A General Buffer-Acid-Catalyzed C–O Cleavage Reaction in the Hydrolysis of Phenyl *N*-(Phenoxycarbonyl)sulfamate Ester

Patrick Blans and Alain Vigroux*[a]

Abstract: Rate constants and products are reported for the aqueous decomposition (pH 0–14) of phenyl *N*-(phenoxycarbonyl)sulfamate ($pK_a = 1.18$) at 50 °C. The pH–rate profile indicates 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}. The observation of non-first-order behavior in the pH range between 1.6 and 4.1 points to the accumulation of a non-steady-state intermediate that is concluded to be phenyl sulfamate. The latter result, coupled with the observation at low pH of general acid catalysis by buffers, reveals that each of the hydrolytic paths involves i) the anionic form specifically and ii) carbon–oxygen bond fission. Buffer catalysis is assumed to be the result of the nonexistence of the zwitterionic species $PhOSO_2NCO-\overset{+}{O}(H)Ph$. Comparison with previously studied phenyl *N*-(phenylsulfonyl)carbamate[7] indicates that the Brønsted α value associated with such a mechanism increases sharply as the C–O bond which is cleaved becomes stronger (a change in reactivity of ca. 2.3 kcal mol^{-1} gives rise to a change in α of about 0.3). In contrast to C–O cleavage, S–O and P–O fissions involved in related systems such as *N*-(methoxycarbonyl)sulfamate esters and phosphate and sulfate monoesters with good leaving groups do not exhibit buffer-acid catalysis. It is concluded that unambiguous distinction between inter- and intramolecular general acid catalysis is not currently possible for those compounds.

Keywords: acid–base catalysis · hydrolyses · reaction mechanisms · sulfamate esters · zwitterionic intermediates

Introduction

The [(carbonyl)amino]sulfonyl moiety, -SO_2NHCO-, has recently been introduced to biological and medicinal chemistry as a possible surrogate (bioisostere) for the diphosphate group.[1–4] Interestingly, the OSO_2NHCOO isostere of uridine 5′-diphosphate glucose (UDP-Glc) was found to interfere with protein glycosylation, inhibiting the glycosylation of viral proteins to a greater extent than the glycosylation of cellular proteins.[1] Furthermore, studies of structurally related compounds within this series showed that the nucleotide-like 5′-*O*-sulfamoyluridine moiety is an important component for the maintenance of antiviral activity, and it was suggested that this moiety and/or its metabolites could be responsible for the observed inhibition of DNA synthesis and protein glycosylation.[2]

More recently, lipophilic nucleotide mimics in which 2′,3′-dideoxynucleoside (ddN) residues were linked to a glucopyranosyl moiety by the OSO_2NHCOO group were shown to exhibit anti-HIV-1 activity in MT-4 cells at concentrations well below the toxicity threshold.[3] In this case, it was suggested that these compounds do not release the free ddN's, which are known to be potent and selective inhibitors of HIV replication (by inhibiting HIV reverse transcriptase), but may act in their own right.

In recent therapeutic strategies, the extended use of the -SO_2NHCO- moiety (as a replacement for the diphosphate or sulfate group of a variety of critical biomolecules) proved successful as well.[4, 5] Finally, the ionized form of this spacer was also used to design an unusual water-soluble ACAT inhibitor that is well absorbed and thus exhibits improved bioavailability.[6]

The mechanisms of the aqueous reactions of *N*-(oxycarbonyl)sulfamate esters OSO_2NHCOO, although of interest to both chemists and biochemists, have not yet been systematically investigated. Preliminary accounts of some of our work into the chemistry of [(carbonyl)amino]sulfonyl-linked derivatives suggest that the -SO_2NHCO- group may be viewed

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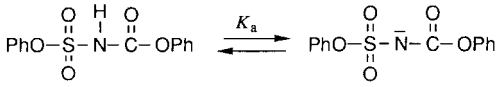
as an attractive analogue of the phosphodiester link of nucleic acid backbones.[7–8] If this group can indeed be used in such a way, it opens the door to novel approaches to putative antisense agents.[9] However, this would demand a fundamental understanding of the chemistry in aqueous media of the OSO_2NHCOO linkage. In the present paper, an investigation of the hydrolysis of phenyl *N*-(phenoxycarbonyl)sulfamate ($pK_a = 1.18$,[10] Scheme 1) is reported.



Scheme 1.

This work sets out to study the mechanistic basis of the aqueous decomposition pathway of the title compound, hydrolysis of which is expected to proceed exclusively with C–O bond cleavage. In fact, from literature precedent, C–O cleavage is easier than S–O by a factor of ca. 10^9.[11] However, hydrolysis of *N*-(oxycarbonyl)sulfamate esters may occur with S–O bond-breaking if the leaving group on sulfur is much better than that on carbon, as previously observed with certain aryl *N*-(methoxycarbonyl)sulfamates, $ArOSO_2NHCO_2Me$.[8] In the latter case, no buffer catalysis was detected in acid for S–O cleavage, while the analogous C–O breaking reaction previously reported for phenyl *N*-(phenylsulfonyl)-carbamate anion ($PhSO_2\bar{N}CO{-}OPh$) was unambiguously demonstrated to be general buffer-acid-catalyzed.[7] The different behaviors observed in acid between the C–O and S–O cleavage reactions of *N*-(oxycarbonyl)sulfamate esters are discussed.

