A General Acid-Catalyzed Anion Breakdown Associated with an E1cB Reaction in the Hydrolysis of Aryl *N*-(Substituted Phenylsulfonyl)carbamates

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Abstract: The hydrolysis of aryl *N*-(substituted phenylsulfonyl)carbamates at 50 °C in the pH range 0–13.5 leading to substituted benzenesulfonamides and phenols involves acyl group transfer. Reaction rates were measured spectrophotometrically and are independent of the concentration of the catalyst for buffers of $pK_{BH} > 8$. With more acidic buffers, a general acid catalysis is observed for the hydrolysis of phenyl *N*-(phenylsulfonyl)carbamate **1a** ($pK_a = 2.85$) leading to a Brönsted relation ($\alpha = 0.46$) including hydronium ion while it does not occur for 4-cyanophenyl *N*-(phenylsulfonyl)carbamate **1d**. In alkaline media, the values of the entropies of activation are positive and lie between 0.20 and 15.0 cal mol^{-1} K^{-1}. The Hammett ϱ^- value for the expulsion rate k_p of phenolate ion from aryl *N*-(phenylsulfonyl)carbamates is positive ($\varrho^- = +2.93$) while, for phenyl *N*-(substituted phenylsulfonyl)carbamates it is negative ($\varrho = -0.66$). An electrophilic intermediate, phenylsulfonyl isocyanate, was trapped with piperidine to give *N*-(piperidinocarbonyl)benzenesulfonamide. These results are consistent with an elimination–addition mechanism $A_{Xh}D_H + D_N$ (E1cB). In HCl solutions, solvent isotope effects $k_{obsd}(H_2O)/k_{obsd}(D_2O)$ equal to 1.68 for **1a** and 2.46 for **1d** have been measured. For molar concentrations of water lying between 40 and 55.5 M^{-1}, the rate of hydrolysis of **1a** in 0.5 M HCl solutions increases in the presence of dioxan while it decreases with chloral. The Hammett ϱ values for the reactivity k_a in acidic media of aryl *N*-(phenylsulfonyl)carbamates ($\varrho = +0.87$) and for phenyl *N*-(substituted phenylsulfonyl)carbamates ($\varrho = +0.22$) agree with the protonation of the oxygen atom of the leaving group. Trapping experiment for the hydrolysis of **1a** and **1d** in a chloroacetate buffer in the presence of 4-chloroaniline gave in both cases *N*-(((4-chlorophenyl)amino)carbonyl)sulfonamide. Reaction carried out in $H_2{}^{18}O$ with ^{16}O-containing substrate indicates that there is no exchange from water to the carbonyl group of the sulfonylcarbamate. These data support a general acid catalysis of the breakdown of the anion which cuts in depending on the leaving group ability.

Acyl[1] and sulfonyl[2] groups transfers have been widely investigated, and their mechanisms are reasonably well understood. In particular, the reactions involving, through elimination–addition, reaction intermediates such as ketenes,[3,4] isocyanates,[5a] or isothiocyanate[5b] for acyl or thioacyl groups transfers and sulfenes[2,6] for sulfonyl group transfer, have been thoroughly studied. Although short-lived, these very reactive electrophilic intermediates could explain the activity of some bioactive molecules. For example, antineoplastic nitrosoureas (CENUs) give rise upon aqueous decomposition to alkyl isocyanates and 2-chloroethanediazonium ions, which may alkylate DNA and other macromolecules within the cell.[7] Moreover, these acyl or sulfonyl group transfers are frequently implied in many reactions catalyzed by enzymes.[1c,8]

Despite the wide applications of sulfonylcarbamates, $ArSO_2NHCOOR$, **1**, and sulfonylureas, $ArSO_2NHCONHR$, in medicinal[9] and agrochemical[10] fields, there are no fundamental studies on their reactivity in aqueous media. Their reaction with nucleophiles NuH might be considered to take place either at the carbonyl or at the sulfonyl groups with the subsequent transfer of these groups. The reactivity of these two electrophilic sites is strongly dependent on their environment, the nucleophilicity of NuH, the leaving ability of the RO^- or $ArSO_2NH^-$ and $ROCONH^-$ groups for **1**, and the acidity of the proton bonded to the nitrogen atom. This proton is very labile as indicated by pK_a values ranging from 3 to 5 for sulfonylureas

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and sulfonylcarbamates,[11] and thus in aqueous solution these compounds are fully ionized over a large range of pH in contrast with previously studied *N*-phenylcarbamates.[5] On the other hand, the phenylsulfonyl moiety is a powerful electron-withdrawing group that can increase significantly the electrophilic character of the carbon atom of the carbonyl function. These sulfonylcarbamates can thus be compared to activated esters in the acyl portion and their reactivity might be similar to that of alkyl or aryl halogen-substituted acetates. The aim of the present work is to determine the mechanism of the hydrolysis of phenyl *N*-(phenylsulfonyl)carbamate **1a** and its analogs **1b**–**i** over the whole pH range through the reactivity of their anionic and neutral forms.

Experimental Section

Materials. All reagents, standardized aqueous solutions of sodium hydroxide and hydrochloric acid, crystalline potassium chloride, and dioxan used for rate and equilibrium constants were of an analytical reagent grade. Water was distilled and deionized on a Water-Purification System Milli-Q (Millipore Apparatus). IR spectra were recorded with a Perkin-Elmer 883 spectrometer while for ^{13}C NMR spectra a Bruker AC-250 spectrometer was used (62.90 MHz).

Substrates. All sulfonylcarbamates except phenyl *N*-((4-nitrophenyl)sulfonyl)carbamate (**1i**) and phenyl *N*-(phenylsulfonyl)-*N*-methylcarbamate (**2**) were obtained by reacting the commercial phenylsulfonyl isocyanate or its 4-methyl and 4-chloro derivatives with the corresponding phenol in anhydrous toluene in the presence of catalytic amounts of triethylamine.[12] All sulfonylcarbamates were routinely checked for purity with TLC in ethyl acetate–dichloromethane (v/v, 3/1).

For example, phenyl *N*-(phenylsulfonyl)carbamate (**1a**) was prepared as follows. Phenol (0.50 g, 5.32 mmol) in dichloromethane (25 mL) was added dropwise to 0.916 g (5 mmol) of phenylsulfonyl isocyanate dissolved in dry dichloromethane (60 mL). The mixture was refluxed for 5 h in a round-bottomed flask equipped with a condenser. The solvent was removed under vacuum, and the residual oil was triturated and washed with petroleum ether. Recrystallization from petroleum ether–ether gave the pure sulfonylcarbamate **1a** (1.31 g, 95%): mp 129 °C (lit.[12] mp 123 °C); ^{13}C NMR (DMSO-d_6) δ 157.23 (C=O), 144.07–115.13 (aryl-C); IR (KBr, cm^{-1}) 3245 (NH), 1763 (C=O), 1342 and 1153 (SO_2).

3-Chlorophenyl *N*-(phenylsulfonyl)carbamate (1b): mp 94 °C; ^{13}C NMR (DMSO-d_6) δ 158.45 (C=O), 144.07–114.13 (aryl-C); IR (KBr, cm^{-1}) 3259 (NH) 1735 (C=O), 1334 and 1162 (SO_2). Anal. Calcd for $C_{13}H_{10}ClNO_4S$: C, 50.09; H, 3.23; N, 4.49. Found: C, 49.89; H, 3.48; N, 4.31.

4-Chlorophenyl *N*-(phenylsulfonyl)carbamate (1c): mp 110 °C (lit.[12] mp 110–112 °C); ^{13}C NMR (DMSO-d_6) δ 156.20 (C=O), 144.03–116.62 (aryl-C); IR (KBr, cm^{-1}) 3231 (NH), 1761 (C=O), 1343 and 1154 (SO_2).

4-Cyanophenyl *N*-(phenylsulfonyl)carbamate (1d): mp 147 °C; ^{13}C NMR (CD_3COCD_3) δ 154.14 (C=O), 149.52–110.68 (aryl-C); IR (KBr, cm^{-1}) 3144 (NH), 2242 (C≡N), 1754 (C=O), 1334 and 1163 (SO_2). Anal. Calcd for $C_{14}H_{10}N_2O_4S$: C, 55.62; H, 3.33; N, 9.27. Found: C, 55.55; H, 3.35; N, 9.25.

4-Acetylphenyl *N*-(phenylsulfonyl)carbamate (1e): mp 135 °C; ^{13}C NMR (DMSO-d_6) δ 195.93 (C=O acetyl), 161.93 (C=O), 144.03–115.05 (aryl-C), 26.12 (CH_3); IR (KBr, cm^{-1}) 3148 (NH), 1770 (C=O carb), 1668 (C=O acetyl), 1357 and 1155 (SO_2). Anal. Calcd for $C_{15}H_{13}NO_5S$: C, 56.43; H, 4.10; N, 4.38. Found: C, 56.60; H, 4.37; N, 3.95.

