. From an analysis of β_{lg}, solvent isotope effects, and solvent isotopic labeling of the products, it is concluded (a) that the C−O cleavage reaction involves protonation of the leaving group methanol and its expulsion from the dipolar intermediate $ArOSO_2N^-CO-O^+HCH_3$ and (b) that the S−O cleavage reaction may involve either an intra- or an intermolecular general acid-catalyzed decomposition of **1** or **1**$^-$, respectively. In contrast to k_a, the spontaneous hydrolysis reaction of **1**$^-$, k_p, takes place exclusively via S−O bond fission. The k_{OH} reaction of **1**$^-$ is rationalized by OH^- attack either at the carbonyl center (**1b**−**h**) or at the aromatic ring (**1a**). It is concluded that the $-SO_2NHCO-$ group may be viewed as an attractive phosphate analogue.

Introduction

Phosphate esters and anhydrides are of fundamental importance in biological systems. The genetic materials DNA and RNA are phosphodiesters, and most of the coenzymes are esters of phosphoric or pyrophosphoric acid. Recently, a new type of analogue of uridine 5′-diphosphate glucose (UDP-Glc), in which the naturally occurring diphosphate group has been replaced by an isosteric $O-SO_2NHCO-O$ group, were found to interfere with protein glycosylation, inhibiting the glycosylation of viral proteins to a greater extent than glycosylation of cellular proteins.[1] Although these analogues were initially



UDP-Glc: X = -PO_2^--O-PO_2^--; $R^1 = R^2 = H$

Analogs: X = -CO-$\bar{N}$-SO_2-; R^1 and $R^2 \neq H$

designed to interfere with the glycosylation process and, do in fact, inhibit it, their mode of action proved to be more complex since they also inhibit DNA synthesis.[1b] In recent therapeutic strategies, the extended use of the $-SO_2NHCO-$ group—as a replacement for the diphosphate or sulfate moiety of a variety of critical biomolecules—proved to be successful as well.[2−5] Also, the ionized form of this spacer was used to design an unusual water-soluble ACAT inhibitor which is well absorbed and thus exhibits improved bioavailability.[6]

Scrutiny of the above-mentioned work clearly indicates that the [(carbonyl)amino]sulfonyl spacer moiety plays an important role in both antiviral and inhibitory activities. Despite the exciting prospects presented by these bioisosterism-based therapeutics,[7] we are unaware of any previously reported study intended to investigate the aqueous reaction chemistry of this attractive phosphate isostere.[8] In addition to successfully mimicking the diphosphate bridge of a variety of biomolecules, including coenzymes and secondary messengers, we wondered whether the $-SO_2NHCO-$ linkage would also be qualified to carry out the biological tasks which naturally lie with the phosphate group in nucleic acids and lipids.[10] For instance, replacement of the phosphodiester backbone by appropriate

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(8) Previous investigations into the mechanisms of this group only focused on synthetic applications in aprotic solvents, to obtain olefins in high yields from sodium *N*-(alkoxycarbonyl)sulfamate derivatives.[9]

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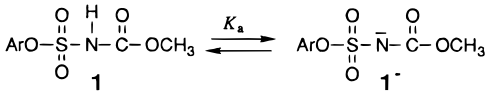
Table 1. Effect of the Aryl Group on Product Distributions, Rate Parameters and Solvent Deuterium Isotope Effects for Hydrolysis of Aryl *N*-(Methoxycarbonyl)Sulfamates **1** at 50 °C in 1.0 M DCl Solution Containing 16% CD_3CN, unless Otherwise Noted, μ = 1.0 M

compd $ArOSO_2NHCO_2CH_3$	phenyl substituent	pK_{ArOH}	% MeOH[a] (C−O cleavage)	% $H_2NCO_2CH_3$[a] (S−O cleavage)	k_{obsd}, s^{-1} [b,c]	k_{CO}, s^{-1} [b,d]	k_{SO_2}, s^{-1} [b,e]	k_{H_2O}/k_{D_2O} [b,f]
1a	2,4-$(NO_2)_2$	4.11	0.0	100	7.38×10^{-4}		7.38×10^{-4}	2.00
1b	2-Cl-4-NO_2	5.45	28.9	71.1	6.75×10^{-5}	1.95×10^{-5}	4.80×10^{-5}	1.55
1c	2-NO_2−4-Cl	6.48	36.6	63.4	7.42×10^{-5}	2.71×10^{-5}	4.70×10^{-5}	1.49
1d	4-NO_2	7.15	51.5	48.5	2.56×10^{-5}	1.32×10^{-5}	1.24×10^{-5}	1.40
1e	4-CN	7.95	63.1	36.9	1.97×10^{-5}	1.24×10^{-5}	7.25×10^{-6}	1.38
1f	4-CH_3CO	8.05	78.1	21.9	1.58×10^{-5}	1.24×10^{-5}	3.46×10^{-6}	1.08
1g	4-Cl	9.38	93.6	6.4	1.30×10^{-5}	1.22×10^{-5}	8.33×10^{-7}	1.03
1h	4-H	9.92	96.9	3.1	1.13×10^{-5}	1.10×10^{-5}	3.50×10^{-7}	1.03

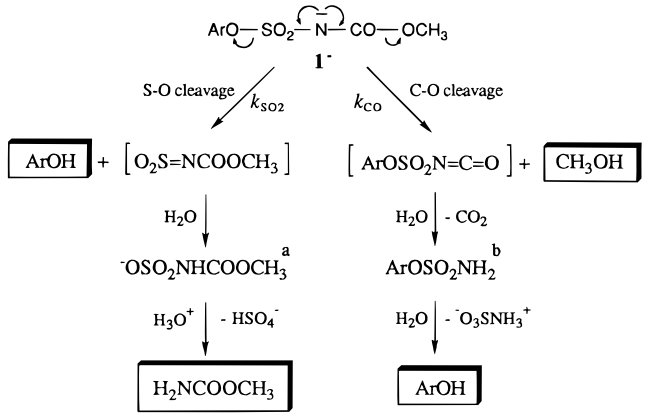
[a] Percentages of methanol and methyl carbamate were determined by ^{1}H NMR spectroscopy with an estimated error ±1% based on an average of three measurements. [b] Standard errors are ±5%. [c] Overall first-order rate constant measured spectrophotometrically. [d] Rate constant of formation of methanol determined from k_{obsd} and product ratio given in the previous column. [e] Rate constant of formation of methyl carbamate determined as indicated in the previous column. [f] Overall first-order rate constants ratio measured spectrophotometrically at 50 °C in 1.0 M LCl solutions containing 0.7% dioxane (μ = 1.0 M).

moieties would be particularly valuable for modified oligonucleotides to be used in antisense and antigene therapies.[11] To address this question, and then help the medicinal chemist to rationally extend the use of the [(carbonyl)amino]sulfonyl moiety in chemotherapy, we have been engaged in a detailed quantitative study of the aqueous chemistry of a wide range of [(carbonyl)amino]sulfonyl-linked derivatives, $G_1-SO_2NHCO-G_2$.[12] In the present work, we report our investigation of the mechanisms of the aqueous chemistry of aryl *N*-(methoxycarbonyl)sulfamates **1** (Table 1).



Due to the low pK_a of compounds **1** (pK_a = 0.5−2.4), our work is relevant to the aqueous chemistry of unusually weak nitrogen anions in comparison with the aqueous chemistry of the oxyanions encountered in phosphate and sulfate esters. From a mechanistic perspective, we wondered whether such anions would (i) decompose through the sulfonyl or the carbonyl group, or through both of them,[13] (ii) behave like oxyanions in the hydrolysis of phosphate and sulfate esters, (iii) thus involving the formation of—diffusible or not—potent electrophiles (Scheme 1) capable of modifying critical macromolecules.

Scheme 1[a,b]



[a] Not detected in strong acidic media due to concomitant hydrolysis affording methyl carbamate. [b] Not detected after completion of the kinetic runs of **1** due to concomitant hydrolysis affording the corresponding substituted phenols.

Experimental Section

In general, chemicals were purchased as the best available commercial grade. Organic chemicals were purified by distillation or recrystallization prior to use. Water was distilled and deionized on a Water-Purification System Milli-Q (Millipore Apparatus). Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed by Analytic Service, University Paul Sabatier. IR spectra were recorded using a Perkin-Elmer 883 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AC-80 or AC-250 spectrometer (250 MHz for ^{1}H and 50.32 MHz for ^{13}C). Chemical shifts for ^{1}H NMR spectra of chloroform-*d* solutions (containing 1 to 2 drops of DMSO-d_6 to improve solubility) are relative to internal TMS. For deuterium oxide solutions, all spectra were recorded with the Bruker AC-250 apparatus (^{1}H chemical shifts are relative to the residual HDO peak at δ 4.68). GC/MS and EIMS spectra were recorded on a Nermag R 10−10 mass spectrometer.

All aryl *N*-(methoxycarbonyl)sulfamates **1** were obtained in 42−61% yield by reacting [*N*-(methoxycarbonyl)sulfamoyl] triethylammonium inner salt with corresponding substituted phenols as described by Burgess et al.[9] *N*-Methylation of compound **1a** by the Mitsunobu reaction,[15] as described by Criton et al.,[16] gave 2,4-dinitrophenyl *N*-methyl-*N*-(methoxycarbonyl)sulfamate **2** in 51% yield. The spectroscopic and analytical data for these compounds are given in the Supporting Information.

