stirred at 25 °C for 1 h. The excess of peracid was then destroyed by addition of 10% sodium sulfite until a test starch iodide paper was negative. The reaction mixture was then transferred to a separatory funnel and washed with 5% sodium bicarbonate solution and then with water. After the mixture was dried, 2.5 g (74%) of the title compound (mp 182 °C) was obtained which was homogenous on TLC: IR (KBr) 1590, 1520, 1490, 1330, 1285, 1220, 1165, 1125, 1060, 1010 cm^{-1}; ^1H NMR δ 3.78 (4 H, m), 4.75 (4 H, m), 7.60 (2 H, d, J = 9 Hz), 8.38 (2 H, d, J = 9 Hz); mass spectrum, m/e 337. Anal. Calcd for $C_{10}H_{12}O_8PNS$: C, 35.60; H, 3.56; N, 4.15. Found: C, 35.32; H, 3.32; N, 4.28.

Dissociation Constants, pH Measurements, and Kinetic Methods. pK_a and pH measurements were performed on a Toshniwal pH meter preset and standardized with standard buffers by using a glass electrode at 35 °C at an ionic strength of 0.2 (KCl) in 45% dioxan/water medium. pH meter readings were corrected for medium effects by using Irving and Mankot's equation.[14] pK_a's were determined potentiometrically.[15] The dissociation constant of water at 35 °C in 45% water/dioxane is 3.63×10^{-16} M^2.[16] The pD was calculated as pD = pH meter reading + 0.29.[17]

A Pye Unicam 500 spectrophotometer with a thermostated cuvette holder was used for kinetic measurements. All kinetic experiments were performed in 45% (v/v) dioxane/water at 35 ± 0.1 °C at μ = 0.2 (KCl). Stock solutions were prepared in dioxane (1–3 and 5) or in dimethylformamide (4). The hydrolysis rate at pH 8.0 and above was conveniently followed at 405 nm. At low pH, the reaction was monitored by the decrease in absorption at 280 nm and the increase at 320 nm. The rates were calculated[18] by solving the following simultaneous equations (eq 1 and 2). The pHs of the solutions were measured before and

$$A(320) = C_1\epsilon_1 + C_2\epsilon_1 \quad (1)$$

$$A(280) = C_1\epsilon_2 + C_2\epsilon_2 \quad (2)$$

after each kinetic run. They were within ±0.03 pH unit. In order to find the buffer catalysis, we serially diluted buffers, and an appropriate quantity of KCl was added to bring the ionic strength constant.

Acknowledgment. We thank Drs. P. K. Ramachandran and D. K. Jaiswal and Professor M. V. Bhatt for constructive criticism.

Registry No. 1, 80765-36-2; 2, 80765-37-3; 3, 80765-38-4; 4, 80765-39-5; 5, 80765-40-8; *p*-nitrophenyl phosphorodichloridate, 777-52-6; bis(2-hydroxyethyl)methylamine, 105-59-9; thiodiglycol, 111-48-8; 1,5-pentanediol, 111-29-5.

(14) H. M. N. H. Irving and U. S. Mankot, *J. Inorg. Nucl. Chem.*, **30**, 1215 (1968).
(15) A. Albert and B. P. Seargent, "The Determination of Ionization Constants", Chapman and Hall, London, 1971.
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Carboxyl Group Participation in Sulfate and Sulfamate Group Transfer Reactions

Andrew Hopkins and Andrew Williams*

University Chemical Laboratories, Canterbury, Kent, England

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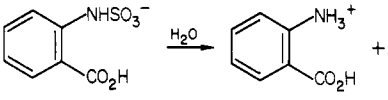
The pH dependence for the hydrolysis of *N*-(2-carboxyphenyl)sulfamic acid exhibits a plateau region corresponding to participation of the carboxyl function. A normal deuterium oxide solvent isotope effect indicates that proton transfer from the carboxylic acid is concerted with sulfamate group transfer to water. Hydrolysis of salicyl sulfate and *N*-(2-carboxyphenyl)sulfamate in ^{18}O-enriched water yields salicylic acid and anthranilic acids with no enrichment, excluding catalysis by neighboring nucleophilic attack on sulfur by the carboxylate group. Intermolecular catalysis by carboxylic acids is demonstrated in the hydrolysis of *N*-(1-naphthyl)sulfamic acid; the mechanism is shown to involve preequilibrium protonation of the nitrogen followed by nucleophilic attack on sulfur by the carboxylate anion. Fast decomposition of the acyl sulfate completes the hydrolysis; this mechanism is considered to be the most efficient but is excluded in the intramolecular case which is constrained by the electronic requirements of displacement at the sulfur atom (6-ENDO-tet).