Abstract in French: *L'étude de l'hydrolyse du N-(phénoxycarbonyl)sulfamate de phényle ($pK_a = 1,18$) a été réalisée à 50 °C entre pH 0 et 14. Le profil de vitesse k_{obs}–pH obtenu comprend deux termes indépendants du pH, k_a en milieu acide et k_p en milieu neutre, avec $k_a > k_p$, et un terme dépendant de la concentration en ion hydroxyde, k_{OH}. Les cinétiques obtenues entre pH 1,6 et 4,1 ne sont pas du premier ordre, ce qui indique l'accumulation d'un intermédiaire réactionnel qui, par ailleurs, a été identifié au sulfamate de phényle. Ce résultat, associé au fait que l'on observe en milieu acide une catalyse acide générale par les tampons, indique que la réaction d'hydrolyse s'effectue, quel que soit le pH, uniquement sur la forme anionique du substrat avec rupture de la liaison carbone–oxygène. La catalyse générale observée est vraisemblablement la conséquence de la non-existence en milieu aqueux de l'espèce zwittérionique $PhOSO_2\bar{N}CO{-}\overset{+}{O}(H)Ph$. Une comparaison avec l'hydrolyse du N-(phenylsulfonyl)carbamate de phényle précédemment étudié[7] montre que la valeur α de Brønsted associée à ce type de réaction croît fortement avec l'énergie de la liaison C–O à rompre (une stabilisation da la liaison C–O d'environ 2,3 kcal mol^{-1} se traduit par une augmentation de α d'environ 0,3). Contrairement à la rupture C–O, les coupures des liaisons S–O et P–O mises en jeu dans des systèmes apparentés tels que les esters de N-(methoxycarbonyl)sulfamate et les monoesters de phosphate et de sulfate avec de bons groupes partants s'effectuent sans catalyse apparente des tampons. En conclusion, la distinction sans équivoque entre une catalyse acide générale inter- et intramoléculaire n'est pas actuellement possible pour ces composés.*

Results and Discussion

Rate law: The pH–rate constant profile, $\log k_{obsd}$ vs pH, for hydrolysis at 50 °C and $\mu = 1.0$ M of phenyl *N*-(phenoxycarbonyl)sulfamate is shown in Figure 1 (●). It is characterized by

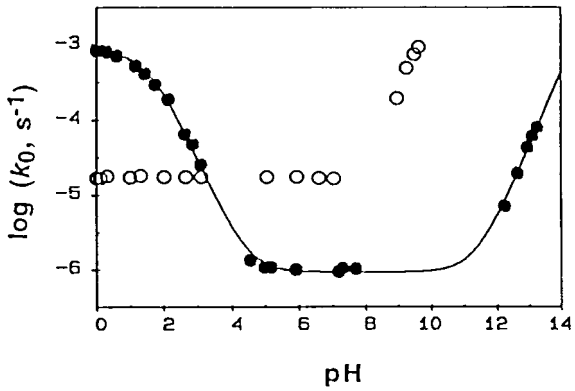


Figure 1. Plot of log k_0, the buffer-independent rate constant for hydrolysis of phenyl *N*-(phenoxycarbonyl)sulfamate (●) and phenyl sulfamate (○), against pH in aqueous solutions, 50 °C, $\mu = 1.0$ M (with KCl). The solid line is fit to Equation (1) using constants k_a, k_p, k_{OH}, and K_{app}, given in the text.

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 last reaction is characterized by a linear plot of $\log k_{obsd}$ vs pH with a slope of +1.0.

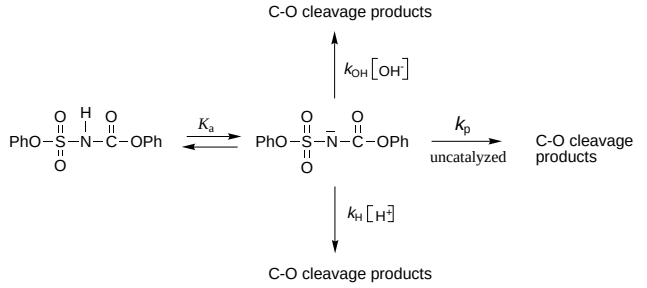
The hydrolysis reaction of phenyl *N*-(phenoxycarbonyl)-sulfamate was followed in the pH regions 0–3 and 12–14 up to at least 90% completion by spectrophotometric monitoring of either the formation of phenol at $\lambda = 270$ nm (pH < 3) or the disappearance of the substrate at $\lambda = 240$ nm (pH > 12). Excellent pseudo-first-order kinetics were obtained in those pH ranges, except in the region extending about 1.5 units to either side of pH 3, where two kinetic processes were observed (see below). Between pH 4 and 11 the hydrolysis reaction was followed at $\lambda = 270$ nm (buffer concentration 0.05 M) to only ca. 10% completion owing to the very slow hydrolysis of the title compound in this pH region. The pseudo-first-order rate constants k_{obsd} were determined in this pH portion by the method of initial rates [Eq. (5) in the Experimental Section]. The experimental data points (Figure 1, ●) were fit to Equation (1), where a_H is the hydrogen-

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

ion activity measured at 50 °C, K_W is the autoprotolysis constant of water at 50 °C, and K_{app} the apparent acid dissociation constant of the substrate at the same temperature. The values of the constants k_a, k_p, k_{OH}, and K_{app} required to fit the experimental rate constants k_{obsd} to Equation (1) are: $k_a = (8.23 \pm 0.4) \times 10^{-4}$ s^{-1}, $k_p = (9.36 \pm$

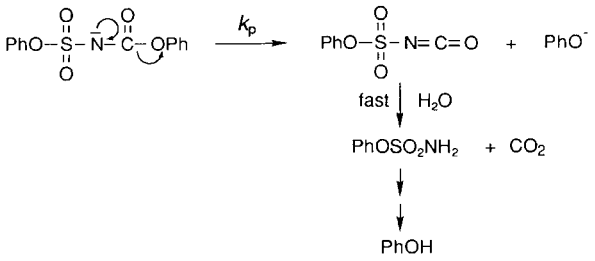
$0.4) \times 10^{-7}\,s^{-1}$, $k_{OH} = (8.02 \pm 0.4) \times 10^{-5}\,M^{-1}s^{-1}$, and $K_{app} = (2.73 \pm 0.2) \times 10^{-2}\,M$. The second-order rate constant value for hydroxide ion determined at 50 °C from the linear plot of k_{obsd} vs $[OH^-]$ in the alkaline pH-dependent region (pH = 11 – 13) is $k_{OH} = (8.42 \pm 0.3) \times 10^{-5}\,M^{-1}s^{-1}$. The value of K_a determined spectrophotometrically at 25 °C and $\mu = 1.0\,M$ (with KCl) is $K_a = (6.61 \pm 0.2) \times 10^{-2}\,M$.