3-Nitrophenyl *N*-(phenylsulfonyl)carbamate (1f): mp 114 °C; ^{13}C NMR (DMSO-d_6) δ 158.16 (C=O), 148.54–109.48 (aryl-C); IR (KBr, cm^{-1}) 3223 (NH), 1737 (C=O), 1354 and 1160 (SO_2). Anal. Calcd for $C_{13}H_{10}N_2O_6S$: C, 48.45; H, 3.12; N, 8.68. Found: C, 48.54; H, 3.54; N, 8.27.

Phenyl (4-tolylsulfonyl)carbamate (1g): mp 106 °C (lit.[12] mp 112 °C); ^{13}C NMR ($CDCl_3$) δ 149.7 (C=O), 148.99–121.25 (aryl-C), 21.78(CH_3); IR (KBr, cm^{-1}) 3259 (NH), 1768 (C=O) 1301 and 1157 (SO_2).

Phenyl *N*-((4-chlorophenyl)sulfonyl)carbamate (1h): mp 101 °C (lit.[13] mp 101–104 °C); ^{13}C NMR ($CDCl_3$) δ 149.63 (C=O), 148.93–121.18 (aryl-C); IR (KBr, cm^{-1}) 3199 (NH), 1731 (C=O), 1360 and 1161 (SO_2).

Phenyl *N*-((4-Nitrophenyl)sulfonyl)carbamate (1i). Compound **1i** was synthesized by treating phenyl chloroformate with the 4-nitrobenzenesulfonamide anion in anhydrous tetrahydrofuran, the latter being obtained from 4-nitrobenzenesulfonamide and lithium diisopropylamide (LDA) according to the following procedure. A solution of 4-nitrobenzenesulfonamide (1.01 g, 5 mmol) in THF (40 mL) was added to a LDA solution (prepared at 0 °C by the addition of a 1.6 M solution of *n*-butyllithium in hexane (3.22 mL, 5 mmol) to a solution of diisopropylamine (0.535 g, 5 mmol) in 10 mL of THF). The mixture was stirred for 1 h, and then phenyl chloroformate (0.78 g, 5 mmol) was added dropwise. The solution was maintained at 0 °C for 1 h and then stirred at room temperature for 5 h, and NH_4Cl aqueous solution was added to the reaction mixture. It was extracted with ethyl acetate, and the organic phases were dried over $MgSO_4$ and evaporated under vacuum to give a residue which crystallized as beige flakes upon addition of ether. Recrystallization was carried out by dissolving the product in a minimum amount of ethyl acetate followed by addition of ether (0.51 g, 32%): mp 109 °C; ^{13}C NMR (DMSO-d_6) δ 152.56 (C=O), 156.73–121.87 (aryl-C); IR (KBr, cm^{-1}) 3192 (NH), 1743 (C=O), 1546 (C-NO_2), 1365 and 1132 (SO_2). Anal. Calcd for $C_{13}H_{10}N_2O_6S$: C, 48.45; H, 3.12; N, 8.68. Found: C, 48.58; H, 3.45; N, 8.51.

Phenyl *N*-(Phenylsulfonyl)-*N*-methylcarbamate (2). First, *N*-methylbenzenesulfonamide was obtained by reaction of benzenesulfonyl chloride (6.38 mL, 50 mmol) and methylamine 35% aqueous solution (10.85 mL, 110 mmol) for 2 h in refluxing $CHCl_3$ (60 mL): 93% yield. Compound **2** was then synthesized by treating phenyl chloroformate (6.45 mL, 50 mmol), triethylamine (2.33 mL, 15 mmol), and *N*-methylbenzenesulfonamide (1.71 g, 10 mmol). The mixture was stirred at 80 °C for 48 h. Ether was then added to the reaction mixture. The organic phase was washed with 1 M HCl, dried over $MgSO_4$, and evaporated under vacuum. The liquid residue was then added to petroleum ether. Phenyl *N*-(phenylsulfonyl)-*N*-methylcarbamate crystallizes as white pure crystals (0.87 g, 27%): mp 105 °C; ^{13}C NMR ($CDCl_3$) δ 151.15 (C=O), 150.03–121.21 (aryl-C), 33.65 (CH_3); IR (KBr, cm^{-1}) 1743 (C=O), 1362 and 1171 (SO_2). Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81. Found: C, 58.12; H, 4.50; N, 4.80.

***N*-(Piperidinocarbonyl)- and *N*-(((4-Chlorophenyl)amino)carbonyl)benzenesulfonamides (3a and 3b).** Piperidine (0.99 mL, 10 mmol) in dichloromethane (15 mL) was added dropwise to 1.83 g (10 mmol) of phenylsulfonyl isocyanate dissolved in dry dichloromethane (15 mL). The reaction was exothermic, and after refluxing for 3 h, the mixture was allowed to cool to room temperature and was washed with acidic water. The organic phases were dried over $MgSO_4$, and the solvent was removed *in vacuo* to near dryness. The residue was triturated with petroleum ether, and the yellowish precipitate was filtered off and then rinsed twice with petroleum ether to give **3a** as yellow plates (2.62 g, 98%): mp 101 °C; ^{13}C NMR ($CDCl_3$) δ 151.54, 140.18, 133.13, 128.82, 128.04, 45.22, 25.52, 24.09; IR (KBr, cm^{-1}) 3198 (NH), 1652 (C=O), 1338 and 1171 (SO2). Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.72; H, 6.00; N, 10.44. Found: C, 54.00; H, 6.07; N, 10.42.

3b was prepared according to the same procedure using 4-chloroaniline instead of piperidine (2.95 g, 95%): mp 178 °C (lit.[14] mp 180 °C); ^{13}C NMR (DMSO) δ 149.32 (C=O), 139.83–120.57 (Ar-C); IR (KBr, cm^{-1}) 3362, 3273 (NH), 1708 (C=O), 1337 and 1164 (SO_2).

Methods. Kinetics were measured by the following general procedure. Stock solutions of substrate (5×10^{-3}–10^{-2} M) were

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prepared in dioxan. Reactions were initiated by injecting 30 μL of stock solution into a 1.0 cm quartz cuvette placed in the thermostated compartment of a spectrophotometer (Perkin Elmer Lambda 7), equilibrated at 50.0 ± 0.2 °C, and containing 3.0 mL of HCl, NaOH, or buffered solutions. Suitable wavelengths for the kinetic studies were selected by repetitive spectral scanning of the reaction on the Perkin-Elmer instrument. Reaction rates were performed at pH values ranging from 1 M NaOH to 1 M HCl, and ionic strength was maintained at 1.0 throughout by addition of KCl. For each substrate, the reaction was carried out under pseudo-first-order conditions, the first-order dependence of rate being linear for at least 4−5 half-lives. All absorbances *vs* time data were collected on a Perkin-Elmer 3600 Data Station microcomputer operating on line through an interface and using 60 individual absorbance measurements which were uniformly spread over >90% of the reaction. Pseudo-first-order rate constants (k_{obsd}) were calculated according to the Guggenheim method by fitting these data via an iterative procedure based on a generalized least-squares method. The program LSG used was adapted in our laboratory by M. Tran. Owing to the instability of **1a** in acidic media at 50 °C, the ionization constant was determined at 25 °C from the plot of $\log[(OD - OD_{AH})/(OD_A^- - OD)]$ *vs* pH, where OD_{AH}, OD_A^-, and OD are optical densities at the same wavelength of the unionized and ionized forms of the substrate and of their mixture respectively at several pH values. OD_{AH} was determined in 0.1 M HCl and OD_A^- in a borax buffer (pH 9.18). After each kinetic run, the pH of the reaction solution was measured on a Tacussel pH-meter (TT processeur 2) using a XC111 combination electrode with calibration against standard buffer solutions in a cell thermostated at 50 °C. Eyring plots and Hammett correlations of the various thermodynamic and kinetic parameters were made using a curve-fitting program based upon a generalized least-squares method.

Product Analysis, Trapping Experiments, and Oxygen Exchange. The products of the hydrolysis reaction of sulfonylcarbamates were characterized by comparing the UV spectrum of the products at the end of kinetic runs with those of the mixture of authentic samples of the expected products, *i.e.*, benzenesulfonamide and phenol and their derivatives. The trapping experiment in alkaline media was carried out for 3-nitrophenyl *N*-(phenylsulfonyl)carbamate **1f**. This compound (966 mg, 3 mmol) dissolved in dioxan (3 mL) was added to a solution of piperidine (100 mL, 0.25 M total buffer concentration, fraction base = 0.5, 1.0 M ionic strength), and the reaction mixture was stirred for 3 h at 50 °C. The solution was allowed to cool to room temperature, and the pH was adjusted to 8.4 with sodium bicarbonate. The aqueous phase was extracted with dichloromethane, and the organic phase was separated to eliminate 3-nitrophenol. The combined aqueous layers were then acidified, extracted with dichloromethane, and dried over $MgSO_4$. The solvent was evaporated to leave the (phenylsulfonyl)-urea **3a** (yield > 90%). The IR and ^{13}C NMR spectra of the trapped product were found to be identical to those of the sample synthesized independently.