Methods. a. Kinetics. Decomposition reactions of substrates **1** and **2** in aqueous media were monitored either by UV−vis spectrophotometry or ^{1}H NMR spectroscopy or by use of the HPLC technique depending on specific experimental requirements. All of these reactions gave, except where otherwise stated, satisfactory first-order rate constants. The solutions employed were HCl (pH 0−2.0),[17] trichloroacetate (pH 0.5−1.1), difluoroacetate (pH 0.9−1.5), dichloroacetate (pH 1−1.5), cyanoacetate (pH 2.1−3.2), acetate (pH 4−5.3), phosphate (pH 5.9−7.2), borate (pH 8.3−9.6), generally at 0.5 M, and NaOH (pH 11−13). The pH of the reaction mixtures was measured upon initiation and after completion of the runs using a Tacussel pH-meter

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(13) Given that nitrogen anions decompose ca. 10^9 times faster through carbonyl than sulfonyl group,[14] compounds **1** might prove to be good candidates to exhibit ambivalent reactivity due to the difference in pK_a that may lie between methanol and ArOH (e.g., when ArOH is *p*-nitrophenol, $\Delta pK_a \approx 8.5$).

(14) The rate constants ratio, k_{CO}/k_{SO_2}, for the E1cB decompositions of the corresponding conjugate bases of $CH_3NHCO-OAr$ (k_{CO}) and CH_3-NHSO_2-OAr (k_{SO_2}), was estimated from the literature data to ca. 10^9 when the leaving group is *p*-nitrophenol. See: (a) Al-Rawi, H.; Williams, A. *J. Am. Chem. Soc.* **1977**, *99*, 2671. (b) Williams, A.; Douglas, K. T. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1727.

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(17) No correction was applied for the small error incurred in reading pH values between pH 0 and 1.

Table 2. Values of Equilibrium and Rate Constants Determined as Kinetically Apparent Constants (50 °C and μ = 1.0 M with KCl) and via Spectrophotometric Titration (25 °C and μ = 1.0 M with KCl)

compd	pK_{app} [a]	pK_a [b]	k_a, s^{-1} [a,c]	k_p, s^{-1} [a,d]	k_{OH}, $M^{-1}\ s^{-1}$ [a]	k_{OH}, $M^{-1}\ s^{-1}$ [e]
1a	0.79 ± 0.30	0.46 ± 0.04	(1.54 ± 0.09) × 10^{-3}	(1.07 ± 0.01) × 10^{-3}	(1.05 ± 0.03) × 10^{-2}	(1.32 ± 0.09) × 10^{-2}
1b	1.21 ± 0.06	1.16 ± 0.02	(1.18 ± 0.06) × 10^{-4}	(2.09 ± 0.09) × 10^{-6}	(9.51 ± 0.4) × 10^{-5}	(1.07 ± 0.02) × 10^{-4}
1c	1.06 ± 0.02	0.97 ± 0.03	(1.28 ± 0.03) × 10^{-4}	(4.37 ± 0.08) × 10^{-7}	(9.74 ± 0.2) × 10^{-5}	(9.23 ± 0.3) × 10^{-5}
1d	1.58 ± 0.03	1.55 ± 0.02	(3.17 ± 0.1) × 10^{-5}	(1.40 ± 0.06) × 10^{-8} [f]	(6.72 ± 0.3) × 10^{-5}	(7.50 ± 0.2) × 10^{-5}
1e	1.56 ± 0.01	1.71 ± 0.01	(2.19 ± 0.02) × 10^{-5}	(3.05 ± 0.03) × 10^{-9} [f]	[g]	[g]
1f	1.80 ± 0.08	1.85 ± 0.02	(1.57 ± 0.1) × 10^{-5}	(2.48 ± 0.3) × 10^{-9} [f]	(3.74 ± 0.3) × 10^{-5}	(4.54 ± 0.2) × 10^{-5}
1g	2.13 ± 0.17	2.10 ± 0.02	(9.25 ± 2) × 10^{-6}	(1.44 ± 0.4) × 10^{-9} [f]	(2.18 ± 0.4) × 10^{-5}	(3.35 ± 0.1) × 10^{-5}
1h	2.16 ± 0.12	2.40 ± 0.04	(8.22 ± 0.8) × 10^{-6}	(3.06 ± 0.5) × 10^{-9} [f]	(1.87 ± 0.2) × 10^{-5}	(2.29 ± 0.07) × 10^{-5}

[a] Kinetically apparent constant obtained at 50 °C by fitting of eq 1 to experimental data points. [b] Ionization constant determined at 25 °C by spectrophotometric titration. The effect of pK_{ArOH} (given in Table 1) on the pK_a of the corresponding aryl *N*-(methoxycarbonyl)sulfamates **1** measured at 25 °C obeys the following equation: $pK_a = (0.32 \pm 0.03)pK_{ArOH} - (0.8 \pm 0.2)$. [c] Overall first-order rate constant corresponding to the acidic pH-independent region of the pH-rate profiles shown in Figure 1. [d] Spontaneous first-order rate constant corresponding to the plateau region of the pH-rate profiles (Figure 1) around neutral pH. [e] Second-order rate constant for hydroxide ion determined at 50 °C from the linear plots of k_{obsd} vs $[OH^-]$ in the alkaline pH-dependent region (pH 11−13). [f] Determined from extrapolation of an Eyring plot obtained between 100 and 90 °C by the initial rates method using UV−vis spectrophotometry. [g] Interference from reaction of hydroxide ion with the cyano group prevented measurement.

Table 3. Activation Parameters[a] and Solvent Deuterium Isotope Effects for the Hydrolysis Reactions of Compounds **1** and **2**

compd	reaction[b]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/(deg mol)	k_{H_2O}/k_{D_2O}[c]
1a	k_p (k_a)	20.4 ± 0.3[d] (21.9 ± 0.2)[d]	−9.2 ± 0.9[d] (−4.0 ± 0.7)[d]	1.16[e] (2.00)[e,f]
	k_{OH}	16.6 ± 0.2[g]	−17.0 ± 0.8[g]	
1b	k_p (k_{obsd})	23.8 ± 0.4[h]	−11.0 ± 1.3[h]	(1.25)
1c	k_p (k_{obsd})	24.9 ± 0.6[h]	−10.9 ± 1.8[h]	(1.09)
1d	k_p (k_{obsd})	24.2 ± 1.3[i]	−19.6 ± 3.6[i]	(0.91)
1e	k_p (k_{obsd})	21.3 ± 0.9[i]	−31.8 ± 2.4[i]	(1.05)
1f	k_p (k_{obsd})	21.8 ± 0.9[i]	−30.7 ± 2.5[i]	(0.89)
1g	k_p (k_{obsd})	23.2 ± 0.2[i]	−27.2 ± 0.5[i]	(0.91)
1h	k_p (k_{obsd})	21.3 ± 0.3[i]	−31.7 ± 0.8[i]	(0.84)
2	k_{OH} (k_a)	21.0 ± 0.2[g] (19.9 ± 0.4)[h]	−4.5 ± 0.8[g] (−26.7 ± 1.4)[h]	(1.93)

[a] The temperature dependence of rate constants is given in Table S3 in the Supporting Information. [b] k_a refers to the pH-independent reaction in strong acidic media, k_p to the spontaneous pH-independent hydrolysis reaction around neutral pH, k_{obsd} to the pH-dependent reaction observed at pH = 3.60 in formate buffer (0.5 fraction base) and k_{OH} to the hydroxide ion-catalyzed hydrolysis reaction at pH > 12 for **1a** and at pH > 6 for **2**. [c] At 75 °C for 3 half-lives unless otherwise stated. [d] Measurements at six temperatures ranging between 35 and 60 °C in phosphate buffer pH 5.95 (k_p) and in 1.0 M HCl solution (k_a). [e] At 50 °C. [f] See Table 1 for the solvent deuterium isotope effects for the k_a reaction of **1b**−**h**. [g] Measurements at five temperatures ranging between 30 and 50 °C. [h] Measurements at five temperatures ranging between 50 and 70 °C (initial rates method used by UV−vis spectrophotometry). [i] Determined at three temperatures (90, 95, and 100 °C at pH = 7.25 in phosphate buffer 0.8 fraction base) by means of the initial rates method using UV−vis spectrophotometry, see Experimental Section.

(TT processor 2) using XC 111 or U402-M3-S7/60 Ingold combination electrodes with calibrations carried out with commercially available standards at 50 °C. Kinetic runs exhibiting pH drift greater than ±0.02 unit were discarded. The kinetic runs in D_2O were carried out under the same conditions described for H_2O. The value of pD was obtained by adding 0.29 to the observed pH of solutions in D_2O.[18]

UV−vis spectrophotometry was used for all reactions except those of substrates **1f**−**h** in the pH range 0−2 (see below). Reactions were monitored at the appropriate wavelengths using either a Perkin-Elmer Lambda 7 or a Hewlett-Packard 8453 UV−vis spectrophotometer attached to thermostated water bath. Runs were carried out in 3 mL of reaction solution contained in a 1.0 cm quartz cuvette equilibrated at 50.0 ± 0.2 °C. Suitable wavelengths for the kinetic studies were selected by repetitive spectral scanning of the reactions. The very slow hydrolysis of compounds **1** at 50 °C in the pH range 3−10 was measured by following initial rates of release of the phenols. This method was generally used for reactions with half-lives longer than ca. 1 day at 50 °C (see Table S4 in the Supporting Information for the specific method employed for each compound studied in this work). For compounds **1d**−**h**, k_{obsd} values at neutral pH were extrapolated at 50 °C from measurements carried out at 100, 95, and 90 °C (initial rates method used) using activation parameters given in Table 3. In the pH range 0−2, decomposition reactions of substrates **1f**−**h** were monitored by means of the HPLC technique due to the concomitant hydrolysis of the aryl sulfamate intermediates formed during the reaction (see Scheme 1) which prevents reliable measurements of first-order rate constants by UV−vis spectrophotometry. ^{1}H NMR Spectroscopy was used to complement the kinetic study of compounds **1** carried out by UV−vis spectrophotometry. The experimental procedures for kinetic measurements carried out either by UV−vis spectrophotometry, ^{1}H NMR spectroscopy or by use of the HPLC technique are given in the Supporting Information.