Mechanisms: The overall mechanistic pathway for hydrolysis (pH range 0 – 14) of phenyl *N*-(phenoxycarbonyl)sulfamate is depicted in Scheme 2. Each of the hydrolytic paths of Scheme 2 involves i) the anionic form specifically and ii) carbon – oxygen bond fission.



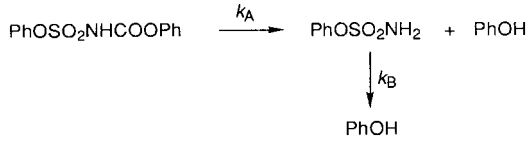
Scheme 2. Overall mechanistic pathway for hydrolysis of phenyl *N*-(phenoxycarbonyl) sulfamate ester in the entire pH range 0 – 14.

a) pH-Independent hydrolysis (k_p): From the dissociation constant K_a, simple calculation shows that, at pH > 3.2, more than 99% of the title compound is present as the anion. In agreement with our expectation, namely, that anion breakdown is much more likely to take place through the carbonyl group (C–O cleavage) than through the sulfonyl group (S–O cleavage) when there are two possible oxy leaving groups of identical pK_a attached one on each side of the -SO_2NCO- moiety,[11] we found that the spontaneous hydrolysis reaction in the pH range 5 – 11 (k_p in Scheme 2) occurs like that of previously studied aryl *N*-(phenylsulfonyl)carbamate esters,[7] that is, by way of a dissociative E1cB mechanism with C–O bond cleavage leading to phenyloxysulfonyl isocyanate as intermediate (Scheme 3).



Scheme 3.

The observation of non-first-order behavior in the pH range between 1.6 and 4.1 indicates the accumulation of a non-steady-state intermediate that is concluded to be phenyl sulfamate. The latter compound results from the rapid addition of water on the electrophilic phenyloxysulfonyl isocyanate intermediate followed by fast decarboxylation. This conclusion is based on the coincidence of the pH – rate profile for hydrolysis of phenyl sulfamate (Figure 1, ○) with part of the pH – rate profile for the title compound (Figure 1, ●). The non-first-order kinetic behavior between pH 1.5 and 4.5 is expected for a system such as that in Scheme 4 when



Scheme 4.

$k_A \approx k_B$, and is quantitatively consistent with the interpretation in terms of Scheme 4. Kinetic expression for the appearance of phenol is given in Equation (2), in which $r =$

$$A_t = A_\infty + 0.5\,(A_\infty - A_0)\,[(r-1)^{-1}\,e^{-rk_At} + (1-2r)(r-1)^{-1}\,e^{-k_At}] \qquad (2)$$

k_B/k_A, and where A_t, A_∞, and A_0 represent the observed absorbance at time t, $t = \infty$, and $t = 0$, respectively, at $\lambda =$ 270 nm. Values of k_A for the hydrolysis of phenyl *N*-(phenoxycarbonyl)sulfamate were computed from excellent fit of the data to Equation (2) using the experimental values of A_∞ and A_0 as just defined, and k_B, the rate constant for hydrolysis of phenyl sulfamate (measured directly at $\lambda =$ 270 nm from an authentic sample of phenyl sulfamate under the same conditions used in the hydrolysis of phenyl *N*-(phenoxycarbonyl)sulfamate[12]).

The hydrolysis reaction at pH = 4.60 in acetate buffer 0.5 fraction base (i.e. in the pH region where $k_{obsd} \approx k_p$, see Figure 1) is characterized by $\Delta H^{\neq} = 29.3 \pm 0.4$ kcal mol^{-1} and $\Delta S^{\neq} = +5.3 \pm 1.3$ cal K^{-1} mol^{-1}.

It is of interest to note that phenolate expulsion from phenyl *N*-(phenoxycarbonyl)sulfamate anion resulting from the C–O cleavage reaction (k_p, this work) occurs 35 times more slowly than that from phenyl *N*-(phenylsulfonyl)carbamate anion ($k_p = 3.27 \times 10^{-5}$ at 50 °C[7]). Thus, the presence of an additional oxygen atom at the sulfonyl moiety has a stabilizing effect of ca. 2.3 kcal mol^{-1} at 50 °C.

b) Hydroxide ion reaction (k_{OH}): As previously observed with aryl *N*-(methoxycarbonyl)sulfamate esters,[13] the OH^- reaction observed with phenyl *N*-(phenoxycarbonyl)sulfamate very likely involves attack of OH^- at the carbonyl moiety of the anion. The increased reactivity of the title compound compared to phenyl *N*-(methoxycarbonyl)sulfamate,[8] by a factor of ca. 4 at 50 °C, is as expected for a mechanism involving a rate-limiting nucleophilic attack at the carbonyl center with different leaving groups such as phenol and methanol. It should be noted that in the case of aryl *N*-(phenylsulfonyl)carbamates, no hydroxide ion reaction was detected up to pH 13 at 50 °C.[7] This is consistent with the fact that the negative charge of *N*-(sulfonyl)carbamate esters, which is less extensively delocalized to the sulfonyl moiety than in *N*-(oxycarbonyl)sulfamate esters, should provide more electrostatic repulsion toward OH^- attack at the carbonyl center.