In acidic media, trapping experiments were carried out for 4-cyanophenyl and phenyl *N*-(phenylsulfonyl)carbamates **1d** and **1a** in a chloroacetate buffer (fraction base = 1/4, pH = 2.20). Chloroacetate solution (70 mL) was added to a mixture of 4-chloroaniline (1.27 g, 10 mmol) and **1d** (604 mg, 2 mmol) dissolved in dioxan (2 mL), and the reaction mixture was stirred for 3 h at 50 °C. The solution was allowed to cool to room temperature, and the pH was adjusted to 0.5 with concentrated HCl. The aqueous phase was extracted with diethyl ether, and the organic phase was washed with 3 M HCl and water to eliminate 4-chloroaniline. The solvent was evaporated to leave 4-cyanophenol and sulfonylurea **3b** characterized by TLC (ethyl acetate/petroleum ether, v/v, 3/2; R_f values are 0.52 and 0.18, respectively, and identical to those of authentic samples). Recrystallization of the crude product from diethyl ether gave *N*-(((4-chlorophenyl)amino)-carbonyl)sulfonamide **3b** (yield >90%). Its structure was confirmed by the comparison of ^{13}C NMR and IR spectra with those of an authentic sample of **3b**. For **1a**, the same procedure was used and the reaction mixture stirred for 5 h at 50 °C. After a similar workup as for **1d**, **3b** was obtained after recrystallization from diethyl ether/petroleum ether (v/v, 2/1) and was characterized as previously described (yield >90%).

Experiments were carried out to investigate the possibility of exchange of the carbonyl oxygen of phenyl *N*-(phenylsulfonyl)-carbamate **1a** with that of water enriched in $H_2{}^{18}O$. A mixture of a HCl solution in $H_2{}^{16}O$ (8 mL) at the appropriate concentration and 1.5 mL of $H_2{}^{18}O$ (95 atom %, C.E.A.) leading to a 0.5 M HCl solution with a content of 15.00% of ^{18}O was poured into a solution of **1a** (55 mg) dissolved in dioxan (2 mL). After 1 half-live, the reaction mixture was extracted with ether. After evaporation of the solvent, the ternary mixture (unreacted **1a** and the products of hydrolysis of the substrate, *i.e.*, benzenesulfonamide and phenol) was then analyzed by desorptive chemical ionization mass spectrometry (NH_3, gas). A control assay was carried out for the hydrolysis of **1a** in $H_2{}^{16}O$ using the same procedure described for the experiment in $H_2{}^{18}O$.

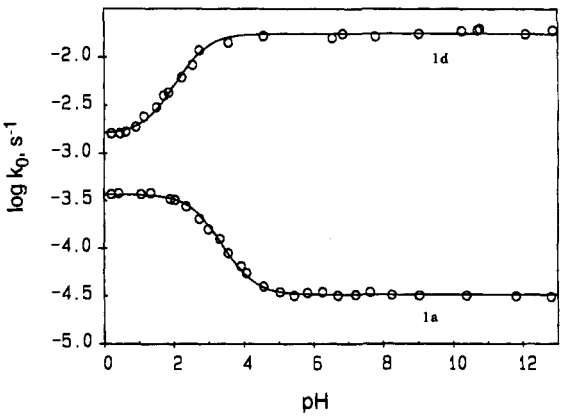

Figure 1. Plot of log k_o *vs* pH for the hydrolysis of phenyl *N*-(phenylsulfonyl)carbamate **1a** and 4-cyanophenyl *N*-(phenylsulfonyl)-carbamate **1d** at 50 °C with μ = 1.0 M (KCl).

Results

Evidence of Acyl Group Transfer. Phenol and benzenesulfonamide were characterized as the products of alkaline and acidic hydrolysis (1 M NaOH and 0.5 M HCl at 50 °C) of the phenyl *N*-(phenylsulfonyl)carbamate **1a** by thin-layer chromatography (silica; eluant: ethyl acetate/petroleum ether, 1/1). R_f values (0.65 and 0.44) were identical to those obtained from authentic samples of phenol (R_f = 0.65) and benzenesulfonamide (R_f = 0.43). Moreover, after completion of the hydrolysis of **1a**, the ultraviolet spectrum was found to be identical to that of a synthetic mixture of phenol and benzenesulfonamide recorded under the same experimental conditions (1 M NaOH and 0.5 M HCl, 50 °C, 5×10^{-5} M concentration in substrate or in products). UV spectra recorded against time exhibited a sharp isosbestic point (*e.g.*, **1e**: λ = 277 nm) suggesting no build-up of an intermediate species. These results suggest that the hydrolysis of compounds **1** occurs by acyl group transfer.

pH−Rate Profile and Buffer Catalysis. The rate constants for the hydrolysis of phenyl *N*-(phenylsulfonyl)carbamate **1a** were measured either in aqueous HCl and NaOH solutions or in buffer solutions (cyanoacetate, chloroacetate, formate, acetate, cacodylate, phosphate, Tris, borax, carbonate, triethylamine, and piperidine) at 50 °C and μ = 1.0 M with KCl. Under these experimental conditions, the hydrolyses were found to follow first-order kinetics with respect to the substrate as far as at least 90% completion of the reaction. Experimentally significant buffer catalysis was not observed in the hydrolysis of **1a**−**i** in buffer solutions of pK_{BH} > 8, while with cyanoacetate, chloroacetate, formate, acetate, cacodylate, and phosphate buffers the reaction rate constant k_{obsd} for **1a** increased linearly with the concentration of the catalyst,

$$k_{obsd} = k_o + k'_{cat}[\text{buffer}]_{Tot} \quad (1)$$

The rate constants k_o were then obtained for the acidic pH region (0−7) by extrapolation of k_{obsd} values to zero buffer concentration. The plot of log k_o *vs* pH for hydrolysis of **1a** is presented in Figure 1. It is characterized by three distinct regions, a

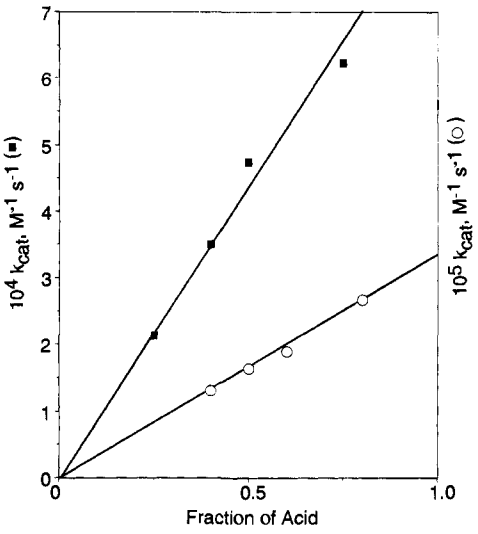

Figure 2. Dependence of the second-order rate constant k_{cat} for buffer catalysis of hydrolysis of phenyl *N*-(phenylsulfonyl)carbamate **1a** on the composition of cyanoacetate (■) and cacodylate buffers (○) at 50 °C (μ = 1.0 M, KCl).

plateau below pH 2 followed by a *decrease* of k_o with pH up to pH 6 then a large pH independent region in alkaline media. The observed behavior is fitted by eq 2:

$$k_o = k_a a_H/(a_H + K_a) + k_p K_a/(a_H + K_a) \quad (2)$$

where k_a and k_p are the rate constants for the reaction of **1a** in acidic and alkaline media, respectively, and K_a is the dissociation constant of the substrate. The theoretical curve was drawn in Figure 1 from eq 2 employing the following constants: k_a = 3.71 × 10^{-4} s^{-1}; k_p = 3.27 × 10^{-5} s^{-1}; K_a = 1.41 × 10^{-3} M. This kinetic pK_a value (pK_a = 2.85) at 50 °C is quite compatible with the spectrophotometric value measured at 25 °C (pK_a = 2.85 ± 0.05). For this compound, k_a is greater than k_p and the pH−rate profile corresponds then to $k_o = k_a a_H/(a_H + K_a) + k_p$.