b. Product Distributions. The product distributions for the hydrolysis of aryl *N*-(methoxycarbonyl)sulfamates **1** in DCl and buffered deuterium oxide solutions were determined using ^{1}H NMR spectroscopy. In the pH range 0−2, reactions were initiated in a 5 mL vial by mixing acetonitrile solutions containing substrates into acidic buffers preincubated at 50 °C (ionic strength maintained at 1.0 M with KCl) affording initial substrate concentrations of (3.3−4.3) × 10^{-2} M. The final concentrations of acetonitrile were 16 vol % for reasons of solubility. When the reactions were complete (at 4−6 half-lives, determined from the corresponding k_{obsd} values obtained by UV spectrophotometry in D_2O, using the same experimental conditions and the same amounts of acetonitrile as cosolvent), the solutions were transferred to NMR tubes. A spectrum was recorded at 4 and 6 half-lives of the stated reaction time in order to check products' stability. Methanol, methyl carbamate, and substituted phenols were identified at completion by a comparison of NMR peaks with those of authentic samples of pure material obtained in the same experimental conditions (the ^{1}H NMR signal for the methyl group of methanol obtained from the hydrolysis of substrates **1** appears at δ 3.1−3.5 and the signal for the methyl group of methyl carbamate at δ 3.5−3.8, depending on acidity). Yields of product methanol, methyl carbamate, and substituted phenols were checked at 6 half-lives and were within 3% of those determined at 4 half-lives in the case of all substrates studied, attesting to the stability of these products under the reaction conditions.

The pH-independent acidic hydrolysis reactions (k_a) of aryl *N*-(methoxycarbonyl)sulfamates **1** produce two sets of products (Scheme 1). The first set is methanol and substituted phenylsulfamates which

(18) Fife, T. H.; Bruice, T. C. *J. Phys. Chem.* **1961**, *65*, 1079.

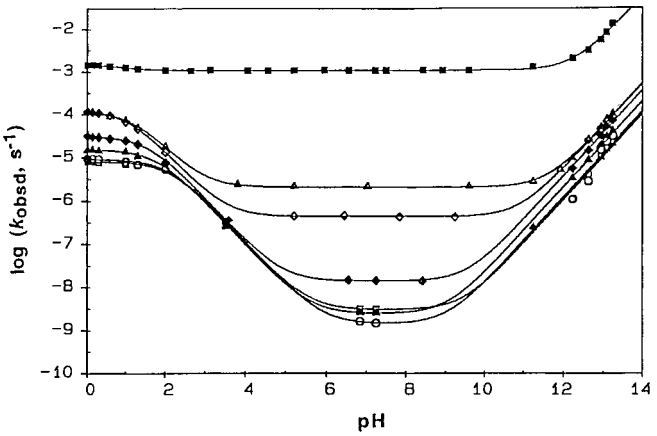


Figure 1. Plots of log k_{obsd}, the overall first-order rate constants for hydrolysis of aryl *N*-(methoxycarbonyl)sulfamates **1**, as a function of pH at 50 °C and 1.0 M ionic strength (KCl). The curves (solid lines) were computer-generated by iteratively fitting the experimental points to eq 1 given in the text (see Results). The values of constants that provided the optimal fits are summarized in Table 2. Compounds **1** are represented by symbols as follows: **1a**, (■); **1b**, (△); **1c**, (◇); **1d**, (◆); **1f**, (▲); **1g**, (○); **1h**, (□). The numbering system for substrate identification is in Table 1. Data points for which log k_{obsd} is lower than −7.5 were extrapolated from Eyring plots obtained between 100 and 90 °C by the initial rates method using UV−vis spectrophotometry. Fit for **1e** is omitted for clarity (due to the competitive reaction of hydroxide ion with the cyano group of **1e**, it has not been possible to study this compound in solutions of pH > 8).

decompose during the kinetic runs into the corresponding substituted phenols. The second set is methyl carbamate and substituted phenols. At the pH-independent portion k_a of the pH-rate profiles shown in Figure 1, the relative amounts of the two sets of products depend on the aryl group of substrates. The relative amount of methanol was determined in 1.0 M DCl solutions by measuring the ratio of the intensity of the signal due to this product ($\delta = 3.1$) to the combined signal intensities due to methyl carbamate ($\delta = 3.35$) and methanol. For each set of product analysis, particular precautions were taken to check the stability of methyl carbamate with respect to its possible convertion into methanol. Partial rates for the two modes of breakdown (k_{CO} and k_{SO2}) were obtained from the product ratios and the first-order rate constants observed (k_{obsd}) at 50 °C in DCl solutions containing the appropriate percentage of acetonitrile (16 vol %).

The experimental procedures for $H_2{}^{18}O$ experiments and pK_a determinations are given in the Supporting Information.

Results

Compounds 1a−h. pH-Rate Profiles. Figure 1 shows the plots of the log of the overall first-order rate constants k_{obsd} vs pH at 50 °C. The pH-rate constant profiles for hydrolysis of compounds **1a−h** shown in Figure 1 are characterized by four distinct regions: (i) the appearance of a plateau below pH 1 (k_a) followed by (ii) a decrease of log k_{obsd} with increasing pH, then (iii) a pH-independent region (k_p) preceding (iv) a hydroxide ion-catalyzed hydrolysis reaction (k_{OH}) at high pH. The latter reaction is characterized by plots of log k_{obsd} vs pH which are linear with slopes of +1.0. The experimental points were fit to eq 1, where a_H is the hydrogen ion activity measured at 50 °C. The values of the constants k_a, k_p, k_{OH}, and K_{app} required to fit the experimental rate constants to eq 1 are recorded in Table 2. K_W is the autoprotolysis constant of water

$$k_{obsd} = (k_a a_H{}^2 + k_p K_{app} a_H + k_{OH} K_W K_{app})/(a_H{}^2 + K_{app} a_H) \quad (1)$$

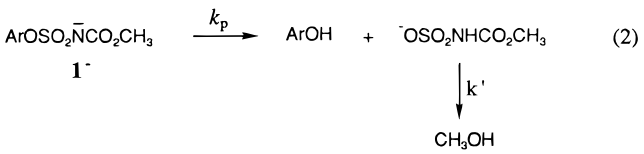
at 50 °C, and K_{app} the apparent acid dissociation constant of substrates **1** at the same temperature. The values of K_a determined spectrophotometrically at 25 °C and $\mu = 1.0$ M with KCl, are also summarized in Table 2. These values are in reasonable agreement with the apparent K_{app} values obtained at 50 °C by fitting of eq 1 to experimental data points.

Products. The pH-independent acidic hydrolysis of compounds **1**, k_a, yields four products in two sets of two. One set is methanol and substituted phenylsulfamates (the C−O cleavage products, k_{CO} in Scheme 1). Detection of the aryl sulfamate esters in acidic media was complicated (except for compounds **1f−h**) by concomitant hydrolysis affording the corresponding substituted phenols (Scheme 1). The second set is methyl carbamate and substituted phenols (the S−O cleavage products, k_{SO2} in Scheme 1). In 1.0 M DCl solution, the relative amounts of the two sets of products vary linearly from 0 to 100% when the pK_a of the leaving group ArOH lies between ca. 4.2 and 9.5 (see Figure S1 in the Supporting Information). For p$K_a{}^{ArOH}$ values less than 4.2, the hydrolysis reaction occurs only via k_{SO2} pathway whereas for those p$K_a{}^{ArOH}$ values greater than 9.5 k_{CO} is the unique pathway (Table 1).

The pH-independent rate constant k_p for hydrolysis of compounds **1a−c** in the pH region around 7 yields the corresponding substituted phenols ArOH and *N*-(methoxycarbonyl)sulfamate $^-OSO_2NHCOOMe$ as the final products, indicating the k_{SO2} route in Scheme 1 is the unique pathway for spontaneous hydrolysis of these compounds: $k_p = k_{SO2}$. The ^{1}H NMR signal due to the methyl group of product *N*-(methoxycarbonyl)sulfamate formed during the kinetic runs of **1a−c** was found to be identical ($\delta = 3.65 \pm 0.05$) to that of an authentic sample of *N*-(methoxycarbonyl)sulfamoyl chloride $ClSO_2NHCOOMe$ recorded in the same reaction conditions. Since rapid hydrolysis of S−Cl bond is expected to occur from the latter compound to yield *N*-(methoxycarbonyl)sulfamate, we actually consider this similarity of NMR peaks as good evidence for the formation of $^-OSO_2NHCOOMe$ during spontaneous hydrolysis of **1a−c**. To ensure complete comparability with the S−O cleavage products formed in acidic media (i.e., substituted phenols coupled with methyl carbamate), we checked and confirmed that *N*-(methoxycarbonyl)sulfamate hydrolyzes to methyl carbamate during the kinetic runs of compounds **1** performed at 50 °C in 1.0 M DCl solution.