We are interested in the acid catalysis of sulfamate group transfer from sulfamates to acceptor nucleophiles as a mild sulfonation method. There is strong evidence that transfer of sulfonate from sulfamates to aqueous or alcohol acceptors involves a preequilibrium protonation of the reagent followed by rate-limiting degradation to yield products (eq 1).[4] We considered the possibility of

$$RNHSO_3^- + H^+ \rightleftharpoons RN^+H_2SO_3^- \xrightarrow{R'OH} RNH_3^+ + R'OSO_3^- \quad (1)$$

intramolecular catalysis of the above sulfation reaction and looked at the kinetics of hydrolysis of *N*-(2-carboxyphenyl)sulfamic acid (eq 2). The effect of carboxyl group



(2)

interaction in analogous salicyl sulfate transfer reactions where sulfonate is transferred from phenolic oxygen is quite complicated although catalysis by the acid group has been demonstrated.[2]

The present study looks at both inter- and intramolecular catalysis of sulfonate group transfer from sulfamates. We demonstrate these mechanisms to be different.

Experimental Section

Materials. Sulfonation of amines was carried out by using the method of Audrieth and Sveda.[3] *N*-(1-Naphthyl)sulfamate was prepared by adding chlorosulfonic acid (4.6 mL) slowly to a stirred solution of 1-naphthylamine (10 g) in chloroform (100 mL) kept below 10 °C with an ice bath. When the addition was

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complete, the precipitate was collected and added to Na_2CO_3 solution (200 mL, 1 M). The solution was extracted three times with ether to remove excess amine and the aqueous layer evaporated; the residue was recrystallized from ethanol/water (95% v/v) and dried in vacuo. Anal. Calcd for $C_{10}H_8NO_3SNa$: C, 49.0; H, 3.2; N, 5.7; S, 13.1. Found: C, 48.8; H, 3.3; N, 5.8; S, 12.9.

Disodium *N*-(2-carboxyphenyl)sulfamate was prepared by hydrolysis of sodium *N*-[2-(methoxycarbonyl)phenyl]sulfamate with 1 equiv of NaOH. Methyl anthranilate (15 mL) was reacted with chlorosulfonic acid (3.8 mL) to yield the sulfamate. The residue from hydrolysis was recrystallized from ethanol/water (85% v/v) and dried in vacuo. Anal. Calcd for $C_7H_5NO_5SNa_2$: C, 32.2; H, 1.9; N, 5.4; S, 12.2. Found: C, 32.2; H, 2.0; N, 5.2; S, 12.0.

Salicyl sulfate was prepared by the method of Burkhardt.[3b] Structures of the substrates were confirmed by using infrared (Perkin-Elmer 297 instrument) and NMR (JEOL 100-MHz machine) spectroscopy. We are grateful to Dr. D. O. Smith for running the NMR spectra.

Carboxylic acid buffers were prepared from standard laboratory reagents by using either the redistilled acid or dried sodium salt. Deuterium oxide (99.8% D) and a solution of DCl in D_2O were obtained from Merck Sharp and Dohme Ltd. Acetonitrile was dried and glass distilled from P_2O_5. $NaClO_4$ and $HClO_4$ were of AnalaR grade and were used without further purification.

Methods. Buffers were prepared with 1 M ionic strength and a fraction of base (FB) of 0.5 and 0.2 and were diluted with KCl (1 M) to vary the concentrations while maintaining the ionic strength. Buffers with pH 0–3 were prepared from HCl (1 M) and KCl (1 M). Kinetic measurements at 10 M ionic strengths were made by using perchlorate buffers. Measurement of pH was carried out by using a Radiometer pH meter (PHM 62) to ±0.02 units, and this instrument was calibrated with E.I.L. standard pH buffer solutions.

The substrate (3–4 mg) was dissolved in water (1 mL) and was added (25 μL) to the buffer (2.5 mL) in the silica cell in a temperature-controlled cell compartment of a Unicam SP 800 UV machine. The reaction was followed by repetitive scanning to determine the best wavelength for kinetic study. Kinetics were measured at a constant wavelength, and the decrease in absorbance was recorded by using a Servoscribe potentiometric recorder. Accurate start points were obtained by activating the recorder at the precise moment of mixing. The substrate was introduced on the flattened tip of a glass rod which was "pumped" rapidly three times in the solution in the cuvette. Pseudo-first-order rate constants were obtained by plotting $A_t - A_\infty$ vs. time on semilogarithmic graph paper. Infinity values were generally obtained by calculation from eq 3, where A_1, A_2, and A_3 are the absorbancies

$$A_\infty = (A_2 - A_1)^2/(2A_2 - A_3 - A_1) \quad (3)$$

at t_1, t_2, and t_3 such that $t_2 - t_1 = t_3 - t_2$. It was shown, by allowing the reaction to go to completion in selected cases, that the kinetics were accurately pseudo first order. Routinely the reactions were allowed to proceed to at least 80% of the total.

At pH values greater than 2 the rate constants were slow, and here the pseudo-first-order rate constants were computed from initial rates divided by the overall change in absorbance. The latter value was obtained by allowing an aliquot of substrate to hydrolyze quickly at low pH at a smaller volume and then adjusting the pH and volume to that at the higher pH.