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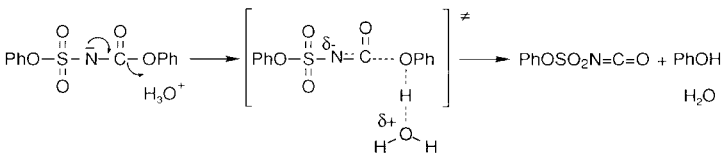
c) Acid-catalyzed hydrolysis (k_a): The mechanism shown in Scheme 5 is consistent with the observed rate law in acid, and is supported by the observation at low pH of general buffer-acid catalysis.



Scheme 5.

The observation of buffer-acid catalysis at pH < 5 requires that the anionic form of the substrate, S^-, is the reactive species in acid. In the pH region 0–5 one may then interpret Equation (1) in terms of Equation (3), the explicit rate law for the mechanism of the reaction in Scheme 5. According to Equation (3), the observed pH-independent rate constant k_a

$$k_{obsd} = k_H a_H K_{app}/(a_H + K_{app}) \quad (3)$$

is equal to $k_H K_{app}$ when $a_H \gg K_{app}$ (i.e. at pH < 1, Figure 1, ●); k_H in Equation (3) refers to the second-order rate constant for hydronium ion (Scheme 2). As shown in Scheme 5, the catalytic role of hydronium ion is to assist departure of the leaving group PhO^- during the course of the rate-limiting C–O cleavage. Consistent with this picture is the relatively large isotopic dependence measured in 1.0 M LCl solutions at 50 °C ($k_{H_2O}/k_{D_2O} = 1.53$).

The effect of the buffer concentrations on the rate of hydrolysis of phenyl *N*-(phenoxycarbonyl)sulfamate was determined by varying the total buffer concentration over a tenfold range at constant pH values (see Table S1 in the Supporting Information). With the more acidic buffers of $pK_a < 5$, that is, CCl_3COOH, CCl_2HCOOH, $NCCH_2COOH$, and CH_3COOH, a significant buffer catalysis was observed. Typically the values of k_{obsd} changed, linearly, by ca. 40% with changes in buffer concentration that routinely ranged from 0.05 to 0.5 M. The pseudo-first-order rate constants k_{obsd} were determined in trichloroacetic acid buffer (pH range 0.4–1.1) by means of complete kinetic runs, while Equation (2) had to be used in dichloro- and cyanoacetic acid buffers owing to the non-first-order behavior observed in the pH portion 1–3 (vide supra). In acetic acid buffer (pH 4–5), the rate constants k_{obsd} were obtained from the method of initial rates by means of Equation (5) (given in the Experimental Section). The data were analyzed by least-squares fitting of Equation (4). The

$$k_{obsd} = k_0 + k'_{cat}[buffer] \quad (4)$$

rate constants k_0 were then obtained for the acidic pH region (0–5) by extrapolation of k_{obsd} values to zero buffer concentration or else by direct measurements carried out in HCl solutions at several concentrations ($k_{obsd} = k_0$).

In order to obtain a linear relationship between the buffer catalytic coefficient, k_{cat}, and the fraction of buffer present in the acid form, f_A, it is necessary to divide k'_{cat} in Equation (4) by α, the molar fraction of S^- present at a given pH value {$\alpha = K_a/(a_H + K_a)$} (the detailed kinetic analysis employed to determine the catalytic coefficients k_{cat} is given in the Supporting Information). The k_{cat} values so obtained are summarized in Table S1 (Supporting Information) and are plotted against the molar fraction f_A of the acid form of the buffer; an example of such an analysis is shown in Figure 2.

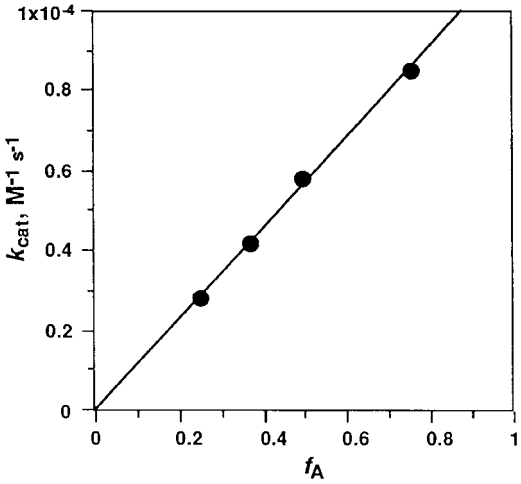


Figure 2. Dependence of the second-order rate constant k_{cat} for buffer catalysis of hydrolysis of phenyl *N*-(phenoxycarbonyl)sulfamate on the fraction of cyanoacetic buffer present in the acid form, f_A. The slope of the line is $k_{HA} = (1.14 \pm 0.03) \times 10^{-4}\,M^{-1}s^{-1}$.