For compounds **1d−h**, the spontaneous hydrolysis reaction k_p was found to yield, in phosphate buffers, substituted phenols, and methanol as the final products. Although methanol is obtained from the latter compounds, we still interpret k_p as the k_{SO2} route of Scheme 1. In effect, while *N*-(methoxycarbonyl)-sulfamate ($\delta = 3.44$) hydrolyzes to methyl carbamate ($\delta = 3.35$) in 1.0 M DCl solution, we found that its neutral hydrolysis investigated in phosphate buffer (pD 7.84) at 100 and 95 °C led to the formation of methanol ($\delta = 3.28 \pm 0.05$) with the observed first-order rate constants $k' = 1.26 \times 10^{-4}$ s^{-1} at 100 °C and $k' = 8.40 \times 10^{-5}$ s^{-1} at 95 °C (kinetic runs carried out by ^{1}H NMR for 3 half-lives) giving rise to k'/k_p values ranging between ca. 50 (**1d**) and 580 (**1g**). Since the k_p terms for compounds **1d−h** were extrapolated at 50 °C from measurements carried out at 100, 95, and 90 °C (see the Experimental Section), we explain the formation of methanol during hydrolysis of **1d−h** at those temperatures by the fact that *N*-(methoxycarbonyl)sulfamate is a steady-state intermediate in the pH(D)-independent decay of **1d−h** ([**1d−h**] = (5−8) × 10^{-2} M, [buffer] = 0.5 M). In every case, i.e., from **1d** to **1h**, the putative *N*-(methoxycarbonyl)sulfamate intermediate is substantially more reactive—with regard to its conversion into methanol—than its substrate precursors **1d−h** ($k' > k_p$ in eq 2

below) so that the rate of methanol formation measured by ^{1}H NMR by the initial rates method (see Supporting Information) can be considered a measure of k_{SO2}:$k_{obsd} = k_p = k_{SO2}$.



(2)

Additional evidence that *N*-(methoxycarbonyl)sulfamate is a steady-state intermediate was found in the ^{1}H NMR spectra which were recorded versus time during the first 15% of the hydrolysis reaction of **1d** in phosphate buffer ([**1d**] = 6.5 × 10^{-2} M, pD = 7.84) at 100, 95, and 90 °C. In each case the methyl group of *N*-(methoxycarbonyl)sulfamate was identified at $\delta = 3.65 \pm 0.05$ at the steady concentration of ca. 1.0 × 10^{-3} M whereas methanol concentration increased in the same time from ca. 1.0 × 10^{-3} M to 9.8 × 10^{-3} M (i.e., more than 830% increase). While the observed rate constant k_p markedly decreases on going from substrate **1a** to **1d**, it remains virtually constant on going from **1e** to **1h** suggesting a change in mechanism as the leaving group ArOH becomes poorer than ca. 4-nitrophenol. In the hydrolysis process of **1e**−**h**, the point at which $k' \gg k_p$ is reached and the sulfamate intermediate is no longer detected.

Product analysis performed in the pH portion where **1a**−**h** hydrolysis is hydroxide ion catalyzed suggests that compound **1a** differs from the others compounds in that it produces 2,4-dinitrophenol and *N*-(methoxycarbonyl)sulfamate as the ultimate products whereas the final products for **1b**−**h** hydrolysis are substituted phenols and methanol. In contrast to the spontaneous reaction k_p, the formation of methanol cannot be explained from the basic hydrolysis of the putative intermediate *N*-(methoxycarbonyl)sulfamate, as in eq 2, since the latter compound was found to be quite stable during the hydrolysis reaction time of **1b**−**h** at high pD. Indeed, hydrolysis of *N*-(methoxycarbonyl)-sulfamate was examined by ^{1}H NMR spectroscopy. Only 5.6% hydrolysis into methanol could be detected after 5 days at 50 °C in 0.5 M NaOD solution while all substrates **1b**−**h**, during the same period of time and in the same reaction conditions, were found to give methanol in quantitative yields. Since *N*-(methoxycarbonyl)sulfamate was never detected in the basic hydrolysis of **1b**−**h**, it may be deduced that it never forms.

Buffer Catalysis. The overall first-order rate constants k_{obsd} were found to be quite insensitive (typically, the values of k_{obsd} changed by less than 2%) to changes in buffer concentrations that spanned from 0.05 to 0.5 M, indicating that the hydrolysis of compounds **1** is not buffer-catalyzed. The buffer solutions employed for detecting catalysis were trichloroacetate (pH 0.5−1.1), difluoroacetate (pH 0.9−1.5), dichloroacetate (pH 1−1.5), cyanoacetate (pH 2.1−3.2), acetate (pH 4−5.3), phosphate (pH 5.9−7.2), and borate (pH 8.3−9.6).

Effect of Added Nucleophiles on 1a. The kinetics of the reaction of amine nucleophiles with **1a** are satisfied by the expression given in eq 3. The nucleophilic reaction k_{nuc} may occur via attack on the aromatic ring leading to C−O bond cleavage and anilide formation or attack on sulfur leading to S−O bond fission and *N*-(methoxycarbonyl)sulfamoylamine.

$$k_{obsd} = k_p + k_{nuc}[\text{nuc}] \qquad (3)$$

Our primary interest is focused on the amine reactions that lead to S−O bond cleavage, i.e., those for which 2,4-dinitrophenol is obtained in approximately quantitative yields. In Tables S1 and S2 in the Supporting Information are listed rate data and the second-order rate constants k_{nuc} for the reactions of sodium azide, pyridine, and substituted pyridines with the SO_2 group of **1a** measured at 39 °C in 0.5 M Tris buffer (pH 8.2, ionic strength 1.0 M with KCl). Measurements were carried out by UV−vis spectrophotometry at 360 nm. Attack of pyridines at the aromatic ring would give a stable cationic product[19] with no free electron pair on nitrogen; the latter product does not absorb at 360 nm so that the fraction of optical density at 360 nm due to 2,4-dinitrophenolate absorption was considered as a measure of the fraction of S−O bond cleavage.[20] Since the release of 2,4-dinitrophenolate anion in most of the pyridine-catalyzed reactions is nearly quantitative, one may conclude that pyridines must attack predominantly at sulfur.[21] In Figure S2 (Supporting Information) is shown the linear plot of log k_{nuc} for S−O bond cleavage versus pK_a of the attacking nucleophile for the reaction of sodium azide and substituted pyridines with **1a**. The Brönsted-type coefficient is $\beta_{nuc} = 0.14 \pm 0.02$.

$H_2{}^{18}O$ Experiments. In an attempt to determine the positions of bond cleavage during the acidic and basis hydrolyses of compounds **1a** and **1d**, experiments were conducted to examine if ^{18}O oxygen atoms originally present in an isotopically mixed ^{16}O/^{18}O reaction mixture would be incorporated into products methanol and 4-nitrophenol (**1d**) and 2,4-dinitrophenol (**1a**). At the end of the acidic (1.0 M HCl) and basic (1.0 M NaOH) hydrolysis reactions of **1d**, product methanol was analyzed by use of the GC/EIMS technique, and the analysis in every case indicated no detectable signal corresponding to Me^{18}OH. The isotopic abundance of ^{18}O in 4-nitrophenol formed in acidic and basic 42.1% ^{18}O-enriched reaction mixtures was found to be 0.71 and 0.77%, respectively, for a theoretical value of 0.84% based on "natural abundance." On the contrary, the ^{18}O content in product 2,4-dinitrophenol formed after basic hydrolysis of **1a** in the same isotopically mixed ^{16}O/^{18}O reaction mixture was found to be 43.7%, for a theoretical value of 1.28% based on "natural abundance".[22]

Further experiments were carried out to investigate the possibility of exchange of the carbonyl oxygen of **1d** with that of water enriched in $H_2{}^{18}O$. Unreacted **1d** from acidic (1.0 M HCl) and basic (1.0 M NaOH) hydrolysis in enriched water (42.1% $H_2{}^{18}O$) gave abundance ratios $(M + 2)^+/M^+$ equal to 5.63 and 5.25%, respectively, compared to a theoretical value of 27.46% assuming there is total incorporation of ^{18}O only at the carbonyl moiety of **1d**. A control value for $(M + 2)^+/M^+$ ratio of unreacted **1d** hydrolyzed in $H_2{}^{16}O$ was shown to be 5.47 and 5.07% in 1.0 M HCl and NaOH solutions, respectively, for a theoretical value of 6.41% based on "natural abundance".

Compound 2. The hydrolysis of the nonionizable *N*-methyl analogue of **1a**, namely, 2,4-dinitrophenyl *N*-methyl-*N*-(methoxycarbonyl)sulfamate **2**, gave under the same reaction conditions used in the hydrolysis of **1a** (at 50 °C and $\mu = 1.0$ M),

(19) The second-order rate constant for attack of pyridine on 1-chloro-2,4-dinitrobenzene is several hundred times smaller than that measured for attack on **1a** and the product of attack at carbone, *N*-2,4-dinitrophenylpyridinium chloride is hydrolyzed 44 times more slowly (k_{obsd} = 8.0 × 10^{-6} s^{-1}) than **1a** (3.5 × 10^{-4} s^{-1}) under the same reaction conditions.

(20) Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc*. **1965**, *87*, 3209.

(21) Some C−O fission occurs with 4-aminopyridine (38% at 0.1 M free amine concentration) and sodium azide (17% at 0.25 M total azide concentration).

(22) Control runs indicated that the $(M + 2)^+/M^+$ ratio of signals in authentic methanol, 4-nitrophenol, and 2,4-dinitrophenol that were subjected to the same hydrolysis conditions than **1d** and **1a** (i.e., at 50 °C in exactly the same acidic or basic isotopically mixed $H_2{}^{16}O/H_2{}^{18}O$ reaction mixtures) is not appreciably different than predicted on the basis of "natural abundance".