Product analysis was carried out by comparing the product UV spectrum with that of the parent amine at the same concentration.

Deuterium Oxide Solvent Isotope Effects. Deuterium chloride solution was standardized by titration against standard KOH. Dichloroacetic acid buffer (FB = 0.2) was prepared by the addition of DCl (1 M) to sodium dichloroacetate in D_2O. Measurement of the pD was by use of a pH meter and eq 4.

$$pD = \text{meter reading} + 0.37 \quad (4)$$

Measurement of pK. The sulfamate stock solution (25 μL) was added to 2.5 mL of KCl solution (1 M) in a silica cell in the thermostated cell compartment (50 °C) of an SP-500 UV–vis spectrophotometer. The contents of the cell were stirred by a magnetic stirrer constructed as described elsewhere.[4] The pH was varied by the addition of 1 M HCl through a micropipet, and the absorbance values were measured as a function of the pH registered by a microprobe in the cell. The results were fitted to a normalized curve by using two-cycle semilogarithmic graph paper.

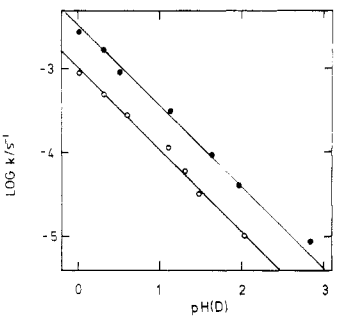


Figure 1. Hydrolysis of *N*-(1-naphthyl)sulfamate in HCl (○) and DCl (●) buffers at a 50 °C and 1 M ionic strength. The lines are theoretical from $k_H = 9.6 \times 10^{-4}$ M^{-1} s^{-1} and $k_D = 2.7 \times 10^{-3}$ M^{-1} s^{-1}.

Labeling Experiments with ^{18}O-Enriched Water. Salicyl sulfate (0.5 g) was kept at pH 3.55 at 50 °C in water (10 mL) with ^{18}O enrichment at 2.03% or 5.796%. The pH was monitored and held at 3.55 with ^{18}O-enriched NaOH or HCl in enriched water. As judged from the published kinetics,[2] the reaction was complete after 6 days, and the precipitated salicyclic acid was collected and recrystallized from water. The product had a melting point of 157–158 °C (lit.[5] mp 159 °C).

Disodium *N*-(2-carboxyphenyl)sulfamate (0.5 g) was kept in enriched water at pH 2.22 for 46 h with adjustment of pH. The mixture was then adjusted to pH 3 and extracted with ether, and the ether was evaporated to yield anthranilic acid which was recrystallized from water; mp 144–146 °C (lit.[5] mp 146–147 °C). Mass spectral analysis was carried out by Mr. P. Smith under the supervision of Dr. J. F. J. Todd on an AEI MS 902 high-resolution mass spectrograph.

Results

Kinetic Methods. Repetitive UV spectral scanning during the progress of the hydrolyses indicated tight isosbestic wavelengths consistent with simple 1:1 stoichiometry. Product analysis showed that the UV spectra of the substrates all returned to those of the parent amines. The rate constants were accurately pseudo first order over at least 80% of the reaction. The rate constants for the hydrolysis of sodium *N*-(1-naphthyl)sulfamate are linearly dependent on hydrogen ion concentration from pH 0 to 3 and possess an inverse deuterium oxide solvent isotope effect ($k_H/k_D = 0.36$). The data are illustrated in Figure 1 and agree with those of Spillane, Regan, and Scott.[6]

The pseudo-first-order rate constants were linear in carboxylic acid concentration (Figure 2) and gave intercepts at zero buffer concentration consistent with those calculated from the oxonium ion catalysis in HCl buffers. The acid component of the buffer system was shown to be responsible for the catalysis by carrying out the reaction at different pH's for the dichloroacetic acid buffer. The acid catalytic term (k_A) derived by assuming the absence of base catalysis was 1.07×10^{-4} M^{-1} s^{-1} at FB = 0.2 and 0.91×10^{-4} M^{-1} s^{-1} at FB = 0.5; these are within the experimental error, and we therefore analyzed the data for the other acids in terms of only acid catalysis. The catalytic terms (Table I) together with that for proton catalysis obey a Brønsted relationship with slope $\alpha = 0.67$ (Figure 3). The deuterium oxide solvent isotope effect on dichloroacetic acid catalysis ($k_A^H/k_A^D = 1.44$) should strictly be regarded as a lower limit as the effect of changing the

(5) R. C. Weast, Ed., "Handbook of Chemistry and Physics", The Chemical Rubber Co., Cleveland, OH, 1970–1971, p C-53.
(6) W. J. Spillane, N. Regan, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 445 (1974).