Aryl *N*-(substituted phenylsulfonyl)carbamates are very acid (pK_a value for **1a** is equal to 2.85). Therefore, two species, SH and S^-, are present in acidic media and the pH−rate profile in this region can be analyzed as an attack of water on the neutral form SH ($k_a = k_{H_2O}[H_2O]$) and/or an acid-catalyzed reaction of the anion carbamate S^-, the conjugate base of the substrate ($k_a = k_{H_3O^+}K_a$). The observed general catalysis k'_{cat} may be then interpreted as a general base-catalyzed reaction of the neutral species and/or a general acid-catalyzed reaction of the anion, leading to the equation

$$k'_{cat}[\text{buffer}]_{Tot} = k_{BH}[BH][K_a/(a_H + K_a)] \quad (3)$$

where k_{BH} and k_B are the general acid and base catalytic constants and [BH] and [B] the concentrations of acid and base forms of the buffer. This equation can be transformed into the equivalent linear relationship

$$k_{cat} = k'_{cat}/\alpha = (k_{BH} + k_B K_T/K_a)[BH]/[\text{buffer}]_{Tot} \quad (4)$$

where α is the molar fraction of the anion of the substrate and K_T is the ionization constant of the buffer. The k_{cat} values obtained for the various buffers are summarized in Table S1 (supplementary material) and are plotted against the molar fraction of the acid form of the buffer (Figure 2). The substrate **1a** is completely ionized in buffers with pK_T values higher than the pK_a value of **1a** (pK_T > pK_a + 2.5) and in this case, α = 1 and $k_{cat} = k'_{cat}$. For all the buffers examined, the straight lines obtained are characterized by a zero intercept at 0% free acid and positive slopes equal to ($k_{BH} + k_B K_T/K_a$). This general

Table 1. Catalytic Coefficients for the Hydrolysis of Phenyl *N*-(Phenylsulfonyl)carbamate **1a** at 50 °C (μ = 1.0 M, KCl)

catalyst	pK_{BH}	k_{BH}, $M^{-1} s^{-1}$
H_3O^+	−1.74	(2.53 ± 0.30) × 10^{-1}
$ClCH_2CO_2H$	2.64	(1.96 ± 0.40) × 10^{-3}
$CNCH_2CO_2H$	2.65	(8.22 ± 0.90) × 10^{-4}
HCO_2H	3.60	(3.31 ± 0.50) × 10^{-4}
CH_3CO_2H	4.70	(7.80 ± 0.20) × 10^{-5}
$(CH_3)_2AsO_2H$	6.20	(3.38 ± 0.20) × 10^{-5}
$H_2PO_4^-$	7.05	(3.10 ± 1.60) × 10^{-5}

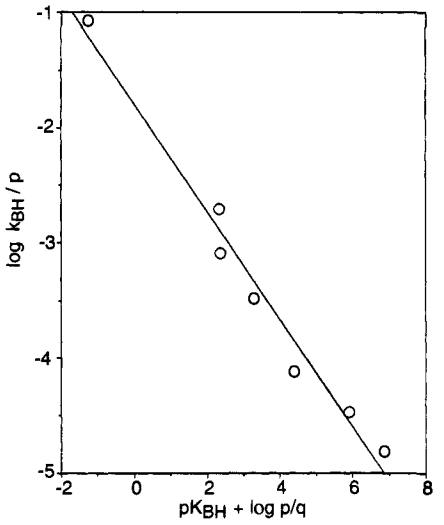

Figure 3. Brönsted plot for the general acid catalysis of the hydrolysis of phenyl *N*-(phenylsulfonyl)carbamate **1a**.

catalysis was interpreted as a general acid-catalyzed reaction of the anion (see discussion) and the resulting catalytic constants k_{BH} (Table 1) plotted against the pK_a's of the corresponding acids in Figure 3 give a α Brönsted parameter of 0.46 ± 0.03 (r = 0.987). The point corresponding to the catalysis by H_3O^+ was calculated from the rate constant value k_a on the plateau of the pH−rate profile in acidic solution divided by K_a and lies on the Brönsted line.

In contrast to **1a**, 4-cyanophenyl *N*-(phenylsulfonyl)carbamate **1d** shows a quite different pH−rate profile. No significant buffer catalysis was observed with dichloroacetate and buffers used for **1a**, *i.e.*, cyanoacetate, chloracetate, formate, acetate, cacodylate, and phosphate. The plot of log k_{obsd} *vs* pH for hydrolysis of **1d** is also presented in Figure 1. It shows three distinct regions, a plateau in more acidic media followed by an *increase* of k_{obsd} with pH from pH 1 up to pH 3.5 and then a large pH-independent region from this pH value to pH 13. The observed behavior is also fitted by eq 2, but in this case k_a is lower than k_p. The reactivity of the anion of the substrate is greater than that of the species in acidic media, then the pH−rate profile obeys the simplified eq 2: $k_{obsd} = k_a + k_p K_a/(a_H + K_a)$. The theoretical curve is drawn in Figure 1 employing the following constants: k_a = 1.61 × 10^{-3} s^{-1}; k_p = 1.75 × 10^{-2} s^{-1}; K_a = 2.69 × 10^{-3} M.

In acidic and alkaline media, the initial UV spectra of phenyl *N*-(phenylsulfonyl)-*N*-methylcarbamate **2** and those of the expected products of hydrolysis, *N*-methylbenzenesulfonamide and phenol, are different. After 5 days in 1.0 M HCl solution at 50 °C no UV spectral variation was observed for **2** while in alkaline media it is quickly hydrolyzed to products. The bimolecular rate constant k_{OH} was determined at three concentrations in 0.01−0.1 M NaOH solutions and is equal to (3.75 ± 0.02) × 10^{-1} $M^{-1} s^{-1}$ at 25 °C and 1.66 ± 0.03 at 50 °C.

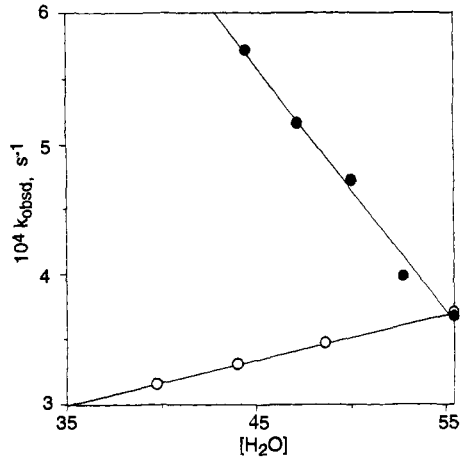

Figure 4. Plot of k_{obsd} *vs* [H_2O] for the hydrolysis of phenyl *N*-(phenylsulfonyl)carbamate **1a** in dioxan–water (●) and chloral–water (○) mixtures at 50 °C in 0.5 M HCl (μ = 1.0 M, KCl).

Solvent, Substituent, and Temperature Effects. From experiments in HCl and DCl at 50 °C, solvent deuterium effects were measured in the region of pH where the substrate is completely unionized ($a_H \gg K_a$) so that no correction for substrate ionization is necessary giving a ratio $k_{obsd}(H_2O)/k_{obsd}(D_2O)$ = 1.68 ± 0.04 for **1a** (0.5 M HCl) and 2.46 ± 0.05 for **1d** (1 M HCl). In order to examine the role of water on the hydrolysis of **1a**, we carried out kinetics at 0.5 M HCl (μ = 1.0, KCl) in the presence of an organic cosolvent, either dioxan as an aprotic and apolar solvent, or chloral as a protic one. The latter was chosen because it is a strong hydrogen-bond donor as well as a poor nucleophile in contrast with aliphatic alcohols able to react with the substrate. Results plotted in Figure 4 show that these cosolvents have opposite effects on the experimental rate constants which vary linearly with the concentration of the solvent added. For a range of molar concentrations of water (55.5–40.0 M), dioxan significantly enhances the rate of hydrolysis while chloral decreases it.

In alkaline media, the rate constants k_p values at 50 °C for compounds **1a–i** collected in Table 2 were measured in various buffers (Tris, borax, carbonate, piperidine, triethylamine) and in NaOH solutions. For aryl *N*-(phenylsulfonyl)carbamates **1a–f**, k_p values possess a high Hammett σ^- selectivity (ϱ^- = +2.93 ± 0.13; r = 0.995) while for phenyl *N*-(substituted phenylsulfonyl)carbamates **1a** and **1g–i** they are dependent on the Hammett σ value (ϱ = −0.66 ± 0.08; r = 0.985). In acidic media, the rate constants k_a values at 50 °C for compounds **1a–h** reported in Table 2 were measured in HCl solutions at three concentrations (1, 0.75, and 0.5 M). For aryl *N*-(phenylsulfonyl)carbamates **1a–f**, k_a values are best correlated with σ (r = 0.975) than with σ^- (r = 0.962). The ϱ value (ϱ = +0.87 ± 0.09) is much lower than the ϱ^- value obtained for the decomposition of the anions of these substrates. For phenyl *N*-(substituted phenylsulfonyl)carbamates **1a** and **1g,h** they are also dependent on the Hammett σ value, the ϱ value being positive (ϱ = + 0.22 ± 0.09) while it is negative for their hydrolysis in alkaline media. Hammett plots of k_a and k_p for aryl *N*-(phenylsulfonyl)carbamates **1a–f** and phenyl *N*-(substituted phenylsulfonyl)carbamates **1a** and **1g–i** are shown respectively in Figures 5 and 6.