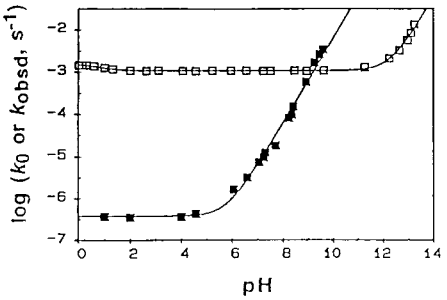
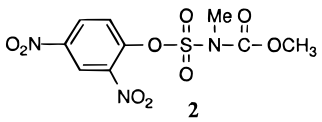


Figure 2. Values of log k_0 and log k_{obsd}, the buffer-independent rate constants for hydrolysis of 2,4-dinitrophenyl *N*-methyl-*N*-(methoxycarbonyl)sulfamate **2** (■) and 2,4-dinitrophenyl *N*-(methoxycarbonyl)-sulfamate **1a** (□), respectively, against pH in aqueous solutions, 50 °C, μ = 1.0 M (with KCl).

quantitative amounts of 2,4-dinitrophenol. Decomposition



2

reaction of compound **2** in aqueous media was monitored by UV−vis spectrophotometry at appropriate wavelengths which allowed us to follow either the disappearance of the starting compound **2** (λ = 250 nm) or the formation of 2,4-dinitrophenol (λ = 360 nm at pH > 4 and λ = 340 nm at pH < 4). The kinetics obtained at either wavelength given above were identical and cleanly first-order for between 4 and 5 half-lives of reaction. In contrast to compounds **1**, the hydrolysis reaction for **2** was found to be buffer-catalyzed in the whole pH range investigated (pH 1−10). In the typical buffer concentration range of 0.05−0.5 M, increases in k_{obsd} due to catalysis of up to approximately 4-fold were observed. Values of the rate constants, k_0, for the buffer-independent rate constant for hydrolysis were determined as the intercepts of plots of k_{obsd} against buffer concentration. Plot of log k_0 as a function of pH is presented in Figure 2. The data in Figure 2 (for **2**) are well fit, at zero buffer concentration, by the rate law of eq 4 for which $k_0 = k_{H2O} + k_{OH}a_{OH^-}$. The k_{H2O} and k_{OH} values are $(3.8 \pm 0.5) \times 10^{-7}$ s^{-1} and 11.6 ± 0.9 M^{-1} s^{-1}, respectively.

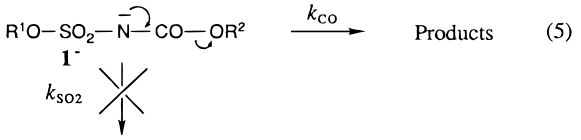
$$k_{obsd} = k_{H2O} + k_{OH}a_{OH^-} + k_B[B] \qquad (4)$$

Deuterium Solvent Kinetic Isotope Effects and Activation Parameters. These are summarized for compounds **1** and **2** in Table 3. For compounds **1**, solvent deuterium isotope effects measured in 1.0 M LCl solutions are presented in Table 1.

Discussion

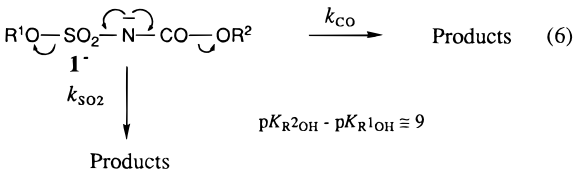
Acid-Catalyzed Hydrolysis. Reactive Species. The sharp difference obtained in the pH-rate profiles (Figure 2) of **1a** and its structurally related *N*-methylated analogue **2**, for which a simple bimolecular displacement by a molecule of water probably occurs at pH < 5, is suggestive of different mechanistic paths for the two ester types. Such a difference, very likely, bears directly on the ability of substrates **1** to ionize at low pH.

Identity and distribution of products formed during the acidic hydrolysis of compounds **1a**−**h** are consistent with the mechanistic pathway shown in Scheme 1 in which two competitive E1cB reactions (k_{CO} and k_{SO2}) are involved. From the literature data,[14] one may estimate the rate constant ratio k_{CO}/k_{SO2} at ca. 10^9 when the oxy leaving groups attached to either side of the [(carbonyl)amino]sulfonyl moiety are identical. This large value of k_{CO}/k_{SO2} reflects the greater ease for the C−O bond to be cleaved during anion breakdown. Therefore, the most likely E1cB reaction that might take place in the hydrolysis process of these compounds is anion decomposition through carbonyl group as in eq 5. However, if one considers that the sensitivities



1$^-$ (5)

of log k_{SO2} and log k_{CO} toward the basicities of the leaving groups R^1O^- and R^2O^-, respectively, are close to unity (i.e., $\beta_{lg} \approx -1$),[23] one may then expect an ambivalent reactivity to show up, i.e., $k_{CO} \approx k_{SO2}$, if the acidity of the leaving group R^1OH attached to the sulfonyl moiety becomes ca. 9 orders of magnitude greater than that of R^2OH, i.e., $\Delta pK_a = pK_{R^2OH} - pK_{R^1OH} \approx 9$ (eq 6). That is the case of compounds **1a**−**h** whose



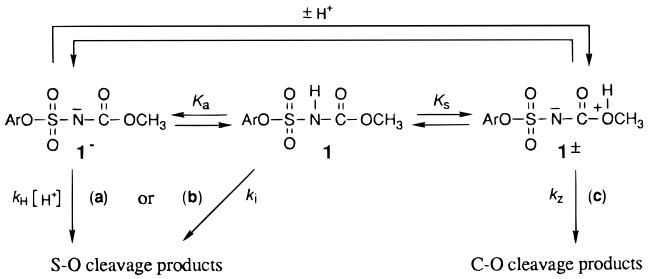
1$^-$ (6)

ΔpK_a values, as just defined, range from 11.4 to 5.6 on going from **1a** to **1h**, respectively. The product distributions obtained in 1 M DCl solution (Table 1) show that the relative amounts of methanol and methyl carbamate vary linearly within this ΔpK_a range from ca. 0 to 100% (see Figure S1 in the Supporting Information). According to the linear equation of Figure S1, an equal partitioning between methanol and methyl carbamate should set up at $\Delta pK_a = 8.6 \pm 1$, a value that agrees well with that estimated above.

However, any reaction pathway involving **1**$^-$ as the single reactive species is considered unlikely. Such a possibility might be suggested on the basis of the above consideration and the fact that compounds **1** have pK_a values (Table 2) that are far below the pK_a values usually observed for >N−H bond ionization. This is due to the combined electron-withdrawing conjugative effects of sulfonyl and carbonyl groups which strongly contribute to stabilizing the negative charge on the nitrogen atom. There should therefore be a significant amount of anion present in solution even in the more acidic media (e.g., at pH = 1, more than 77% of **1a** is present in the anionic form at 25 °C), so that it does not seem unreasonable to envisage that **1**$^-$ could be the reactive species over the entire pH range as suggested by Scheme 1. However, to be consistent with the observed rate law at pH < 7, either reaction of Scheme 1 should be general acid-catalyzed. In that case, the catalytic role of hydronium ion would be to assist—by proton transfer—departure of the leaving groups ArO^- *and* CH_3O^- during the course of the two rate-limiting S−O and C−O bond fissions, respectively. Reactions involving general acid/base catalysis and rate-limiting proton transfer are known to exhibit a significant solvent deuterium isotope effect k_{H2O}/k_{D2O}. While the reaction with S−O bond cleavage shows relatively large isotopic dependence (k_{H2O}/k_{D2O} = 2 for **1a**), that with C−O bond cleavage exhibits only low values of k_{H2O}/k_{D2O} (see compounds **1f**−**h** in Table 1). The absence of isotopic effect on k_{CO} is then inconsistent

(23) The Brönsted exponent, β_{lg}, for the E1cB reaction of aryl *N*-methylsulfamates in 50% aqueous ethanol is −1.8.[14b] In pure aqueous media, the β_{lg} values for the E1cB reactions of aryl *N*-methylcarbamates,[14a] aryl carbamates[14a] and aryl sulfamates[24] are −1.1, −1.15, and −1.2, respectively.

Scheme 2[a]

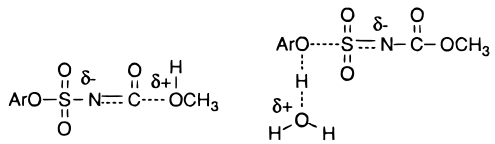


[a] In acid $k_{obsd} = k_a$ with $k_a = k_H K_a + k_z$ (paths **a** and **c**) or $k_a = k_i + k_z$ (paths **b** and **c**).

with a mechanism in which the expulsion of methanol from $\mathbf{1}^-$ would be general acid-catalyzed.

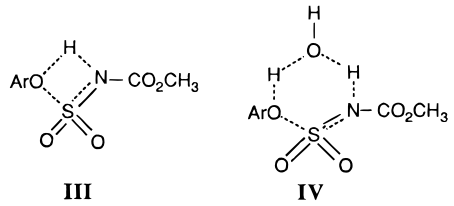
The reaction pathway shown in Scheme 2 is consistent with the rate law for decomposition of substrates **1** in acid (where $k_{obsd} = k_a$, see eq 1) and is not inconsistent with any other experimental results obtained in the present work.

According to Scheme 2, the reaction with C−O bond cleavage (k_{CO}) involves protonation of the leaving group methanol and its expulsion from the dipolar intermediate $\mathbf{1}^{\pm}$ with k_z (path **c**) and a transition state (**I**). This provides both an internal nucleophile in the form of a nitrogen anion and an activated methanol leaving group. As is shown in Scheme 2, our



I **II**

experimental results do not distinguish between two possible alternatives, paths **a** and **b**, for the reaction with S−O bond cleavage, k_{SO2}. Specifically, $k_H[H^+]$ (path **a**) represents hydronium ion-catalyzed decomposition of $\mathbf{1}^-$ with a transition state (**II**), while k_i (path **b**) refers to intramolecularly acid-catalyzed expulsion of ArO^-: the proton transfer to the leaving group may either be direct (**III**) or via a bridging water molecule (**IV**); the latter would avoid ring strain at the transition state and is more likely. The kinetic ambiguity between paths **a** and **b** bears directly on the failure to observe buffer catalysis for the reactions of **1** (Results).