Table I. Catalysis of the Hydrolysis of *N*-(1-Naphthyl)sulfamic Acid by General Acids[a]

acid	p*K*	$10^4 k_A$, M^{-1} s^{-1} [b]	FB	*N*[e]
oxonium ion	−1.7	9.6 (27)[c,f]		7 (7)[f]
trifluoroacetic acid	0.27	4.89	0.5	4
trichloroacetic acid	0.65	3.09	0.5	4
dichloroacetic acid	1.31 (1.76)[d]	0.96 (0.63)[c,g]	0.2, 0.5, (0.2)	8 (4)
cyanoacetic acid	2.43	0.11	0.5	3[h]
chloroacetic acid	2.86	0.076	0.5	3[h]
cacodylic acid monocation	1.57	0.51	0.42	4

[a] 50 °C, ionic strength maintained at 1 M with KCl. [b] Wavelength for study was 306 nm. [c] Result for deuterium oxide solvent. [d] pK^D. [e] Number of data points. [f] k_H/k_D = 0.36. [g] k_A^H/k_A^D = 1.5. [h] Determined by the method of initial rates.

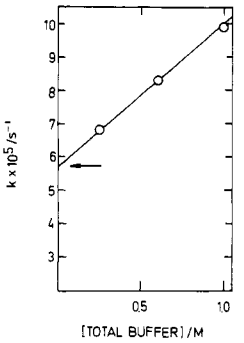


Figure 2. Dependence of the hydrolysis of *N*-(1-naphthyl)-sulfamate on dichloroacetic acid concentration at 50 °C and 1 M ionic strength (pH 1.31 and FB = 0.5). The line is theoretical from the data in Table I, and the arrow denotes the intercept expected from data from Figure 1 (pH constant at 1.31).

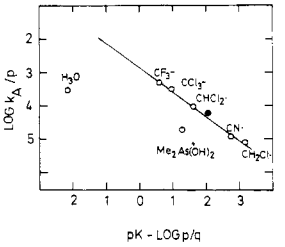


Figure 3. Brønsted dependence of the acid-catalyzed hydrolysis of *N*-(1-naphthyl)sulfamate at 50 °C and 1 M ionic strength (● = dichloroacetic acid in deuterium oxide). The line is theoretical (log k_A = 0.67p*K* − 3.0).

dichloroacetic acid buffer concentration (in D_2O) is greater than the effect of altering the acetonitrile concentration (a nonacidic analogue of the dichloroacetic acid) but is of the same order of magnitude. Over a range of 0.8 M the change in rate constant is 18% for the acid and 5% for the acetonitrile (see Figure 4). We are reasonably confident that the 18% change is real and hence that the isotope effect is close to the lower limit because the k_A^D could be an upper limit.

The pH dependence of the hydrolysis of disodium *N*-(2-carboxyphenyl)sulfamate (Figure 5) indicates a plateau region from pH 1.2 to 2. The kinetics obey a rate law (eq 5) The steric explanation of the plateau is excluded by

$$k_{obsd} = (k_P + k_H a_H)/(1 + K/a_H) \quad (5)$$

measuring the pH dependence of the hydrolysis of sodium *N*-[(2-methoxycarbonyl)phenyl]sulfamate which is shown in Figure 5. The pD dependence of the hydrolysis of the anthranilate derivative exhibits no inflection over a range of pD covering the p*K* of the acid in deuterium oxide (2.53). Since no inflection is seen in the pD dependence, we may calculate that the plateau region for the deutero species should be less than that for the protio species by an amount equal to antilog ($pK^D - pK^H$); thus k_P^H/k_P^D = 2.88. Measurements carried out at high ionic strength (10 M in perchlorate buffers) show a rate constant dependent on an apparent ionization with p*K* = −0.3. The p*K* of the *N*-(2-carboxyphenyl)sulfamate (CO_2H, CO_2^-) in water was found to be 2.07.

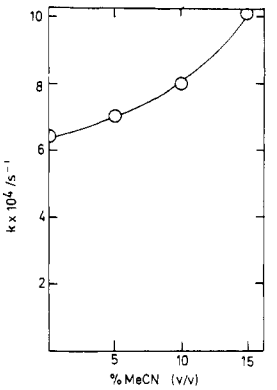


Figure 4. Dependence on acetonitrile concentration of the hydrolysis of *N*-(1-naphthyl)sulfamate in HCl buffer at pH 0.3, 50 °C, and a 1 M ionic strength. The molarities at 5%, 10%, and 15% MeCN are 0.96, 1.91, and 2.87, respectively.