Temperature dependence of the acid hydrolysis of **1a** and **1d** was analyzed from rate constants values determined at 1.0 M HCl for four temperatures varying from 30 to 60 °C. When we consider a general base-assisted attack of water at the ester bond of the neutral substrate involving two water molecules in the transition state (one acting as a nucleophile, the other as a general base), the $\Delta S^{\ddagger}$ values, derived from the rate constant values equal to k_a divided by (55.5 M)^2,[15,16] are negative, $\Delta S^{\ddagger}$ = −11.7 cal mol^{-1} K^{-1} and −14.4 cal mol^{-1} K^{-1} for **1a** and **1d**, respectively. On the contrary, if the general acid-catalyzed of the anion is operating, on the plateau $k_a = k_{H_3O^+}K_a$ is a composite term and the $\Delta S^{\ddagger}$ values obtained for k_a are slightly positive: +4.1 and +0.4 cal mol^{-1} K^{-1} for **1a** and **1d**, respectively. The temperature dependence on the rate constants k_p for the studied sulfonylcarbamates **1a–i** was measured in 0.01 M NaOH solution at three temperatures from 30 to 75 °C. Except for compound **1i** ($\Delta S^{\ddagger}$ = −4.4 cal mol^{-1} K^{-1}), the values of entropies of activation for all others sulfonylcarbamates were found to be positive (0.2 < $\Delta S^{\ddagger}$ < 15.0 cal mol^{-1} K^{-1}) and are reported in Table 2.

Trapping Experiments and Oxygen Exchange. The rate constant for the disappearance of sulfonylcarbamate **1f** at pH 10.70 is independent of the concentration of piperidine, indicating that this nucleophile is not involved in the rate-determining step. Thus, the trapping experiment involved analysis of the product of the reaction between piperidine buffer (0.25 M total buffer concentration, fraction base = 0.5, 1.0 M ionic strength, 50 °C) and 3-nitrophenyl *N*-(phenylsulfonyl)carbamate **1f** (3 × 10^{-2} M). After workup (see the Experimental Section) product analysis using ^{13}C NMR indicated that in the presence of piperidine the sulfonylcarbamate is almost quantitatively converted to *N*-(piperidinocarbonyl)benzenesulfonamide **3a** as suggested by the comparison of the NMR spectra of the trapped product with that of an authentic sample of this sulfonylurea.

Trapping experiments for the hydrolysis of phenyl and 4-cyanophenyl *N*-(phenylsulfonyl)carbamates **1a** and **1d** in chloroacetate buffer (pH = 2.20) were carried out with 4-chloroaniline as nucleophile. In both cases, the trapped product was identified to *N*-(((4-chlorophenyl)amino)carbonyl)-sulfonamide **3b**, and the rate constants of hydrolysis of **1a** and **1d** are independent of the concentration of 4-chloroaniline (Table S2, supplementary material). These data show that this nucleophile is not involved in the rate-determining step but reacts with an electrophilic intermediate, the sulfonyl isocyanate, to give **3b**. Unreacted phenyl *N*-(phenylsulfonyl)carbamate **1a** from the hydrolysis in enriched water (^{18}O = 15.00%) in 0.5 M HCl gave an abundance ratio (M NH_4^+ + 2)/(MNH_4^+) equal to 6.07 compared to a theoretical value of 13.72% if there was total incorporation of ^{18}O. A control value for natural abundance ratio of unreacted **1a** hydrolyzed in $H_2{}^{16}O$ was shown to be 6.11 for a theoretical value of 6.22%. These results indicate that there is no exchange from water to carbonyl group of **1a**.

Discussion

The pH–rate profile for the hydrolysis of phenyl *N*-(phenylsulfonyl)carbamate **1a** (Figure 1) displays three distincts regions corresponding to two separate reactions according to eq 2, both giving *N*-benzenesulfonamide and phenol as final products.

Mechanism of Alkaline Hydrolysis. For the uncatalyzed hydrolysis of **1a** observed in a large pH-independent region, two major types of reaction mechanisms, as depicted in Scheme 1, can be envisaged for acyl group transfer: (i) an elimination–addition mechanism (path A) $A_{xh}D_H + D_N$ (E1cB)[17] involving deprotonation of the nitrogen atom to form an anion which decomposes in a monomolecular rate-determining step into phenylsulfonyl isocyanate and an aryl oxide ion. This highly

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Table 2. Rate Constants k_a and k_p and Entropies of Activation $\Delta S^{\ddagger}$ for the Acid and Alkaline Hydrolysis of Aryl *N*-(Substituted phenylsulfonyl)carbamates $YC_6H_4SO_2NH\ CO_2C_6H_4X$ at 50 °C (μ = 1.0 M, KCl)

compd	Y	X	k_a, s^{-1} [a]	k_p, s^{-1} [b]	k_a/k_p	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1} [c] (E1cB reaction)
1a	H	H	$(3.60 \pm 0.01) \times 10^{-4}$ [d]	$(3.27 \pm 0.09) \times 10^{-5}$ [d]	11.0	8.4 ± 0.4 [d]
1b	H	3-Cl	$(7.38 \pm 0.02) \times 10^{-4}$	$(6.38 \pm 0.41) \times 10^{-4}$	1.15	2.3 ± 0.2
1c	H	4-Cl	$(5.36 \pm 0.02) \times 10^{-4}$	$(2.06 \pm 0.11) \times 10^{-4}$	2.60	4.7 ± 0.2
1d	H	4-CN	$(1.58 \pm 0.01) \times 10^{-3}$	$(1.78 \pm 0.07) \times 10^{-2}$	0.088	15.0 ± 1.5
1e	H	4-Ac	$(1.07 \pm 0.01) \times 10^{-3}$	$(8.88 \pm 0.51) \times 10^{-3}$	0.12	3.2 ± 0.2
1f	H	3-NO_2	$(1.30 \pm 0.01) \times 10^{-3}$	$(5.39 \pm 0.33) \times 10^{-3}$	0.24	0.20 ± 0.01
1g	4-Me	H	$(3.08 \pm 0.02) \times 10^{-4}$	$(5.20 \pm 0.25) \times 10^{-5}$	5.92	11.5 ± 1.2
1h	4-Cl	H	$(3.80 \pm 0.02) \times 10^{-4}$	$(2.34 \pm 0.03) \times 10^{-5}$	16.23	3.2 ± 1.2
1i	4-NO_2	H		$(1.14 \pm 0.10) \times 10^{-5}$		-4.4 ± 0.4

[a] Ionic strength made up to 1.0 M with KCl, k_a values were the mean of three measurements in HCl solutions at three concentrations (1, 0.75, and 0.5 M). [b] Ionic strength made up to 1.0 M with KCl, k_p values were the mean of three measurements at seven pH values in various buffers (borax, carbonate, triethylamine, piperidine) and in 0.01−1.0 M NaOH solutions. [c] Rate constants were measured in a 0.01 M NaOH solution at three temperatures from 30 to 75 °C. [d] Uncertainties are given in terms of standard deviation.

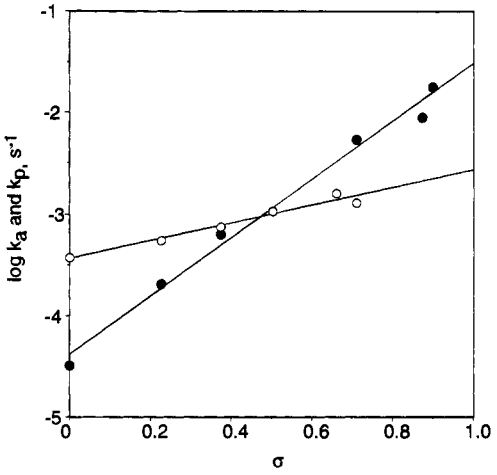


Figure 5. Hammett plots of log k_p (●) and log k_a (○) for the hydrolysis of substituted phenyl *N*-(phenylsulfonyl)carbamates at 50 °C.