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_{HA}. When the spectrophotometrically determined pK_a of phenyl *N*-(phenoxycarbonyl)sulfamate at 25 °C ($pK_a = 1.18$) is used to calculate the molar fraction α, the resulting catalytic constants k_{HA} (Table 1) plotted against the

Table 1. General acid catalytic coefficients for the hydrolysis of phenyl *N*-(phenoxycarbonyl)sulfamate at 50 °C ($\mu = 1.0$ M with KCl).

catalyst HA	pK_{HA}, 50 °C[a]	(25 °C)[b]	k_{HA} [$M^{-1}s^{-1}$][c]
H_3O^+	−1.74	(−1.74)	$(3.01 \pm 0.4) \times 10^{-2}$[d]
Cl_3CCO_2H	0.69	(0.70)	$(2.21 \pm 0.06) \times 10^{-3}$
Cl_2CHCO_2H	1.45	(1.48)	$(7.43 \pm 0.2) \times 10^{-4}$
$CNCH_2CO_2H$	2.63	(2.65)	$(1.14 \pm 0.03) \times 10^{-4}$
CH_3CO_2H	4.55	(4.75)	$(2.28 \pm 0.02) \times 10^{-6}$

[a] Apparent pK_a values determined—except for H_3O^+—at ionic strength 1.0 M and 50 °C from either the pH of half-neutralized solutions or the degree of neutralization and the pH. [b] pK_a values at 25 °C from D. R. Lide, *Handbook of Chemistry and Physics*, 71st ed., CRC, **1990–1991**. [c] See text and Supporting Information for determination. [d] Calculated from the rate constant value k_a corresponding to the acidic plateau of the pH–rate profile of Figure 1 (●) divided by K_a, the ionization constant of the title compound determined at 25 °C (see text and ref. [14]).

pK_a of the corresponding acids lead to an α Brønsted parameter of 0.78 ± 0.04.[14]

The Brønsted plot for general acid catalysis by carboxylic acid buffers is illustrated in Figure 3. The value of the slope ($\alpha = 0.78$) is probably not directly comparable with that previously obtained with phenyl *N*-(phenylsulfonyl)carbamate ($\alpha = 0.46$) insofar as in the latter case the Brønsted line was established with different classes of catalysts including hydronium ion. Nevertheless, allowing for H_3O^+ in the Brønsted correlation[15] gives a smaller α value ($\alpha = 0.67$) which still remains significantly larger than that of phenyl *N*-(phenylsulfonyl)carbamate anion. This variation of α value

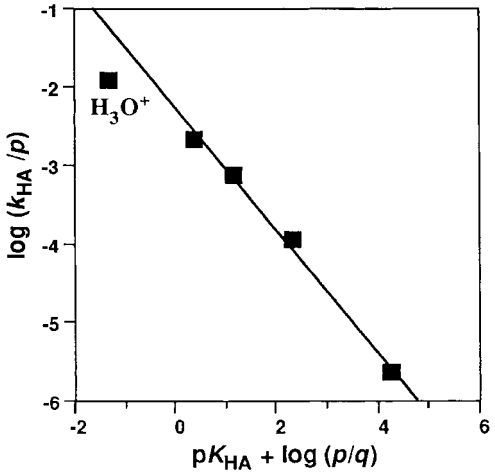
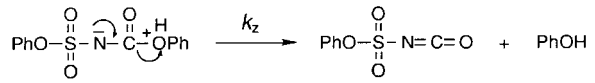


Figure 3. Statistically corrected Brønsted plot for the general acid-catalyzed hydrolysis of phenyl *N*-(phenoxycarbonyl)sulfamate by carboxylic acid buffers at 50 °C. The linear regression equation is: $\log (k_{HA}/p) = (-0.78 \pm 0.04)(pK_{HA} + \log(p/q)) - (2.26 \pm 0.1)$. The position of hydronium ion relative to the solid line obtained is indicated in the graph. Data are from Table 1.

follows closely what would be predicted from the discussion of More O'Ferrall.[16] Indeed, inspection of a two-dimensional reaction coordinate diagram[17] for the general buffer acid-catalyzed decomposition of phenyl *N*-(phenylsulfonyl)carbamate anion in which the transition state contains a reasonable diagonal component ($\alpha = 0.46$) indicates that the change to the less reactive title compound should increase the value of Brønsted α.

General buffer acid-catalyzed E1cB reaction for C–O cleavage: As far as we are aware, the C–O bond fission involved in the hydrolysis of both the title compound and phenyl *N*-(phenylsulfonyl)carbamate ester provides the first example of an $(E1cB)_{rev}$ reaction that is general buffer acid-catalyzed. Indeed, extensive studies[18] performed on dissociative mechanisms involving rate-limiting anion decomposition in aqueous media indicate that $(E1cB)_{rev}$ mechanisms are not typically general buffer acid-catalyzed.[19]

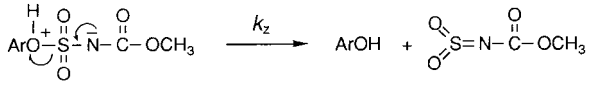
Buffer-acid catalysis observed for the above-mentioned C–O cleavages is assumed to be the result of the nonexistence of hypothetical zwitterionic species. In fact, extrapolation of the Brønsted plot $\log k_p$ vs pK_{lg} obtained for the uncatalyzed decomposition of the anions of aryl *N*-(phenylsulfonyl)carbamates,[7] as indicated in ref. [8], suggests that the zwitterionic species $PhSO_2\overset{-}{N}CO-\overset{+}{O}(H)Ar$ (**I**) do not exist as discrete species for leaving groups of $pK_a <$ ca.13.4 (at 50 °C), that is, for all leaving phenols.[21] Similarly, taking into account the stabilizing effect (ca. 2.3 kcal mol^{-1}) due to the presence of an additional oxygen atom at the sulfonyl moiety (vide supra), one may roughly estimate this pK_a limit to be ca. 12.2 (at 50 °C) for the corresponding zwitterionic species $PhOSO_2\overset{-}{N}CO-\overset{+}{O}(H)Ar$ (**II**). Thus, according to the notions developed by Jencks about enforced general acid–base catalysis,[22, 23] the concerted general acid catalysis of Scheme 5 appears to be enforced by the disappearance of the barrier for leaving group expulsion from the zwitterionic species in Scheme 6 (i.e., $k_z > 10^{13}$ s^{-1}).



Scheme 6.