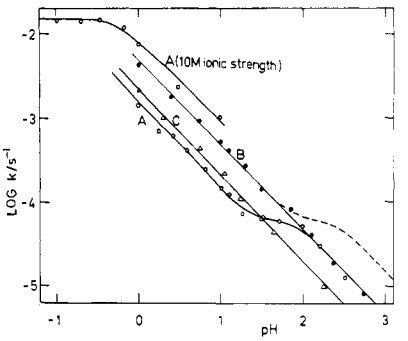


Figure 5. pH dependence of the hydrolysis of *N*-(2-carboxyphenyl)sulfamate in water (A), deuterium oxide (B), and *N*-[2-(methoxycarbonyl)phenyl]sulfamate (C) at 50 °C and a 1 M ionic strength. The dashed line represents the pD profile expected for the anthranilate derivative obeying the ambiguous rate law involving proton attack on the dianionic species (see text). Other lines are theoretical: A (from eq 5) $k_P = 7.1 \times 10^{-5}$ s^{-1}, $k_H = 1.36 \times 10^{-3}$ M^{-1} s^{-1}, $K = 10^{-2.07}$; B, $k_D = 4.18 \times 10^{-3}$ M^{-1} s^{-1}; C, $k_H = 2.0 \times 10^{-3}$ M^{-1} s^{-1}.

Oxygen-18 Labeling Studies. Table II collects the mass spectral results for anthranilic acid and salicyclic acid from hydrolysis in ^{18}O-labeled water. The results indicate that oxygen-18 is not incorporated into either of the two acids in amounts greater than the experimental error during their formation from sulfamate or sulfate.

Discussion

Intramolecular Mechanism. The rate constant for the hydrolysis of *N*-(2-carboxyphenyl)sulfamic acid at very low pH fits an ionization mechanism where an acid of p*K* = −0.3 decomposes in a rate-limiting step. The apparent

Table II. Oxygen-18 Labeling Studies[e]

product acid	% ^{18}O in H_2O	% ^{18}O in product acid	A^a	B^b
salicylic acid	2.03	1.091	0.871	2.874
	5.796	0.930	0.871	6.667
	d	0.870[c]		
anthranilic acid	2.03	0.720	0.696	2.726
	5.796	0.715	0.696	6.492
	d	0.710[c]		

[a] Calculated from published isotopic abundances[f] for no incorporation. [b] Calculated from published natural abundances[f] and the enrichment of the added water by assuming full incorporation. [c] Control sample of natural abundance. [d] Natural abundance. [e] Comparison of control sample[c] with calculated isotope enrichment $(A)^a$ gives a good measure of the errors in these experiments. [f] R. C. Weast, Ed., "Handbook of Chemistry and Physics", 51st ed., section B247, The Chemical Rubber Company, Cleveland, OH, 1970-1971, p B-247.

pK determined kinetically is close to that which may be calculated (0.95)[7] for zero ionic strength at 25 °C. The difference in conditions we believe is sufficiently great for there to be a good correspondence between calculated and observed values and thus with the ionization mechanism (eq 1). The inverse deuterium oxide solvent isotope effect for the proton-catalyzed hydrolysis of the anthranilate derivative is in accord with the results of previous work[6,8,9] and is consistent with rate-limiting decomposition of the N-protonated species.

The plateau rate constant k_P (eq 5) is kinetically ambiguous and could involve proton catalysis of the dianionic species or decomposition of the anionic form containing a 2-carboxylic acid group. We may resolve this ambiguity by considering the deuterium oxide solvent isotope effect for the monoanion (k_P^H/k_P^D = 2.88). The alternative kinetic formulation, namely, proton attack on dianion, should yield an inverse isotope effect which is calculable from the inverse isotope effects observed for proton attack on other sulfamates. The rate constants for the two ambiguous forms are connected by eq 6, where k_H is the

$$k_P^H = k_H K^H \quad (6)$$

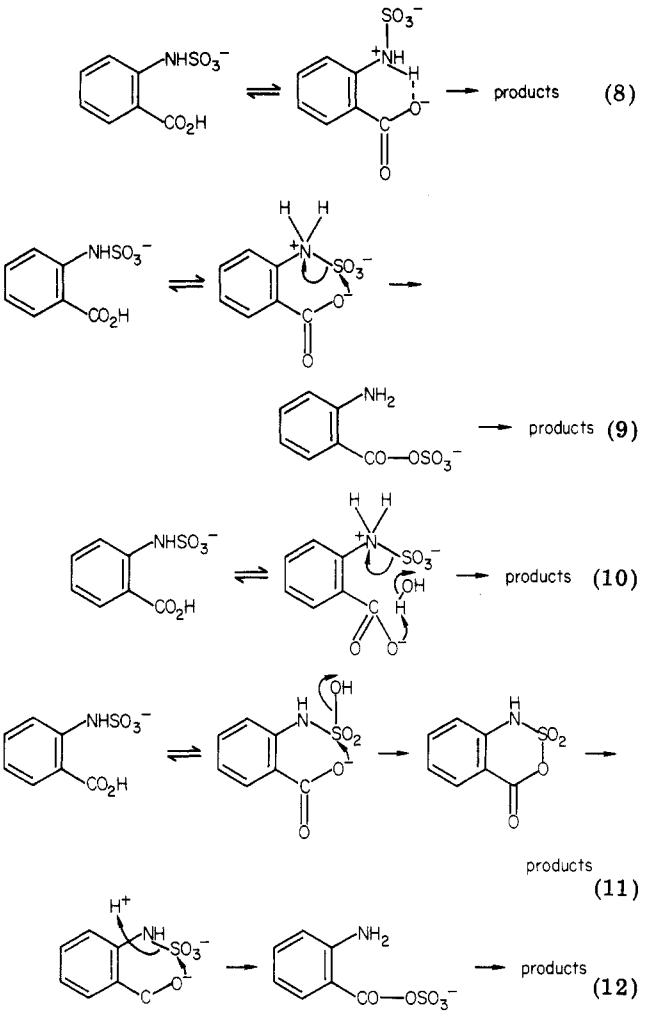
second-order rate constant for proton attack on the dianionic sulfamate and K^H is the ionization constant (in water) of the carboxylic acid. The deuterium oxide solvent isotope effect for k_P is thus given by eq 7. The value of k_H/k_D