III **IV**

Methanol Route. The following accumulated evidence led us to propose transition state **I** (path **c**) as the most likely mechanism for the reaction with C−O bond cleavage.

(1) Aryl sulfamate esters were detected as intermediates during the kinetic runs of compounds **1** while, in the same reaction conditions, *N*-(methoxycarbonyl)sulfamate anion was shown to hydrolyze to methyl carbamate, not methanol (see Scheme 1). This indicates that the reaction site for methanol formation is neither at the sulfur atom nor at the aromatic ring but instead at the *N*-(methoxycarbonyl) moiety.

(2) The Brönsted coefficient for the leaving group ArOH, β_{lg}, for the partial rate of release of methanol and arylsulfamates (k_{CO}) is 0, consistent with the absence of S−OAr bond cleavage at the transition state **I**.

(3) The absence of detectable signal of $Me^{18}OH$ at the end of the acidic hydrolysis reaction of **1d** conducted in 42% ^{18}O-enriched water indicates that product methanol is not formed from a bimolecular attack of water on the methyl group of compounds **1** (an S_N2 reaction with methyl−oxygen fission). The results given in points 1−3 definitely locate the reaction site at the −NHCOO− moiety.

(4) The possibility of reversible attack of water at the carbonyl group of the neutral species **1** can be ruled out because of the absence of ^{18}O exchange from $H_2{}^{18}O$ into unreacted starting material after 1 half-time of hydrolysis in 42% ^{18}O-enriched 1.0 M HCl solution.

(5) Also, the possibility that the nucleophilic addition of water at the carbonyl group of the neutral form of **1** occurs at the rate determining step is ruled out based on the following facts: (i) The observed rate constants k_{CO} (Table 1) are ca. 50-fold larger than observed for hydrolysis of **2** in acid ($k_{H2O} = 3.8 \times 10^{-7}$ s^{-1}, Figure 2). If the reactions of **1** that lead to methanol proceed by addition of water to the carbonyl group, then the rate constants k_{CO} for compounds **1** should be similar to that observed for **2** in acid, i.e. k_{H2O}, which, very likely, corresponds to nucleophilic addition of water to the carbonyl group. (ii) Buffer bases are known to increase the nucleophilic reactivity of water toward addition to the carbonyl group, and such catalysis is generally associated with large values of k_{H2O}/k_{D2O} and large negative values of $\Delta S^{\ddagger}$ as observed for **2** (see Results and Table 3). In contrast, the k_{CO} pathway for **1** is characterized by the absence of both buffer acid−base catalysis and solvent isotope effect (see compounds **1f**−**h** in Table 1).

(6) Extrapolation of the Brönsted plot log k_p vs pK_{lg} obtained for the uncatalyzed decomposition of the anions of aryl *N*-(phenylsulfonyl)carbamates,[25] as indicated in footnote 26, and taking into account the stabilizing effect of the phenolic oxygen of **1** (estimated to ca. 2.3 kcal/mol[27]) suggests that the zwitterions $\mathbf{1}^{\pm}$ involved in Scheme 2 may exist as discrete species in aqueous solutions[28] with $k_z < 1 \times 10^{10}$ s^{-1}.

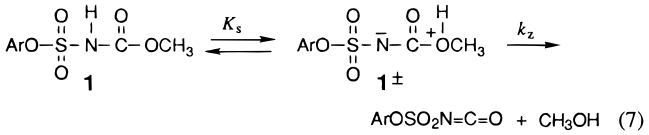
(24) Thea, S.; Cevasco, G.; Guanti, G.; Williams, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1582.

(25) The rate constant k_p for the decomposition of the anions $PhSO_2N^-CO-OAr$ obeys the following equation: $\log(k_p, s^{-1}) = -1.29\ pK_{ArOH} + 8.4$ (50 °C), see ref 12.

(26) (a) From the linear Brönsted relationship given in footnote 25 one may calculate pK_{ROH2^+} values for which k_p is greater than 10^{13} s^{-1}. An important assumption involved in this calculation is that the Brönsted relationship of footnote 25 can be applied to the zwitterionic species $PhSO_2N^-CO-HO^+R$ with $k_p = k_z$ and neutral leaving groups ROH. Otherwise this calculation gives $pK_{ROH2^+} < -3.6$ (at 50 °C). Assuming $\Delta pK_a = pK_{ROH} - pK_{ROH2^+} \approx 17$ (based on the fact that for methanol and phenol ΔpK_a is $15.5 - (-2.5) = 18$ and $10 - (-6.7) = 16.7$, respectively) the trend obtained in terms of pK_{ROH2^+} would then correspond to $pK_{ROH} <$ ca. 13.4. (b) A similar calculation can be made to estimate the pK_{ROH} range for which $10^{10} < k_p = k_z < 10^{13}$, which corresponds to the kinetic case where the diffusion-controlled formation of the zwitterion, arbitrary taken to 10^{10} M^{-1} s^{-1}, is partially or fully rate determining (in this case the zwitterion is assumed to exist as an identifiable species but is too unstable to diffuse through the solvent; also, the assumption that the formation of the zwitterion may be limited by diffusion implicitly suggests that the proton is transferred by a water mediated proton switch mechanism). This calculation gives ca. $13.4 < pK_{ROH} <$ ca. 15.8 (at 50 °C).

(27) The C−O bond cleavage reaction leading to phenolate expulsion from phenyl *N*-(phenoxycarbonyl)sulfamate anion ($k_p = 9.36 \times 10^{-7}$ s^{-1} at 50 °C, unpublished results) occurs 35 times slower than from phenyl *N*-(phenylsulfonyl)carbamate anion ($k_p = 3.27 \times 10^{-5}$ s^{-1} at 50 °C, see ref 12). Assuming that the same stabilizing effect holds for the zwitterionic species $Ph(O)SO_2N^-CO-HO^+R$, one may re-estimate the pK_{ROH} range obtained in footnote 26b for which $10^{10} < k_z$ (Scheme 2) $< 10^{13}$. This gives $12.2 < pK_{ROH} < 14.6$.

(7) The small values of k_{H2O}/k_{D2O} observed for k_{CO} in 1.0 M LCl are not incompatible with the elimination pathway **c** (eq 7). The solvent deuterium isotope effect on the mechanism of



eq 7 is due solely to secondary effects at exchangeable sites. The expected effect can then be deduced on the basis of fractionation factor theory.[29] The expression for the solvent deuterium isotope effect is presented in eq 8, where ϕ_{NH}, ϕ_N-, $\phi_{OH}+$, and k_z^H/k_z^D represent the fractionation factors for the NH group, its anion in **1**$^{\pm}$, the oxonium ion in **1**$^{\pm}$, and the isotope effect on k_z (eq 7), respectively. A suitable value for $\phi_{OH}+$ is

$$k_{CO}^{H}/k_{CO}^{D} = \phi_{NH}(1/\phi_N-)(1/\phi_{OH}+)k_z^H/k_z^D \qquad (8)$$

the fractionation factor for the lyonium ion ($\phi = 0.69$);[29] the value of $\phi_{NH}/\phi_N- = 0.77$ for **1f** can be estimated from the measured solvent deuterium isotope effect on equilibrium ionization of this compound, K_a^H/K_a^D, using $\phi_{OH}+ = 0.69$ for the hydronium ion.[30] Thus, the isotope effect on K_s (eq 7) is found to be slightly greater than 1: $K_s^H/K_s^D = (\phi_{NH}/\phi_N\text{-})(1/\phi_{OH}+) = (0.77)(1.45) = 1.12$. The value of k_z^H/k_z^D is unknown, but some consideration allows $k_z^H/k_z^D \approx 1$ to be deduced.[31] Thus, it is conceivable that the small values of k_{H2O}/k_{D2O} observed for k_{CO} (Table 1) could result from the solvent deuterium isotope effect on K_s in eq 8.

Methyl Carbamate Route. The transition state structures shown in **II**, **III**, and **IV** are supported by the following accumulated evidence.

(1) Methyl carbamate was shown to be the hydrolysis product of *N*-(methoxycarbonyl)sulfamate anion in acidic conditions (see Scheme 1). The latter compound may result from the nucleophilic attack of water on the neutral species of **1** either at the aromatic ring leading to C−O bond cleavage or at the sulfur atom leading to S−O bond fission. However, the sharp difference obtained in the pH-rate profiles (Figure 2) of **1a** and its *N*-methylated analogue **2**, for which a simple bimolecular displacement by a molecule of water probably occurs at pH < 5, is suggestive of different mechanistic paths for the two ester types.[32]

(2) Partial formation of 4-nitrophenol via a S_NAr mechanism can be ruled out for **1d** because of the absence of ^{18}O incorporation from $H_2{}^{18}O$ into the fraction of 4-nitrophenol that is formed in association with methyl carbamate (corresponding to 48.5% of total 4-nitrophenol formed in 1.0 M DCl solution).

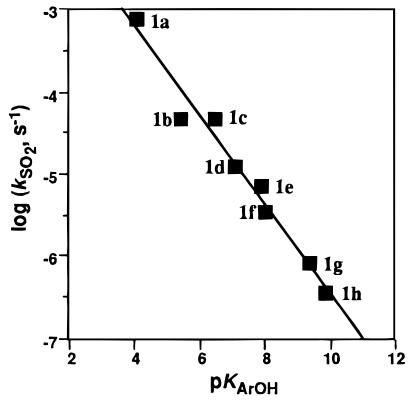
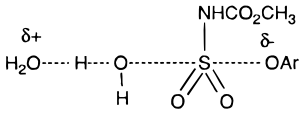


Figure 3. Values of log k_{SO2}, the partial rate constant for the formation of substituted phenols and methyl carbamate (the S−O cleavage products) determined from product ratio, for hydrolysis of aryl *N*-(methoxycarbonyl)sulfamates **1** at 50 °C in 1.0 M DCl solution containing 16% CD_3CN ($\mu = 1.0$ M), against pK_a of the corresponding leaving group ArOH. The linear regression equation is log k_{SO2} = (−0.54 ± 0.04)pK_{ArOH} − (1.0 ± 0.3).