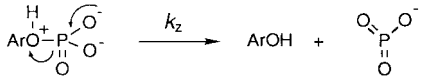
Absence of buffer catalysis in related systems involving S–O and P–O cleavages: The requirement for the involvement of general buffer-acid catalysis for the above C–O cleavage reactions is without precedent in the aqueous reaction chemistry of any structurally related system. Indeed, the aqueous decompositions of weakly basic anions proceeding with C–O bond breaking are notable by comparison with those proceeding with S–O (Schemes 7 and 9 below) or P–O (Scheme 8) bond cleavage, in that where there is evidence for an enforced general acid–base catalysis (because of the nonexistence of a putative intermediate), these other bond-breaking reactions (i.e., S–O and P–O cleavages) are not buffer-catalyzed.

From our earlier study of aryl *N*-(methoxycarbonyl)sulfamate esters[8] it was concluded that the zwitterionic species in Scheme 7 probably do not exist as discrete species (i.e., $k_z > 10^{13}$ s^{-1}) for leaving phenols of $pK_a < \approx 9.4$ (at 50 °C) and, therefore, that only a concerted mechanism is possible for the observed acid-catalyzed S–O cleavage reaction. With the

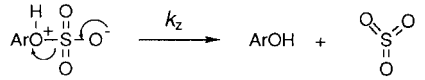


Scheme 7.

objective of detecting buffer-acid catalysis, a number of experiments were carefully conducted in various buffered solutions. However, no buffer effect was detected at any pH for this reaction. Analogously, scrutiny of the literature for the aqueous decompositions of aryl phosphate[24] and aryl sulfate[25] monoesters suggests that for those esters with good leaving groups—that is, for leaving phenols of $pK_a < \approx 10$ in the case of phosphates and of $pK_a < \approx 8$ in the case of sulfates[26]—the zwitterionic species in Schemes 8 and 9 no



Scheme 8.



Scheme 9.

longer have an energy barrier to decomposition ($k_z > 10^{13}$ s^{-1}) so that the acidic hydrolysis reactions presumably proceed through enforced concerted mechanisms.[27] However, as in the case of aryl *N*-(methoxycarbonyl)sulfamate esters, no buffer catalysis was reported for those reactions.

Thus, because of the absence of observed buffer effects in acid for S–O and P–O cleavages, an unequivocal choice between two paths, **a** and **b** in Scheme 10, is not presently possible. Paths **a** and **b** represent the two types of enforced

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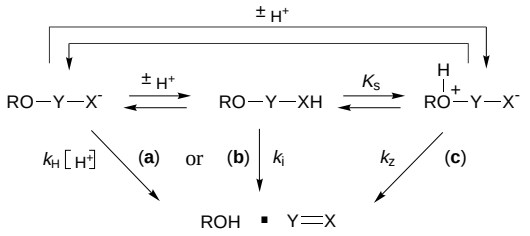


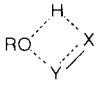
Y = $PO(O^-)$, X = O: Phosphate monoesters

Y = SO_2, X = O: Sulfate monoesters

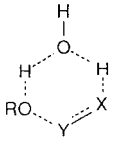
Y = SO_2, X = N-CO_2CH_3: *N*-(Methoxycarbonyl)sulfamate esters

Scheme 10. Schematic view of the mechanisms that may be involved in the acidic hydrolysis reactions of phosphate and sulfate monoesters and aryl *N*-(methoxycarbonyl)sulfamate esters. Paths **a** and **b** represent the two types of enforced inter- and intramolecular general acid catalyses, respectively, that may be considered when k_z (path **c**) approaches the upper limit of 10^{13} s^{-1}. The rate constant k_i (path **b**) refers to the cyclic intramolecular proton transfer with the transition state **III** or **IV**.

general acid catalysis that may be considered when k_z in Scheme 10 (path **c**) approaches the upper limit of 10^{13} s^{-1}.[21] While the observation of buffer catalysis would unambiguously support *intermolecular* acid catalysis (path **a**) with a transition state such as that shown in Scheme 5 for C–O breaking, the absence of buffer effect cannot be taken as proof of *intramolecular* acid catalysis (i.e. path **b**) with a transition state **III** or **IV**.



III



IV

Indeed, it is possible that buffer catalysis which, in principle, should be associated with the mechanism of path **a** becomes unobservable merely because the α Brønsted values for S–O and P–O fissions are close to unity.[22] One way of regarding the change in the α value observed for C–O fission (a change in reactivity of ca. 2.3 kcal mol^{-1} gives rise to a change in α of about 0.3, vide supra) is to say that the less easily the C–O bond is broken the more proton transfer there is in the transition state. This trend presumably also holds for S–O or P–O bond cleavage reactions. Given that the S–O and P–O bonds are much stronger than the C–O bond, it is then possible that the oxygen leaving groups of the anions of Scheme 10 have to be *almost completely* protonated to lead to the commencement of S–O and P–O fissions (complete protonation cannot occur without triggering fission of the S–O and P–O bonds when k_z in Scheme 10 is assumed to be on the order of a bond vibration frequency, i.e. ca. 10^{13} s^{-1}). Therefore, it is not unlikely that for *N*-(methoxycarbonyl)-sulfamate esters and phosphate and sulfate monoesters with good leaving groups the Brønsted α value associated with the mechanism of path **a** approaches a value of 0.9 – 1, and hence, that buffer catalysis becomes unobservable.

On the other hand, the absence of intermolecular proton transfer, as suggested by the absence of general buffer-acid catalysis, may be a function of the geometry of tetrahedral phosphorus and sulfur centers. Indeed, it is possible that the tetrahedral geometry of -$PO(O^-)$- and -SO_2- groups is the key to rendering the *intramolecular* proton transfer of path **b** (via **III** or **IV**) energetically more favorable than the *intermolecular* one of path **a**. Accordingly, the planar geometry of the carbonyl group would explain why *intermolecular* acid catalysis of weakly basic anions is only observed for C–O bond cleavage reactions.