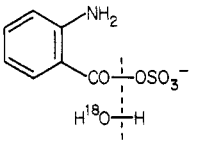
$$k_P^H/k_P^D = k_H/k_D(K^H/K^D) \quad (7)$$

(0.32) may be obtained from the isotope effect on proton attack on *N*-(1-naphthyl)sulfamate acid and K^H/K^D (2.88) is measurable. The final value, k_P^H/k_P^D calculated to be 0.92 thus excludes the dianionic ambiguity. The theoretical curve for the rate constants obeying the dianionic ambiguity is illustrated in Figure 5.

Benkovic[2] has set out the possible mechanisms for carboxyl group interaction in the degradation of salicyl sulphate; these are outlined (Scheme I) for the case of the anthranilic acid derivative. Mechanisms 9 and 12 are excluded by the absence of ^{18}O enrichment in the product anthranilic acid from hydrolysis in enriched water (Table II). Benkovic and Hevey[10] showed that exclusive C–O fission of acetyl sulfate occurred in water. Thus the intermediate product in eq 9 and 12 should add ^{18}O-enriched water to give anthranilic acid labeled on the carboxylate (structure I).

Scheme I





I

Mechanism 11 and a similar one involving attack of the sulfate oxygen on the carboxyl group were eliminated for the salicyl sulfate by Benkovic[2] by the observation that these require hydroxide ion to be expelled by carboxylate or sulfate ion; the same arguments apply to the *N*-(2-carboxyphenyl)sulfamic acid case. The displacement of very basic leaving groups by weakly basic nucleophiles is only known where factors other than basicity are involved. For example, Aldersley, Kirby, and Lancaster[11] indicate that the carboxylate of methyl hydrogen diisopropyl maleate rapidly expels the methoxide ion; the driving force for this reaction is probably the formation of the very stable maleic anhydride and the steric repulsion of the isopropyl groups in the ground state. Bender and Lawlor[12a]

(7) The pK of the N-protonated *N*-(2-carboxyphenyl)sulfamic acid is estimated by using the method of J. Fox and W. P. Jencks [*J. Am. Chem. Soc.*, **96**, 1436 (1974)] for ammonium ions (σ_I = 8.4), $\sigma_I^{-SO_3^-}$ = 0.13 [M. Charton, *J. Org. Chem.*, **29**, 1222 (1964)], and the pK for anthranilic acid (2.04).

(8) W. J. Spillane, N. Regan, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1424 (1976).

(9) J. P. Candlin and R. G. Wilkins, *J. Am. Chem. Soc.*, **87**, 1940 (1965).

(10) S. J. Benkovic and R. C. Hevey, *J. Am. Chem. Soc.*, **92**, 4971 (1970).

(11) M. F. Aldersley, A. J. Kirby and P. W. Lancaster, *J. Chem. Soc., Perkin Trans. 2*, 1504 (1974).

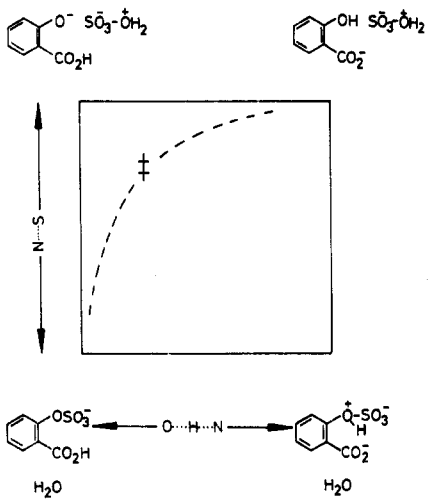


Figure 6. Free-energy three-dimensional contour diagram for the hydrolysis of salicyl sulfate. Contours are omitted for clarity, and the four corners represent the structures shown. The free-energy three-dimensional contour diagram for the hydrolysis of *N*-(2-carboxyphenyl)sulfamate is similar to that for the salicyl ester except that nitrogen replaces the phenolic oxygen: bottom right, $ArN^+H_2SO_3^-$; top right, $ArNH_2$; top left, $ArNH^-$; bottom left, $ArNHSO_3^-$. The transition-state (‡) is in the bottom right segment for the sulfamate.