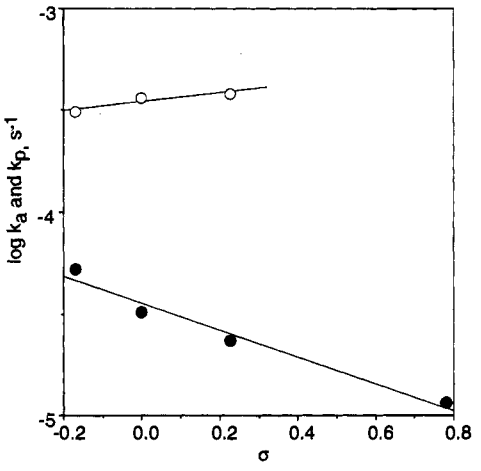
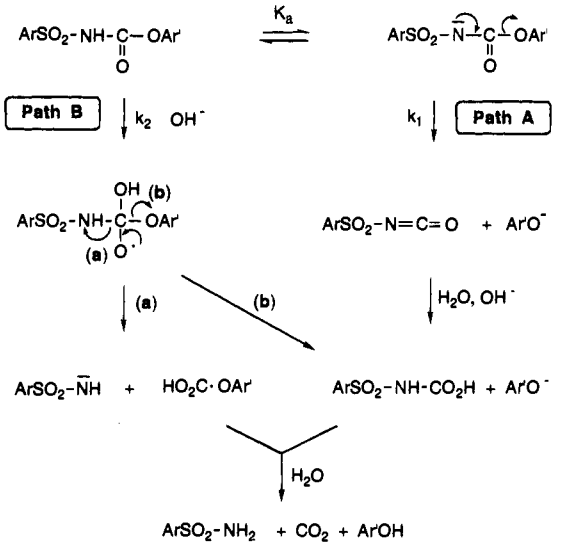


Figure 6. Hammett plots of log k_p (●) and log k_a (○) for the hydrolysis of phenyl *N*-(substituted phenylsulfonyl)carbamates at 50 °C.

reactive isocyanate intermediate then reacts rapidly with water or an hydroxide ion to give the (phenylsulfonyl)carbamic acid which spontaneously decarboxylates to benzenesulfonamide and carbon dioxide; (ii) an addition−elimination pathway (path B) $A_N + D_N$ ($B_{Ac}2$), where the rate-determining nucleophilic attack of an hydroxide ion on the carbonyl group of the neutral substrate takes place to give a tetrahedral intermediate which can decompose in two ways. The pK_a values of benzenesulfonamides $XC_6H_4SO_2NH_2$[18] range from 8.54 to 9.65 for X = 4-NO_2 and 4-Me, *i.e.*, an acidity scale similar to that of phenols. Nevertheless, their nucleofugalities, measured by the logarithm of the rate constant of expulsion of the leaving group Z from $PhSO_2\bar{C}HCH_2Z$ leading to phenyl vinyl sulfone, are different, namely 8.9 and 5.4 for PhO^- and $PhSO_2\bar{N}Me$, respectively.[19] However, Boyd[20] has shown that there is a correlation between the leaving group Z ability and the pK_a of ZH in water and thus the scission of the C−N (path Ba) or the C−O (path Bb) bonds can reasonably be assumed. In the former case, the benzenesulfonamide is formed along with an aryl hydrogen carbonate ion decomposing immediately to aryloxide ion and carbon dioxide. In the latter case, an aryl oxide ion and (phenylsulfonyl)carbamic acid are both liberated (as in path A) leading to the final products.

Scheme 1



The rate constants measured for **1a** and for other sulfonylcarbamates **1b**−**i** did not vary with pH in agreement with the rate laws:

$$\text{for path A} \qquad k_{obsd} = \frac{k_1 K_a}{K_a + a_H} \tag{5}$$

$$\text{for path B} \qquad k_{obsd} = \frac{k_2 K_w}{K_a + a_H} \tag{6}$$

Owing to the pK_a value of **1a**, eqs 5 and 6 simplify to $k_{obsd} = k_p$ in this pH range ($a_H \ll K_a$).

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The two mechanisms presented in Scheme 1 are consistent with the pH−rate profile observed for the alkaline hydrolysis of the sulfonylcarbamates. Distinction between them was made using the following criteria.

The very high sensitivity to the electronic effects of the substituents on the leaving group and the Hammett σ^- dependence of k_p ($\varrho^- = +2.93$) are in favor of an $A_{xh}D_H + D_N$ mechanism (path A) where the C−OAr fission would be well-advanced in the transition state. For the cyano and acetyl electron-withdrawing substituents, the best Hammett correlation is obtained with the σ^- parameter, strongly supporting a dissociative process where the departing oxyanion presents a resonance interaction with these substituents.[5g] In contrast, the associative mechanism (path B) for the hydrolysis of sulfonylcarbamates with good leaving groups would be expected to involve an attack of the hydroxide ion OH^- on the carbonyl group as rate-determining step giving rise to a lower Hammett ϱ value ($\varrho \approx 1$).[5,21]

For phenyl *N*-(substituted phenylsulfonyl)carbamates **1a** and **1g**−**i**, the susceptibility of the reaction to hydrolysis, due to the electronic effects of the substituent on the aromatic ring in the α position to SO_2, is weaker and negative ($\varrho = -0.66$). This negative value is incompatible with a bimolecular mechanism for which the rate-determining step would correspond to an addition of the hydroxyl ion to the carbonyl group of the neutral substrate. As a matter of fact, the hydrolysis of methyl[21] and isopropyl[22] *N*-(substituted phenyl)carbamates by an associative process $A_N + D_N$ (BAc2) is characterized by positive ϱ Hammett values which are respectively 1.06 and 0.98. For such a mechanism with the sulfonylcarbamates **1a** and **1g**−**i**, one would expect a positive but weaker ϱ value ($0 < \varrho < 0.5$) because of the screening effect of the SO_2NH group between the aromatic ring, the site of the substitution, and the carbonyl group, the reaction center. A negative ϱ value implies that electron-donating substituents favor the decomposition of the anion during the dissociative process. Compounds **1a** and **1g**−**i** are very acidic; thus in alkaline pH range their anions are in high concentration, and so the substituent effects can only affect anion reactivity, *i.e.*, the rate of formation of the N=C bond of the isocyanate group. Electron-attracting substituents will stabilize the anion by increasing electronic delocalization and thus defavoring the formation of the isocyanate intermediate, while electron-donating substituents would have the opposite effect. Among the various carbamates studied, the sulfonylcarbamates are the first examples which allow the reactivity of these anions to be easily studied and thus prove such a Hammett relationship.

The values of the entropies of activation for all sulfonylcarbamates, except for **1i**, are positive (Table 2), they provide excellent confirmation of the dissociative nature of the mechanism. In fact, the elimination−addition mechanisms observed for the hydrolysis of the carbamates,[5,22,23] and (methylsulfonyl)-methanesulfonates[24] are characterized by their positive entropy values while the values for associative mechanisms, $A_N + D_N$ involving a carbonyl group of an ester[25] or a carbamate,[5,22] are negative ($\Delta S^{\ddagger}$ about −20 to −40 cal mol^{-1} K^{-1}). The trapping experiment argues that the mechanism must involve a rate-limiting step prior to the step forming the sulfonylurea, consistent with path A of Scheme 1 where piperidine traps the phenylsulfonyl isocyanate.

Table 3. pK_a^{NH} Values and Rate Constants k_p for the Decomposition of the Conjugate Bases of the Carbamates $RNHCOOC_6H_5$ at 25 °C

compd	R	pK_a^{NH}	k_p, s^{-1}
4	Me[a]	17.70	1.7×10^{4}
5	H[a]	15.10	2.8×10^{3}
6	C_6H_5[a]	14.66	2.5×10^{2}
7	4-$NO_2C_6H_4$[b]	12.50	1.54
8	Ac[c]	10.55	8.32×10^{-3}
9	Bz[d]	8.90	1.86×10^{-2}
10	$Cl_3CC(O)$[e]	6.00	4.37×10^{-5}
1a	$C_6H_5SO_2$[f]	2.85	5.02×10^{-7}

[a] Reference 5a. [b] Reference 5e. [c] Reference 5c. [d] k_p value is taken from Bergon, M. Ph.D. Thesis, 1979, Toulouse, and $pK_{a(kin)}^{NH}$ was estimated from ref 26. [e] These values refer to unpublished data. [f] This work; k_p was extrapolated to 25 °C from an Arrhenius plot for the hydrolysis of **1a**.