Conclusions

The present study shows that, in the entire pH range, phenyl *N*-(phenoxycarbonyl)sulfamate ($pK_a = 1.18$) hydrolyzes by way of its anionic form with 100% C–O bond cleavage (Scheme 2). This result confirms the prediction that the two possible decomposition fates, C–O versus S–O cleavage, for the nitrogen anion of *N*-(oxycarbonyl)sulfamate esters become completely unbalanced—in favor of C–O cleavage—when the leaving groups on S and C sites are identical or, at least, do not differ too much in terms of their pK_a value.

In addition, it is confirmed that weakly basic nitrogen anions whose acidic decomposition occurs through C–O bond cleavage exhibit an unusually general buffer-acid catalysis for leaving group expulsion (Scheme 5) which is assumed to be the result of the nonexistence of the zwitterionic species **I** and **II**. Comparison with the previously studied compound phenyl *N*-(phenylsulfonyl)carbamate[7] indicates that the Brønsted α value associated with such a mechanism increases sharply as the C–O bond which undergoes fission becomes stronger (a change in reactivity of ca. 2.3 kcal mol^{-1} gives rise to a change in α of about 0.3).

In contrast to C–O cleavage, S–O and P–O fissions involved in such related systems as *N*-(methoxycarbonyl)sulfamate esters and phosphate and sulfate monoesters with good leaving groups (Scheme 10) are not buffer-acid-catalyzed. The lack of any observed buffer effect could result from the large value (≥ 0.9) of Brønsted α associated with S–O and P–O bond fissions by path **a**. On the other hand, the absence of buffer catalysis might suggest that a concerted cyclic mechanism is energetically preferred (path **b**) because of some geometric characteristics of tetrahedral phosphorus and sulfur centers. Hence, an unequivocal choice between inter- (path **a**) and intramolecular (path **b**) general acid catalysis is not presently possible for those compounds. Unambiguous distinction between paths **a** and **b** in Scheme 10 may have some important implications with conclusions that can be reached for the aqueous decompositions of phosphate and sulfate monoesters in acid.

Experimental Section

Materials: In general, chemicals were purchased as the best available commercial grade. Organic chemicals were purified by distillation or recrystallization prior to use. Inorganic chemicals were generally used without further purification. Water for analytical procedures was distilled and deionized on a Milli-Q water purification system (Millipore). Melting points were measured on a Kofler hot-stage apparatus and are uncorrected.

Elemental analysis was performed by the Analytical Service of the University Paul Sabatier. IR spectra were recorded with a Perkin–Elmer 883 spectrometer. ^{13}C NMR spectra were obtained with a Bruker AC-250 spectrometer (50.32 MHz).

Synthesis: Phenyl *N*-(phenoxycarbonyl)sulfamate was synthesized in 56% yield by treating phenoxysulfonyl isocyanate, prepared from chlorosulfonyl isocyanate and phenol,[30] with phenol according to the method described by G. Lohaus.[30]

Phenyl *N*-(phenoxycarbonyl)sulfamate: M.p. 85 °C; ^{13}C NMR (50.32 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 121.09 - 130.32$ (aryl C^{III}), 148.23–149.86 (aryl C^{IV} and C=O); IR ($CHCl_3$): $\tilde{\nu} = 3382\ cm^{-1}$ (N–H), 1785 (C=O), 1592 and 1489 (aryl C=C), 1439 (SO_2NCO), 1386 and 1148 (SO_2); $C_{13}H_{11}NO_5S$ (293.3): calcd C 53.24, H 3.78, N 4.78; found C 52.96, H 3.63, N 4.76.

Kinetics: The decomposition reaction of phenyl *N*-(phenoxycarbonyl)sulfamate in aqueous media was monitored at 50 °C by UV/vis spectrophotometry. The solutions employed were HCl (pH 0–2.0),[31] 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), at 0.5 M, and NaOH (pH 11–14). The strongest acid buffers used here gave solutions whose pHs varied significantly with concentration that spanned from 0.0625 to 0.5 M. For the diluted solutions 0.0625, 0.125, and 0.250 M, pH values were fit to the pH value measured for the highest buffer concentration (0.5 M) by addition of negligible volumes of concentrated HCl solution. The pH of the reaction mixtures was measured upon initiation and after completion of the runs by means of a Tacussel pH meter (TT processor 2) with XC 111 or U402-M3-S7/60 Ingold combination electrodes calibrated 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 as described for H_2O.

Between pH 4 and 11 the hydrolysis reaction of phenyl *N*-(phenoxycarbonyl)sulfamate (at 50 °C) was so slow that it was followed to only ca. 10% completion by following the formation of phenol at $\lambda = 270$ nm. The pseudo-first-order rate constants k_{obsd} were determined by the method of initial rates using Equation (5), in which *s* is the slope of absorbance versus time, [S] the concentration of substrate, and ε_p the molar extinction coefficient of product phenol and its anion measured at 270 nm at a given pH value between 4 and 11. The values employed for ε_p are: 1500 between

$$k_{obsd} = 0.5s/([S]\varepsilon_p) \quad (5)$$

pH 4 and 7, and 1450 at pH 7.7. Those values were obtained from curves of optical density versus concentration for a standard solution of phenol diluted within reaction mixture. The coefficient 0.5 in Equation (5) arises from the fact that phenol is formed both by k_A (1 equiv) and k_B (1 equiv) (see Scheme 4 in Results and Discussion) and from the fact that the intermediate phenyl sulfamate (see explanations in Results and Discussion) is a steady state intermediate (i.e. $k_B \gg k_A$) at pH > 4.2. The latter statement was checked by conducting complete kinetic runs at higher temperature (75 °C) in acetate buffer at pH ≥ 4.2: good pseudo-first-order kinetics were obtained in each case. The hydrolysis of phenyl *N*-(phenoxycarbonyl)sulfamate (1 equiv) gave, after completion of the first-order kinetic runs performed at 75 °C and pH ≥ 4.2, 2 equiv phenol, whereas only 1 equiv was formed immediately after completion of the first-order kinetic runs carried out at 50 °C and pH < 1.5.