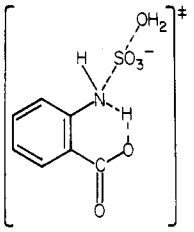
excluded the above mechanisms for salicyl phosphate by labeling studies.

The mechanism of eq 10 may be excluded in the case of salicyl sulfate by the deuterium oxide solvent isotope effect.[2] In the anthranilate derivative we can calculate that the intermediate carboxylate anion–zwitterion (see eq 10) would decompose at approximately the same rate in water as in deuterium oxide because the pH–pD profiles coincide above the $pK^{H(D)}$ of the anthranilate derivative.[12b]

At this point we can exclude the mechanisms of eq 9 and 12 for the salicyl sulfate hydrolyses (see Benkovic)[2] by the observation that ^{18}O-enriched salicylic acid is not recovered from hydrolyses carried out by using enriched water (Table II). A similar experiment excluded these mechanisms for salicyl phosphate.[12a]

Results of Bromilow and Kirby[13] indicate that the salicyl phosphate hydrolysis involves very little proton transfer from the carboxyl to the phenolic oxygen in the transition state. This is consistent with a mechanism passing through a transition state possessing considerable phenolate ion character. We believe that the salicyl sulfate has a similar reaction coordinate. The free-energy surface for the salicyl sulfate reaction is illustrated in Figure 6; the bottom-right energy is likely to be high owing to the unfavorable proton transfer involved whereas the top-left energy is relatively low due to the negative charge residing on phenolic oxygen. The resultant surface is thus "skewed" so that the reaction coordinate passes close to the top-left corner.

The major contribution to the *N*-(2-carboxyphenyl)-sulfamic acid plateau is from the mechanism of eq 8; the substantial deuterium oxide solvent isotope effect is consistent with rate-limiting proton transfer, and the rate constant k_P is many orders of magnitude less than that expected[14] for a proton transfer from heteroatoms with $\Delta pK \approx 4$ in the "uphill" direction ($\sim 10^6$ s^{-1} at 25 °C), and we thus exclude a simple proton transfer as the rate-limiting step. A proton transfer concerted with water attack at the sulfamate group (structure II) is favored by the present results.



II

The three-dimensional free-energy diagram for the anthranilate hydrolysis will differ from that proposed for the salicylate because the anion (NH^-) corresponding to that in the salicylate (O^-) is much less stable. The surface will thus be "skewed" but in the direction favoring the bottom-right corner so that the transition state will correspond to a proton "in flight" rather than to one fully transferred.

Intermolecular General-Acid Catalysis. The rate law for general carboxylic acid catalyzed hydrolysis of sodium *N*-(1-naphthyl)sulfamate is ambiguous (eq 13 and 14). The low value of k_A^H/k_A^D for dichloroacetic acid (for

$$\text{rate} = k_A[ArNHSO_3^-][RCO_2H] \quad (13)$$

$$\text{rate} = k'[ArNH_2{}^+SO_3^-][RCO_2^-] = k_A(K^{NH}/K^{HA}) \quad (14)$$

eq 13) is only consistent with complete or zero proton transfer in the transition state of the rate-limiting step and this is not expected on the basis of the intramolecular reaction above. The isotope effect for k' is given by the relationship in eq 15; the value of K^{NH}/K^{ND} is likely to be

$$k'_H/k'_D = k_A^H/k_A^D(K^{NH}/K^{HA})(K^{DA}/K^{ND})$$
$$k' = 0.5K^{NH}/K^{ND} \quad (15)$$

not very much greater than unity as N-protonated *N*-arylsulfamate is a strong acid. Thus k'_H/k'_D is probably close to 0.5, consistent with the preequilibrium mechanism (eq 14) where the N-protonated sulfamate reacts in a rate-limiting step with carboxylate anion. The β_N value for attack (1 − 0.67 = 0.33) is entirely consistent with the β_N for attack of oxyanions on tertiary amine sulfonates.[15] The value of log k_A for carboxylic acids shows an excellent correlation with pK, but those for cacodylic acid (monocation) and oxonium ion do not correlate well; this is consistent with the specific acid nucleophilic mechanism rather than with the simple general-acid mechanism.

It is possible to calculate the rate constant for reaction of acetate ion with the protonated *N*-(1-naphthyl)sulfamic acid by using k_{HOAc} (6.2×10^{-7} M^{-1} s^{-1}) from the Brønsted type relationship of Figure 3 and the pK^{NH} of the zwitterionic sulfamate (−0.3). The value (3.9×10^{-2} M^{-1} s^{-1}) at 50 °C is close to that for acetate ion attack on a pyridine-*N*-sulfamate (at 25 °C), with a pK similar to that of the 1-naphthylamine (1.56×10^{-2} M^{-1} s^{-1}).[16] We do not

(12) (a) M. L. Bender and J. M. Lawlor, *J. Am. Chem. Soc.*, **85**, 3010 (1963). (b) A referee has pointed out that distinction between mechanisms 10 and 8 might not be clear-cut; carboxylate-catalyzed attack of water in the hydrolysis of dichloroacetyl salicylate has $k_H/k_D = 2.2$.[12c] If preequilibrium protonation at nitrogen has a K^H/K^D of 0.36 (Table I for naphthyl sulfonate), then k_p^H/k_p^D may be calculated to be 0.8 which is close to the observed unity. This ambiguity might be solved by proton inventory techniques with mixed D_2O/H_2O solvent. (c) S. S. Minor and R. L. Schowen, *J. Am. Chem. Soc.*, **95**, 2279 (1973).