(3) The latter result coupled with the fact that quite a good correlation exists for all compounds **1**, including **1a**, between the partial rate k_{SO2} and the pK_a of the leaving group ArOH (Figure 3) strongly suggests that (i) a single mechanism is involved and (ii) that this mechanism is not S_NAr.

(4) Although the transition state structure **V** may account for the observed solvent isotope effect (Table 1) and β_{lg} parameter (see below), it is not likely in view of (i) the near-zero value for the entropy of activation of **1a** given in Table 3 (mechanisms involving water-catalyzed nucleophilic attack of water as **V** are commonly characterized by strongly negative entropies of activation typically in the range −30−60 cal deg^{-1} mol^{-1}), (ii) the lack of buffer catalysis and (iii) the sharp difference obtained between the pH-rate profiles of **1a** and **2**.



V

(5) The Brönsted coefficient for the leaving group, β_{lg}, obtained for k_{SO2} is −0.54 (Figure 3), consistent with some degree of S−OAr bond cleavage at the transition state. Figure S3 under Supporting Information shows the Hammett relationship between the hydrolysis rate k_{SO2} and σ parameter for electron-withdrawing para substituents. The correlation (r = 0.999) exhibits a ρ of 2.03 ± 0.06. This ρ value is probably an overestimate of the expected ρ value in pure water because of

(28) An entity is not considered as an intermediate if its lifetime is less than h/kT (see below), i.e., ca. 1.6×10^{-13} s at 25 °C, that is, if the rate constant for its decomposition is on the order of a bond vibration frequency, i.e., ca. 6.2×10^{12} s^{-1} at 25 °C. h/kT is the universal frequency factor comprising the Boltzmann and Planck constants, and absolute temperature. See: Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*, 2nd ed.; Wiley: 1961; p 91.

(29) Kresge, A. J.; More O'Ferral, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Ed.; Elsevier: Amsterdam, The Netherlands, 1987; Vol 7.

(30) The value of ϕ_{NH}/ϕ_N- for **1**$^{\pm}$ can be estimated from the following equation: $K_a^H/K_a^D = (\phi_{NH}/\phi_N-)(\phi_{OH}+)^{-3}$. For compound **1f**, $\Delta pK_a = pK_a^D - pK_a^H = 0.37 \pm 0.04$ (25 °C) gives $\phi_{NH}/\phi_N- = 0.77 \pm 0.07$. An important assumption involved in this estimate is that the fractionation factor for the nitrogen ion in **1**$^-$ is the same as in **1**$^{\pm}$.

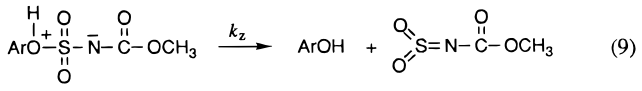
(31) The driving force for methanol expulsion from **1**$^{\pm}$ is likely to be very large. As a result, the transition state **I** should be quite early, that is, it should closely resemble **1**$^{\pm}$. Therefore, the value of $k_z^H/k_z^D = (\phi_N-)(\phi_{OH}+)(1/\phi_{N^{\delta-}}{}^{\ddagger})(1/\phi_{OH^{\delta+}}{}^{\ddagger})$ is expected to be maximal, that is, scarcely below the upper limit of 1 since $(\phi_{N^{\delta-}}{}^{\ddagger})(\phi_{OH^{\delta+}}{}^{\ddagger}) < (\phi_N-)(\phi_{OH}+)$ (the fractionation factor increases in going from **1**$^{\pm}$ $\{(\phi_N-)(\phi_{OH}+) < 1\}$ to the immediate products of the reaction $\{\phi \approx 1\}$ (eq 7)).

(32) The apparent second-order rate constant for a hypothetical bimolecular attack of water on the neutral 2,4-dinitrophenyl ester **1a**, $k_{H2O} = k_a/55.5 = 2.77 \times 10^{-5}$ M^{-1} s^{-1} (50 °C), would be more than 3 orders of magnitude larger than that for its *N*-methyl analogue **2** for which the real second-order rate constant for the water-induced process is $k_{H2O} = (3.8 \times 10^{-7})/55.5 = 6.85 \times 10^{-9}$ M^{-1} s^{-1} (50 °C). Such a difference is considered as good evidence especially against a nucleophilic aromatic substitution for **1a** since, under the assumption of such a mechanism, similar rates would have been expected in acidic media for both compounds (regardless of which step of the S_NAr mechanism is rate determining) due to the presumably comparable electronic effects and leaving group abilities of the *N*-(methoxycarbonyl)sulfamate moieties of **1a** and **2** in the pH region where the N−H bond remains undissociated.

the presence of 16% of acetonitrile[33] (see Experimental Section). However, it means that there is a significant charge buildup on the phenolic oxygen in going from the initial to the transition state consistent with S−O bond cleavage.[34] The "effective charge"[35] on the phenolic oxygen of the reactant ester $\mathbf{1}^-$ is unknown, but its value is expected to be close to that observed on the phenolic oxygen of related esters such as, e.g., monoanions of aryl phosphate (+0.74[36]) and aryl sulfate (+0.7[37]) monoesters.[38] Assuming that the "effective charge" is +0.7 in $\mathbf{1}^-$ and, therefore, > +0.7 in **1**, then the β_{lg} value of −0.54 implies that there must be +0.16 or >+0.16 unit of "effective charge" on the aryl oxygen at the transition state depending on whether the reactant species is $\mathbf{1}^-$ or **1**, respectively. Such positive values are consistent with the fact that the rate constants k_{SO2} are well correlated with σ constants.

(6) There seems to be good evidence that the leaving group expulsion from either $\mathbf{1}^-$ or **1** is assisted by proton transfer as shown in **II**, **III**, or **IV**. The overall change of the "effective charge" (ec) on the aryl oxygen in going from the reactant species $\mathbf{1}^-$/**1** (ec ≥ ca. +0.7 see above) to the final species ArOH (ec = 0) or ArO^- (ec = −1) is ca. −0.7 or −1.7, respectively. A β_{lg} of −0.54 associated to an overall charge change of −1.7 would indicate that the "effective charge" on the aryl oxygen at the transition state is some 32% of the difference between that in ground (compound **1**) and product (ArO^-) states. In comparison, the β_{lg} value for ArO^- expulsion from $\mathbf{1}^-$ is −1.39 (vide infra) indicating that the S−O bond fission is well advanced (82%) in the transition state. The fact that the transition state for the expulsion of ArO^- from **1** would be some 61% earlier than that from $\mathbf{1}^-$ is not consistent with expectation: $\mathbf{1}^-$ has more driving force than **1** to expel ArO^- so that the transition state for ArO^- expulsion should be earlier for $\mathbf{1}^-$. This "contradiction" with expectation can be resolved if there is protonation of the leaving group as in mechanisms **II**, **III**, or **IV**. In that case, the β_{lg} value of −0.54 is associated to an overall "effective charge" change of ca. −0.7 consistent with a late transition state.

Intermolecular (Path a) or Intramolecular (Path b) General Acid Catalysis? The concerted general acid catalysis of path **a** or **b** (Scheme 2) for the reaction with S−O bond cleavage appears to be enforced[39,40] by the disappearance of the barrier for leaving group expulsion from the zwitterionic species in eq 9. By extrapolating the Brönsted line shown in



(9)

Figure 4 (vide infra), in the same way as indicated in footnote 26, we find that the rate constant k_z (eq 9) is greater than 10^{13} s^{-1} for leaving phenols of pK_a < ca. 9.4 (at 50 °C),[28] that is, only a concerted mechanism is possible for compounds **1**. Paths **a** and **b** represent the two types of concerted general acid catalysis that may be considered to "bypass" the zwitterionic species in eq 9. As mentioned in an earlier section, unambiguous distinction between inter- and intramolecular general acid catalysis (i.e., between paths **a** and **b**, respectively) will depend on the observation or not of buffer acid catalysis. While the observation of buffer catalysis should readily resolve the kinetic ambiguity in favor of path **a**, the failure to observe any buffer effect, as in the case of compounds **1**, should maintain the kinetic ambiguity between the two paths.

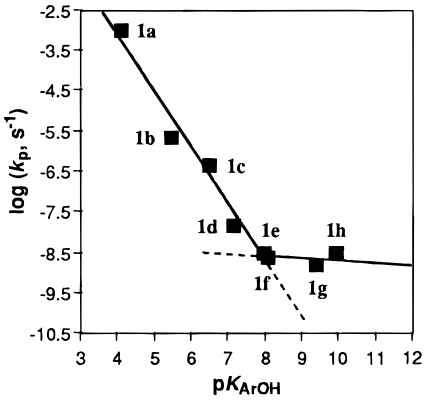


Figure 4. Plot of the log of k_p, the spontaneous hydrolysis reaction for aryl *N*-(methoxycarbonyl) sulfamates **1a**−**h** at 50 °C (μ = 1.0 M with KCl), against pK_a of the corresponding leaving group ArOH. The linear regression equation obtained with compounds **1a**−**f** is log k_p = (−1.39 ± 0.1)pK_{ArOH} + (2.43 ± 0.7), r = 0.987. For compounds **1d**−**h**, values of k_p were extrapolated at 50 °C from Eyring plots obtained between 100 and 90 °C.