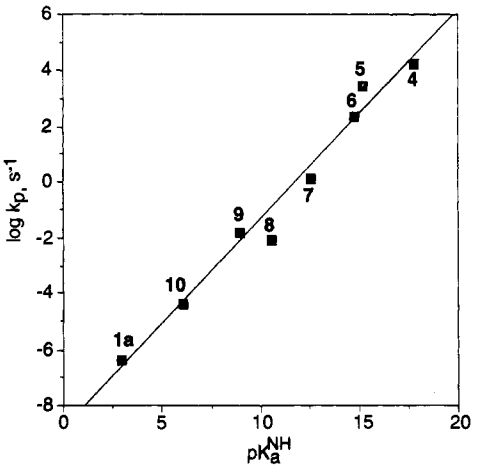

Figure 7. Brönsted type relationship for the decomposition of the anions $R\bar{N}COOC_6H_5$ *vs* the pK_a^{NH} of the conjugate acids at 25 °C (compound, R: **4**, Me; **5**, H; **6**, C_6H_5; **7**, 4-$NO_2C_6H_4$; **8**, Ac; **9**, Bz; **10** $Cl_3CC(O)$; **1a**, $C_6H_5SO_2$).

From the literature values of k_p and those measured in our laboratory, where k_p is the rate constant for liberation of the same leaving group $C_6H_5O^-$ from a series of phenyl carbamates anions $R\bar{N}COOC_6H_5$, a Brönsted-type correlation $\log k_p = 0.74pK_a - 8.75$ including compound **1a** was found ($r = 0.985$), the pK_a values for the NH group ionization varying from 2.85 to 17.7 (Table 3 and Figure 7).

The mechanism of hydrolysis of all these phenyl carbamates takes place through a dissociative process ($A_{xh}D_H + D_N$) *via* an intermediate isocyanate RN=C=O, the rate of its formation decreasing proportionally with the acidity of the substrate. This relation includes phenyl *N*-(phenylsulfonyl)carbamate **1a** and thus confirms the mechanism that we propose from the criteria previously put forward. Moreover, it applies for a large range of pK_a ($\Delta pK_a \approx 15$) and generalizes the relation found by Williams and co-workers,[5a] which was limited to a $7\Delta pK_a$ units variation.

Mechanism of Hydrolysis in Acidic Media

pH−Rate Profiles. Firstly, from the pH-independent rate of hydrolysis below pH 2 observed for **1a** and **1d**, it can be concluded that an acid-catalyzed reaction of the substrate involving nucleophilic attack of water on the protonated carbonyl group does not occur. As it was indicated earlier it is noteworthy that in acidic buffers (pH 2−7) a general catalysis

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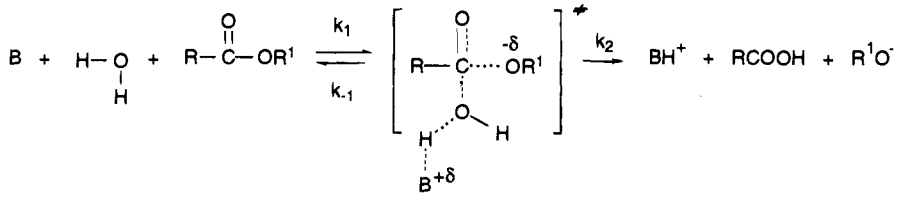
Scheme 2



is observed for **1a** in contrast of **1d** where it does not occur. Moreover, from the examination of the Hammett plots of k_a and k_p for aryl *N*-(phenylsulfonyl)carbamates **1a–f** (Table 2 and Figure 5) their reactivity can be divided among two groups. For aryl *N*-(phenylsulfonyl)carbamates possessing the best leaving groups, *i.e.*, 4-cyano, 4-acetyl, and 3-nitrophenolate ions, k_a is lower than k_p while for those with poorer leaving groups (phenolate and 3- and 4-chlorophenolate ions) k_a is greater than k_p. The ratio k_a/k_p varies from 0.088 for 4-cyanophenyl *N*-(phenylsulfonyl)carbamate to 11.0 for phenyl *N*-(phenylsulfonyl)carbamate. In other terms, for aryl sulfonylcarbamates bearing a substituent on the leaving group with a σ (or σ^-) value greater than 0.5, the pH–rate profile should be similar to that observed for 4-cyanophenyl *N*-(phenylsulfonyl)carbamate **1d** ($k_o = k_a + k_pK_a/(a_H + K_a)$. On the contrary, for substituents with σ values less than 0.5, aryl sulfonylcarbamates would display the same profile as for **1a** ($k_o = k_aa_H/(a_H + K_a) + k_p$). For phenyl *N*-(substituted phenylsulfonyl)carbamates **1a,g,h**, it can be noted that k_a is always greater than k_p (Table 2). As was previously discussed, the plateau k_p for compounds **1a–i** corresponds to a spontaneous breakdown of the anion through an $(E1cB)_{rev}$ mechanism. The same mechanism is operating for compounds **1d–f** in the portion corresponding to $a_H \gg K_a$ of the pH–rate profile characterized by $k_o = k_pK_a/(a_H + K_a)$. On the other hand, in acidic media the increase of k_o when pH decreases followed by a plateau according to the rate law $k_o = k_aa_H/(a_H + K_a)$ observed for **1a** and the plateau k_a for **1d** can correspond either to the water-mediated reaction of the neutral form of the substrate or to the kinetically equivalent H_3O^+-catalyzed reaction of the anion carbamate, the conjugate base of the substrate.

Can Water Act as a Nucleophile? For elimination–addition mechanisms involved for *o*-nitrophenyl cyanoacetate (pK_a = 8.57) and characterized by a pH–rate profile $k_{obsd} = k_{H_2O} + k_pK_a/(a_H + K_a)$ similar to that of **1d**, Bruice[3e] has proposed a general-base water-catalyzed hydrolysis on the unionized ester occurring in acidic media (k_{H_2O}). In the same way, for phenyl *N*-benzoylcarbamate,[26] an activated carbamate, nevertheless to a lower extent than **1a**, the pH–rate profile for its hydrolysis into benzamide and phenol over the complete pH range clearly shows three reactions according to the following mechanisms: (i) in alkaline media, a plateau followed by a linear decrease of the rate with a slope equal to unity corresponding to the decomposition of the anion $(E1cB)_{rev}$; (ii) a pH-independent reaction around pH 4 assigned to the water-catalyzed reaction of the neutral substrate (k_{H_2O} = 5.8 10^{-7} s^{-1} at 37 °C); (iii) a linear increase of the rate with more acidic pH's corresponding to the specific acid-catalysis of the hydrolysis of the substrate. These data led us therefore to consider that the competing water-mediated reaction on the neutral form of the substrate could be envisaged. Indeed, phenyl *N*-(phenylsulfonyl)carbamate bearing a strong electron-withdrawing SO_2 group on the nitrogen atom may be considered as an activated carbamate as suggested by the comparison with phenyl *N*-phenylcarbamate (pK_a^{NH} = 2.85 *vs* 15).[5a] This hypothesis is clearly corroborated by the reactivity of phenyl *N*-(phenylsulfonyl)-*N*-methylcarbamate **2** compared to that of phenyl *N*-methyl-*N*-phenylcarbamate, both involving a $B_{Ac}2$ mechanism for their alkaline hydrolysis. Indeed, at 25 °C the bimolecular rate constant for the former (k_{OH} = 0.375 M^{-1} s^{-1}) is 2.6 × 10^3 times higher than that of the latter (k_{OH} = 1.41 × 10^{-4} M^{-1} s^{-1}).[5h]

Few studies have been reported on neutral hydrolysis of carbamates owing to their stability, k_{H_2O} = 6.57 10^{-7} s^{-1} and 2.76 10^{-6} s^{-1} at 25 °C for 4-cyanophenyl and 4-nitrophenyl *N*-methylcarbamates, respectively.[27a] However, from results concerning the neutral hydrolysis (k_{H_2O}) for 1-naphthyl *N*-methylcarbamate and *N,N*-dimethylcarbamate and substituted phenyl *N*-methylcarbamates, it can be noted that (i) entropies of activation values are quite negative lying between −10.55 and −31.4 cal mol^{-1} K^{-1}; [27b,c] (ii) a decrease of the rate constant k_{H_2O} was observed for 4-nitro and 4-chlorophenyl *N*-methylcarbamates by addition of ethanol as cosolvent.[27b]

According to the hypothesis that the reactivity of **1a** might be compared with that of activated esters, the catalyzed hydrolysis of **1a** could be explained by a general base-catalyzed nucleophilic attack of water on the carbonyl group as was observed for halogen-substituted acetates which have been thoroughly investigated.[25,28–35] For these substrates, characteristic values for solvent isotope effects and activation parameters corresponding to this well-established mechanism (Scheme 2) are clearly defined and listed in Table 4.