Supporting information: Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the authors; it comprises details of the kinetic analysis employed to determine the catalytic coefficients k_{HA} and Table S1, containing kinetic data for the general acid-catalyzed hydrolysis reaction.

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[10] Substrates with a NH moiety between carbonyl and sulfonyl groups are very acidic; their pK_a values are close to the first pK_a's of phosphoric acid and phosphate mono- and diesters, i.e., $pK_a \approx 2$.

[11] The rate constants ratio, k_{CO}/k_{SO_2}, for the C–O and S–O cleavage reactions of the corresponding conjugate bases of $CH_3NHCO-OAr$ (k_{CO}, C–O cleavage) and CH_3NHSO_2-OAr (k_{SO_2}, S–O cleavage), was estimated from the literature data to be about 10^9 when the leaving group is *p*-nitrophenol. See: H. Al-Rawi, A. Williams, *J. Am. Chem. Soc.* **1977**, *99*, 2671; A. Williams, K. T. Douglas, *J. Chem. Soc. Perkin Trans. 2* **1974**, 1727.

[12] The hydrolysis of phenyl sulfamate in aqueous buffers (at 50 °C and $\mu = 1.0$ M) displayed excellent first-order kinetics up to at least 90% of the total reaction. No buffer catalysis was detected in the pH range between 0 and 3 ($k_{obsd} = k_0$) whereas in the presence of varying concentrations (0.05–0.5 M) of acetate, phosphate, tris, and borate buffers, the first-order rate constant k_{obsd} typically increased by less than 30% above the value of the buffer-independent rate constant, k_0. Between pH 0 and 8, k_0 is constant ($k_0 = 1.80 \times 10^{-5}\ s^{-1}$) so that k_B is taken to $k_0 = 1.80 \times 10^{-5}\ s^{-1}$ in Equation (2).

[13] Except for the 2,4-dinitrophenyl ester; see ref. [8].

[14] The same treatment made with use of the kinetically determined pK_a at 50 °C ($pK_{app} = 1.56$) gave less satisfactory results in the sense that the values of k_{cat} at 0% acid form of trichloro-, dichloro-, and cyanoacetic acid buffers were 8, 15, and 5% of the value of the corresponding slope k_{HA} below zero intercept, respectively. A possible explanation is that the values of the molar fraction α at 50 °C calculated from the kinetically determined (at 50 °C) ionization constant, K_{app}, are less representative of the ionization state of the substrate at 50 °C than are the α values obtained from the spectrophotometrically measured K_a at 25 °C. In acetic acid buffer (pH 4–5) α is unity regardless of whether it was calculated with the K_a or K_{app} value so that the general treatment described in the Supporting Information is not affected ($k_{cat} = k'_{cat} = k_{HA}f_A$), and the plot k'_{cat}/α vs f_A is characterized by a zero intercept at 0% free acid in both cases.

[15] The rate constant for catalysis by the proton falls ca. 0.7 log unit below the line containing the carboxylic acids; see Figure 3.

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[19] At first sight, this is not surprising if one considers that most of the $(E1cB)_{rev}$ reactions that have been studied so far involve anions under conditions where buffers are not sufficiently acidic to protonate the leaving group. According to Jencks's rule,[20] a concerted buffer acid–base catalysis is not expected to show up when pH and pK_a of the

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catalyst AH are above pK_a of the leaving (or attacking) group. However, when the anions S^- are weakly basic (i.e., when pK_a of SH is lower than ca. 3–5) and pK_a of the leaving group (pK_{lg}) is above pK_a of the catalyst (pK_{HA}) and pH, then there should not be, in principle, restrictions for the existence at low pH of a general/specific acid catalysis for leaving-group expulsion from the anionic form of the substrate.

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[26] From the linear Brønsted relationships, $\log k_p$ vs pK_{ROH}, obtained with both the dianions and the monoanions of phosphate[24] and sulfate[25] monoesters, respectively, one may calculate $pK_{ROH_2^+}$ values for which $k_z \geq 10^{13}\ s^{-1}$. This calculation (see ref. [8] for limitation) gives $pK_{ROH_2^+} < -7$ (at 100 °C) for phosphates and $pK_{ROH_2^+} < -9$ (at 100 °C) for sulfates. Assuming that for alcohols and phenols $\Delta pK_a = pK_{ROH} - pK_{ROH_2^+} \approx 17$ (see ref. [8]), the trends obtained in terms of $pK_{ROH_2^+}$ for both ester types would then correspond to $pK_{ROH} <$ ca. 10 for phosphates and $pK_{ROH} <$ ca. 8 for sulfates.

[27] Though there has historically been some disagreement, it now appears well established that the acidic hydrolysis of phosphate monoesters with poor alcohol leaving groups proceeds through the zwitterionic form of the monoanion from which neutral alcohol is expelled in a rate-determining step (corresponding to k_z in Scheme 8).[24, 28] Since kinetic data indicate that sulfate esters hydrolyze by the same mechanistic pathway as phosphates,[25, 29] similar considerations then apply to factors that govern changes in mechanism in hydrolysis of sulfate monoesters in acid.

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[31] No correction was applied for the small error incurred in reading pH values between pH 0 and 1.

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