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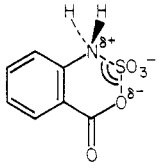
(15) A. Hopkins and A. Williams (unpublished observations, 1981) found $\beta_N = 0.23$ for attack of phenolate ions on isoquinoline-*N*-sulfonate.

(16) A. Hopkins and A. Williams (unpublished observations, 1981) found that pyridine-*N*-sulfonate has a rate constant of 1.17×10^{-3} M^{-1} s^{-1} for reaction with acetate at 25 °C. A reasonable β_{LG} of 0.9 is assumed for calculation of the rate constant of reaction of acetate with the pyridine derivative of the appropriate basicity.

believe that the difference which will exist for these rate constants at the same temperature excludes the proposed mechanism as there are hydrogen bonding solvation differences which must be taken into account in the ground and transition states.[17] It can also be shown that the model for the proton-catalyzed hydrolysis of *N*-arylsulfamates, namely, the attack of water on pyridine-*N*-sulfonates, also reacts faster than the zwitterionic sulfamate. The energy difference between the model and the arylsulfamate is the difference in solvation energy between the transition and ground state in both water and acetate ion attack. This is likely to be less for the transition state where the aniline acidity is less than the acidity in the anilinium ion ground state.

The mechanistic difference demonstrated for inter- and intramolecular catalysis by the carboxyl group is in our opinion due to a stereoelectronic phenomenon. We believe that the intermolecular mechanism is the preferred one but that this is excluded in the intramolecular case by the stereoselectronic requirements of attack by nucleophiles on the sulfur which is collinear with entering and leaving atoms. The six-membered-ring transition state for eq 9 and 12 (6-endo-tet) requires a deviation of about 70° from collinearity (structure III). Similar constraints have been observed to suppress endocyclic S_N reactions at saturated carbon[18,19] because the preferred backside attack is not possible in small rings.[20]



III

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Registry No. sodium *N*-1-Naphthyl sulfamate, 35525-93-0; disodium *N*-(2-carboxyphenyl)sulfamate, 81044-28-2; salicyl sulfate, 89-45-2; sodium *N*-[(2-methoxycarbonyl)phenyl]sulfamate, 81044-29-3.

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Electrophilic Heteroaromatic Substitutions. 5.[1] Acid-Catalyzed Reaction of Ethyl 3,4,5-Trimethylpyrrole-2-carboxylate with Diazonium Salts in Aqueous Acetic Acid[2]

Silvia De Donatis, Maria Teresa Giardi,[3] and Giancarlo Sleiter*

Centro di Studio CNR sui Meccanismi di Reazione, c/o Istituto di Chimica Organica, Università di Roma, I-00185 Roma, Italy

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The reaction with diazonium salts of the title compound, 1, has been examined in detail by chromatographic and spectroscopic methods. In the presence of a strong mineral acid, 1 reacts with *p*-nitrobenzenediazonium ions to give a red, chemically labile, azo dye, 4, in equilibrium with its orange conjugated base 3. Both 3 and 4 slowly undergo α-demethylation in the aqueous reaction medium, affording ethyl 3,4-dimethyl-5-[(*p*-nitrophenyl)azo]pyrrole-2-carboxylate (2), identified by comparison with an authentic specimen. Thus, for the first time, conclusive experimental evidence for α-dealkylation by diazonium ions in monopyrrole derivatives has been obtained. This dealkylation reaction seems to be especially favored by the electron-withdrawing ability of the *p*-nitro group. The red azo dye (analogous to 4) formed when 1 reacts with diazotized sulfanilic acid in the presence of strong acids reverts to the reactants on dilution of the reaction mixture with water. A structure for 4 is proposed, and possible reaction mechanisms are discussed.

The reaction of pyrrole derivatives with diazonium salts has received considerable attention. Besides conventional diazo coupling,[4] a few nonconventional processes have been reported, including α-side-chain substitution[5] and dealkylation reactions.[6-8] Dealkylations are well established in polypyrrolic chemistry (e.g., dipyrrylmethane derivatives), and mechanisms have also been proposed[6b,8] for

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(3) Area della Ricerca di Roma, Laboratorio CNR di Radiobiochimica ed Ecofisiologia Vegetali, I-00016 Monterotondo Scalo, Roma, Italy.

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