As can be seen, high $k_{obsd}(H_2O)/k_{obsd}(D_2O)$ values lying in the range 2–5 and strongly negative entropies of activation are associated with the neutral hydrolysis of activated esters. These parameters have been considered as implying the relatively tight binding of several water molecules into the activated complex. One water molecule is covalently bound to the carbonyl atom in the transition state, a second is abstracting a proton from the first, and many others are present in the immediate neighborhood of the transition state.[33] The rate of hydrolysis of these esters is then very sensitive to the content of water. Thus, it was found that it significantly decreases as the molar concentration of H_2O is lowered in the medium by addition of an organic solvent (ethanol,[28] *tert*-butyl alcohol,[30,31] 2-*n*-butoxyethanol,[32] and acetonitrile[35]).

For the hydrolysis of **1a** and **1d** in 0.5–1.0 M HCl solutions, the greater $\Delta S^{\ddagger}$ values and the smaller solvent isotope effects obtained, $\Delta S^{\ddagger}$ = −11.7 cal mol K^{-1}, $k_{obsd}(H_2O)/k_{obsd}(D_2O)$ = 1.68 for **1a** and $\Delta S^{\ddagger}$ = −14.4 cal mol K^{-1}, $k_{obsd}(H_2O)/k_{obsd}$-

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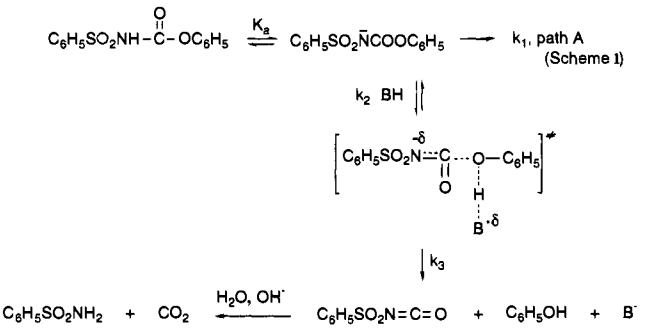
Table 4. Solvent Isotope Effects and Entropies of Activation Values for the Water-Catalyzed Nucleophilic Attack of Water on Di- and Trihalogenated Acetates

RCOOR[1]				
R	R^1	$(k_{obsd})_{H_2O}/(k_{obsd})_{D_2O}$	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}	ref
F_2CH, Cl_2CH	Et	2.0−5.0		28
Cl_2CH	4-$NO_2C_6H_4$	3.10		29
		3.0		30
		3.15	−33.0	31
Cl_2CH	4-$MeOC_6H_4$	3.24	−42.0	31
			−44.0	32
CH_3CCl_2	4-$MeOC_6H_4$		−46.0	32
CCl_3	Et	2.25	−44.0	33
CF_3	Me	3.48	−32.3	34
	Et	3.54	−34.5	34
		3.40[a]	−52.7[a]	16
	Pr	3.74	−37.1	34
	4-$NO_2C_6H_4$[b]	2.29	−68.6	35
	2,4-$(NO_2)_2C_6H_3$[b]	2.30	−59.3	35

[a] In 25% acetonitrile. [b] In water−acetonitrile containing 0.56 M of water.

Scheme 3



$(D_2O) = 2.46$ for **1d** are strikingly different from those reported in Table 4 and from those obtained for carbamates. Furthermore, an increase of k_{obsd} associated with a decrease of water concentration by addition of dioxan was observed for **1a**. So it would seem that these data cannot account for the general base-catalyzed nucleophilic attack of water as rate-determining step (Scheme 2). Moreover, reversible attack of water can be clearly ruled out from the absence of exchange of oxygen from water to the carbonyl group observed for the hydrolysis of **1a** carried out in enriched water (^{18}O = 15.00%) in 0.5 M HCl.

Acid-Catalyzed Breakdown of the Anion. The great stability of phenyl *N*-(phenylsulfonyl)-*N*-methylcarbamate **2** in 1.0 M HCl compared to the reactivity of the aryl *N*-(substituted phenylsulfonyl)carbamates **1a**−**i** shows clearly the key role played by the proton linked to the nitrogen atom in the mechanism of decomposition in acidic media. From the study of substituents effects on k_a for aryl *N*-(phenylsulfonyl)-carbamates **1a**−**f**, the ϱ value, equal to +0.87, is lower than the ϱ^- value observed for the unimolecular decomposition of the anions (k_p) and best correlated with σ rather than σ^-, while for the substitution on the phenyl ring beared on SO_2 group, ϱ is positive (ϱ = +0.22) and opposite to that observed for the spontaneous decomposition (k_p) of the anions of **1a**,**g**,**h** with departure of the phenolate ion (ϱ = −0.66). These data suggest that the leaving group departure is probably assisted by protonation of the oxygen atom involving no or very little charge development in the transition state.

Solvent effects obtained with **1a** (Figure 4) show that the rate of hydrolysis of **1a** in 0.5 M HCl is clearly dependent on the nature of the solvent, being about 1.5 times greater in water−dioxan (4/1, v/v) than in aqueous media. Reactions involving charge development in the transition state usually proceed much more slowly in nonpolar aprotic media like dioxan than in protic or highly polar aprotic ones.[36] Therefore, the increase of the rate of hydrolysis with addition of dioxan seems to be inconsistent with a general base-catalyzed nucleophilic attack of water on the neutral substrate for which a decrease of k_{obsd} would be expected with respect to the *charge developing* in the transition state and the decrease of water concentration. In contrast, this solvent effect does not disagree with a general-acid catalysis mechanism for which an anion is breaking, resulting to a *dispersion of charge* in the transition state as was observed for the decomposition in alkaline media of the anion of trichloroacetaldehyde hydrate.[37] In such a reaction, a decrease in solvent polarity may affect much more the stability of the anion rather than transition state and then a rate enhancement may be observed. Furthermore, specific structural effects may cause either the reactant or transition state to be particularly strongly solvated. This could be the case with an hydroxylic cosolvent like chloral able to strongly solvate an anion by hydrogen bonding so that electrons of the anion appear to be less readily available for the decomposition reaction. Reactivity is then reduced mainly by solvation effects of the reactant and by diminution of water concentration.

The formation of *N*-(((4-chlorophenyl)amino)carbonyl)sulfonamide **3b** as trapped product in the acid hydrolysis of **1a** and **1d** in the presence of 4-chloroaniline without variation of their rate constants hydrolysis argues in favor of the appearance of a sulfonyl isocyanate as electrophilic intermediate. The whole set of these results, including the absence of oxygen exchange for the acid hydrolysis, support a general acid-catalyzed decomposition of the anion of **1a** as the most probable mechanism of acid hydrolysis (Scheme 3). A Brönsted plot including hydronium ion was drawn from the catalytic constants of the various buffers (Figure 3). The observed α coefficient (0.46) for the general acid catalysis of the breakdown of the anion is consistent with a proton transfer in the transition state while the C−O bond is breaking and the C=N bond forming.

Conclusion

According to the results from the literature of extensive studies performed for $(E1cB)_{rev}$ mechanisms and especially those of Bruice,[3f] *decomposition of a carbanion intermediate, or a carbamate anion,[5] through such a mechanism is not dependent upon the concentration of any buffer species, i.e., the rate-limiting step only exhibits specific base-catalysis.*[38] Moreover, for substrates possessing a labile hydrogen atom in position α of a carbonyl group[3,4] and phenyl *N*-(monosubstituted)carbamates,[5] the rate of hydrolysis of the anion, k_p, through an (E1cB) mechanism reported in the literature was until now always higher than that of the $B_{Ac}2$ hydrolysis for the *N*-methyl derivative. As aryl *N*-(phenylsulfonyl)carbamates are very acidic (pK_a around 3), their anions present in acidic media are strongly stabilized by the SO_2 group and weakly reactive. For the first time, we have therefore observed that (i) the *N*-methyl derivative **2** involving a $B_{Ac}2$ mechanism is 5×10^4 times more

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reactive than the phenyl *N*-(phenylsulfonyl)carbamate **1a** for which the $(E1cB)_{rev}$ is operating; (ii) for aryl *N*-(phenylsulfonyl)-carbamates a general acid-catalyzed decomposition of the anion (k_a), conjugate base of the substrate, occurs in acidic media; (iii) the unimolecular rate decomposition of the anions k_p becomes lower than k_a in acidic media for the compounds possessing a leaving group of $pK_a \geq 8.8$.

To our knowledge, this work reports the first example of a decomposition of a carbamate anion through an (E1cB) mechanism involving an acid-catalyzed reaction with strong acid catalysts which cuts in depending on the leaving group ability. Therefore, the formation of powerful electrophilic intermediates, *i.e.*, sulfonyl isocyanates, occurs for the hydrolysis of sulfonylcarbamates over the whole pH range.

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Supplementary Material Available: Rate data for the acid-catalyzed hydrolysis of phenyl *N*-(phenylsulfonyl)carbamate **1a** in various buffers (Table S1) and for the hydrolysis of **1a** and **1d** in a chloroacetate buffer in the presence of 4-chloroaniline (Table S2) (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.