"Neutral" Hydrolysis. In contrast to the acidic hydrolysis reaction k_a, the pH-independent "neutral" hydrolysis k_p (corresponding to the plateau regions around pH 7 in Figure 1) takes place exclusively via S−O bond fission (see Results). The hydrolysis rates for the anions of *N*-(methoxycarbonyl)sulfamate esters **1a**−**f** depend very strongly on the basicity of the leaving group, the slope of log k_p against pK_{lg} being −1.39 (Figure 4). This figure is consistent with a transition state in which the breaking of the bond to the leaving group is well advanced. This is typical of many phosphoryl ($-PO_3^{2-}$)[41] and sulfuryl ($-SO_3^-$)[42] group transfer reactions including hydrolysis. The low Brönsted exponent for attack of sodium azide and substituted pyridines on the sulfur center of **1a** (β_{nuc} = 0.14, Figure S2 in the Supporting Information) indicates weak interaction with nucleophile. Thus, although the second-order kinetics demands that the nucleophiles take part in the rate-limiting step, rate constants are virtually independent of the basicity of the nucleophiles, from pyridines with pK_a of 1.45 to pyridines with pK_a of 9.20 (Tables S1 and S2 in the Supporting Information). Again, this behavior is typical of phosphoryl and sulfuryl transfer reactions.[41,42] The large value of β_{lg} associated with the small β_{nuc} coefficient is consistent with an "exploded" transition state for substitution that may occur by a concerted or stepwise preassociation mechanism.[43] Although there is evidence for free intermediates of type $O_2S{=}NR$ when R = H and Me,[14b,24] we failed in the present case to demonstrate that the putative

(33) For the dissociation of benzoic acids, a maximum increase of 141% is observed for ρ at 25 °C in going from 100% water to 100% acetonitrile. See: Kolthoff, I. M.; Chantooni, M. K. *J. Am. Chem. Soc.* **1971**, *93*, 3843.

(34) The exact charge on the aryl oxygen is not known and not directly comparable to pure water, but the differences in conditions are small and do not invalidate the conclusion that there is significant S−O bond cleavage at the transition state.

(35) Williams, A. *Adv. Phys. Org. Chem.* **1991**, *27*, 1.

(36) Bourne, N.; Williams, A. *J. Org. Chem.* **1984**, *49*, 1200.

(37) Hopkins, A. R.; Day, R. A.; Williams, A. *J. Am. Chem. Soc.* **1983**, *105*, 6062.

(38) The ArO^- species is defined as possessing 1 unit of negative charge on its oxygen, in comparison with zero in the neutral phenol (ArOH). Thus, the "effective charges" of +0.74 and +0.7 on the phenolic oxygen of phosphate and sulfate monoesters, respectively, mean that $-PO_3H^-$ and $-SO_3^-$ groups are effectively more electron withdrawing than the hydrogen (proton) when covalently linked to an aryl oxygen.

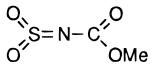
(39) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425.

(40) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161.

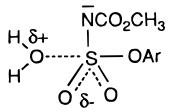
(41) Cox, J. R.; Ramsay, O. B. *Chem. Rev.* **1964**, *64*, 317 and references therein. Benkovic, S. J.; Schray, K. J. In *The Enzymes*; 3rd ed.; Boyer, P. D., Ed.; Academic Press: New York, 1973; Vol. 8, pp 201−238 and references therein.

(42) Williams, A.; Douglas, K. T. *Chem. Rev.* **1975**, *75*, 627 and references therein.

N-(methoxycarbonyl)sulfimide species (below) could be a liberated intermediate in aqueous solution.



With an increase in leaving group basicity there is a change to a coupled concerted mechanism that is characterized by a decrease in β_{lg} and a large negative value of $\Delta S^{\ddagger}$. There is a sharp break in β_{lg} plot as β_{lg} changes from -1.39 to 0 and $\Delta S^{\ddagger}$ changes from -10 eu for compounds **1a**−**c** to -30 eu for compounds **1e**−**h**. This change is presumably due to the larger nucleophilic assistance required for the cleavage of the S−O bond with more basic leaving groups. The fact that the reaction of **1a** with pyridines is a nucleophilic displacement that occurs at the same rate regardless of the nucleophilicity of the incoming reagent suggests that water is also involved in the transition state with weak binding to the sulfur center. However, as in the case of phosphate and sulfate monoesters, the exact role played by water is not clear. In effect, water might provide part of the driving force for fragmentation either by differential solvation of ground and transition states and/or as a nucleophile. Under the latter hypothesis, the question as to whether water behaves rather as a *nucleophilic acceptor* (to quench the forming *N*-(methoxycarbonyl)sulfimide species) or as a *true nucleophile* (which weakly binds to the sulfur center to assist leaving group expulsion) remains uncertain for **1a**−**c**. In contrast the role played by water becomes clearer as the leaving group of compounds **1** becomes poorer. In effect, the Brönsted exponent β_{lg} for aryl *N*-(methoxycarbonyl)sulfamates **1** changes sharply (from -1.39 to ca. 0) when the pK_a of the leaving group exceeds ca. 7.8 (Figure 4), which strongly suggests a changeover in mechanism to stronger participation of water (as a nucleophile) in the transition state.[45] This is further confirmed by the entropies of activation given in Table 3. The difference in the observed $\Delta S^{\ddagger}$ values for compounds **1e**−**h** (range) and **1a**−**c** (range) is such as to suggest considerably more involvement of water in the transition state for the hydrolysis of **1e**−**h**. In fact, entropies of activation of the order of -30 eu are generally associated with bimolecular mechanisms so that it seems reasonable to envisage that the neutral hydrolysis of compounds **1e**−**h** proceeds through an addition−elimination mechanism with a transition state as **VI**.



VI

Hydroxide Ion Catalyzed Hydrolysis. The OH^- reaction observed with compounds **1b**−**h** (except for **1e**, see legend of Figure 1) undoubtedly reflects attack of OH^- at the carbonyl moiety whereas with **1a** the experimental evidence supports attack at the aromatic ring followed by C−O bond cleavage (see Results). For all compounds **1** (except for **1a** and **1e**), the plot of log k_{OH} against the pK_a of the corresponding phenols is linear with a slope $\beta_{lg} = -0.15$ (Figure S4, Supporting Information). The latter value probably reflects the sensitivity of the negative charge of $\mathbf{1}^-$ to be more extensively delocalized to the sulfonyl moiety through the electron-withdrawing effects of the aryl substituents. Consequently, compounds whose negative charge will provide the lowest electrostatic barrier toward OH^- attack are those with powerful electron-withdrawing aryl substituents as illustrated by the k_{OH} values given in Table 2.

It is of interest to note that the hydroxide ion catalyzed reaction of **1a** is characterized by a significantly more negative entropy of activation ($\Delta S^{\ddagger} = -17$ eu) than that observed for its *N*-methylated analogue **2** ($\Delta S^{\ddagger} = -4.5$ eu). Such a relatively large difference may be explained in part by the fact that the attack of OH^- at the aromatic ring of **1a** corresponds presumably to the rate-determining step of the addition−elimination process whereas for **2** the attack (either at the aromatic ring or at the sulfur or carbonyl centers[46]) is likely to be faster than the subsequent breakdown of the corresponding addition intermediate. Under this assumption, the expected $\Delta S^{\ddagger}$ value for **2** should reflect both the associative and dissociative nature of the stepwise process, that is, it should not be far from zero, as observed.

Conclusions

The present study suggests that the $-SO_2NHCO-$ group may be viewed as an attractive phosphate analogue in which the naturally occurring oxyanions of phosphates have been replaced by a nitrogen anion of comparable basicity. Interestingly, according to the criteria developed by Westheimer[10] the $-SO_2NHCO-$ linkage may be envisaged as a possible alternative to phosphate esters in nucleic acids DNA and RNA. Indeed, as phosphodiesters (1) it is conveniently made by ester bonds, (2) it can link two groups (e.g. nucleosides) and still ionize at physiological pH, and (3) it is hydrolytically stable. Moreover, our detailed kinetic study of aryl *N*-(methoxycarbonyl)sulfamates **1** shows that the reaction of **1** that occurs with sulfur−oxygen bond cleavage bears very strong similarities to the hydrolytic mechanisms of both phosphate and sulfate monoesters. Other aspects of the chemistry of the [(carbonyl)amino]sulfonyl group are currently under investigation.

Acknowledgment. We thank professors James Fishbein (Wake Forest University) and John Richard (University at Buffalo, SUNY) for their critical reading and helpful comments. We also thank Susy Richelme, Marie-Pierre Ferté and Eric Leroy from the Service Commun de Spectrométrie de Masse, Université Paul Sabatier, for their assistance with the GC/EIMS technique. Special thanks go to Dr. Marcel Perry for his invaluable help in developing original data analysis programs.

Supporting Information Available: Spectroscopic and analytical data for compounds **1** and **2**; text giving details of procedures for kinetic measurements, $H_2{}^{18}O$ experiments, and pK_a determinations; and figures S1−4 and Tables S1−4 (see text) (13 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(43) Jencks[44] has pointed out that a reaction is necessarily preassociative if either the reaction intermediate, e.g., $O_2S{=}NCO_2Me$, does not exist (in this case the mechanism is preassociative concerted) or if it is so unstable that it collapses back to starting materials faster than the nucleophilic acceptor can diffuse away from the complex (in this case the mechanism is preassociative stepwise).

(44) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345.

(45) A somewhat similar change in β_{lg} was observed for the E1cB decomposition of *N*-methylsulfamate esters with poor leaving groups, see ref 14b.

(46) Clearly our data on the hydrolysis of **2** are insufficient to elucidate the mechanism in greater detail.