an enthalpy effect. Thus there appears a tendency toward compensation, demanding that solvation effects must be considered in explaining the phenomena.[3,4b]

The similarity between phosphate and sulfate esters as revealed in this study does not allow one to speculate on biological mechanisms. Nevertheless, it is intriguing to ask whether there is any dual functionality in the sulfatase and phosphatase hydrolytic enzymes; if none, what mechanistic differences prevail in the enzymic reactions? Of equal importance are model studies directed at uncovering such differences. Our future research is in both directions.

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Studies on Sulfate Esters. II. Carboxyl Group Catalysis in the Hydrolysis of Salicyl Sulfate

Stephen J. Benkovic

Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received August 8, 1966*

Abstract: The pH–rate profile for the hydrolysis of salicyl sulfate reveals hydronium ion and intramolecular carboxyl group catalysis. In contrast the rate of hydrolysis of *p*-carboxyphenyl sulfate is accelerated only by hydronium ion. The acid-catalyzed hydrolysis of aromatic sulfates is viewed as an A1 mechanism on the basis of activation entropies and D_2O solvent isotope and substituent effects. Intramolecular carboxyl group participation is discussed in terms of general acid or specific acid nucleophilic catalysis and compared to other examples involving similar behavior including salicyl phosphate.

In our continuing investigations of the hydrolytic chemistry of sulfate esters it became desirable to investigate a possible intramolecular system since such would more closely resemble an enzyme–substrate complex and experimentally might provide rates of greater magnitude. Suitable juxtaposition of a possible catalytic group might then allow observation of general acid–base catalysis or its kinetic equivalent, even though such behavior was not observed in bimolecular systems.[1] Moreover, it is of interest to determine the boundaries on the apparent analogies between the hydrolytic mechanisms of phosphate and sulfate esters.

Experimental Section

Materials. The *o*- and *p*-carboxyphenyl sulfates were prepared by the method of Burkhardt, *et al.*,[2a,b] modified to yield the dipotassium salt.[3] Kinetic solutions were prepared from freshly boiled distilled water. Reagent grade salts and acids (Fisher, Baker) were used without further purification. Deuterium oxide (99.9%) was obtained through the courtesy of Dr. R. A. Olofson of this department. Deuteriochloric acid was prepared from deuterium oxide and anhydrous hydrogen chloride.

Apparatus. All instrumentation was identical with that previously described.[4] Kinetic runs of greater than 12-hr duration were carried out in Kimax (No. 45066) screw-cap tubes maintained at reaction temperature by immersion in a circulating water bath. Shorter runs were conducted in thermostated, 2-cm stoppered cuvettes.

Kinetics. The hydrolysis of salicyl sulfate was monitored at 296 mμ following the increase in absorption due to salicylic acid formation. Reactions were initiated by the addition of 1 ml of salicyl sulfate solution ($3–7 \times 10^{-4}$ *M*; μ = 1.0, KCl) to 9 ml of the buffer solution (0.2 *M* in total buffer species; μ = 1.0, KCl), solutions having been preequilibrated at the desired temperature. Buffers employed were acetate (pH 3.6–5.3) and formate (pH 2.9–3.6); hydrochloric acid was used to prepare solutions of pH <2.5. No buffer effects (tenfold dilution) were noted. The pH of the kinetic runs was measured at 35° upon initiation and after completion of the runs; those exhibiting pH drift greater than ±0.02 unit were discarded.[5a] Identical techniques were employed for the investigation of the hydrolysis of *p*-carboxyphenyl sulfate with *p*-hydroxybenzoic acid formation being monitored at 282 mμ.

The observed first-order rate constants for hydrolysis of salicyl sulfate were calculated from slopes of plots of log $[OD_\infty/(OD_\infty - OD_t)]$ against time for solutions of pH <4.3 followed to at least one half-life (Figure 1). Kinetic runs of pH <2.8 were followed to OD_∞; OD_∞ for those of pH >2.8 were computed from OD_∞ values obtained for reaction solutions at pH <1.0 related by means of standard curves of OD_{296} *vs.* salicylic acid concentration at the corresponding pH values. Rate constants for the hydrolysis of salicyl sulfate at pH >4.3 were obtained from slopes of OD_∞ *vs.* time divided by the computed OD_∞. Duplicate runs agreed within ±5% at pH >2; ±3%, pH <2.

The observed first-order rate constants for the hydrolysis of *p*-carboxyphenyl sulfate were calculated from slopes of plots of log $[(OD_\infty - OD_t)/(OD_\infty - OD_t)]$ (due to initial absorbance by substrate) against time for kinetic runs of pH <1.6; those at higher pH were calculated as initial rates by the method discussed above.

The observed first-order rate constants for the hydrolysis of salicyl and *p*-carboxyphenyl sulfates, calculated as above, were determined in deuterium oxide (35°, μ = 1.0, KCl), the desired pD being obtained through addition of standardized DCl; the corrected pD was calculated from the formula of Fife and Bruice.[5b] Precautions were taken that the solutions remained anhydrous.

Products. Spectrophotometric scanning (225–335 mμ) of salicyl sulfate kinetic solutions at pH's where a greater percentage of the reaction proceeds *via* carboxyl-group catalysis failed to disclose accumulation of any reaction intermediates. The ultraviolet spectra at OD_∞ is identical with that of salicylic acid. The absence of reaction intermediates at significant concentrations is also implied by the lack of any observable lag phase in the kinetics.

Preparative runs (0.06 and 0.1 *M* in salicyl and *p*-carboxyphenyl

(1) J. L. Kurz, *J. Phys. Chem.*, **66**, 2239 (1962).
(2) (a) G. N. Burkhardt and A. Lapworth, *J. Chem. Soc.*, 684 (1926); (b) G. N. Burkhardt, C. Horrex, and D. I. Jenkins, *ibid.*, 1649 (1936).
(3) M. Loeper, J. Cottet, and J. Parrod, *Compt. Rend. Soc. Biol.*, **135**, 917 (1941).
(4) S. J. Benkovic and P. A. Benkovic, *J. Am. Chem. Soc.*, **88**, 5504 (1966).
(5) (a) No correction was applied for the small error incurred in reading pH values between pH 0 and 1. (b) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

Table I. Rate Constants and Activation Parameters for the Hydrolysis of Salicyl and *p*-Carboxyphenyl Sulfate

Compound	Solvent	k_{H^+}, M^{-1} hr^{-1}	k_0, hr^{-1}	ΔH^*, kcal mole^{-1} [b,f]	ΔS^*, eu [b,f]
Salicyl sulfate[c]	H_2O	6.61×10^{-1} [a]		24.8	+4.5
	D_2O	8.60×10^{-1} [a]			
	H_2O		1.78×10^{-2} [a]	26.5	+3.2
	D_2O		1.48×10^{-2} [a]		
p-Carboxyphenyl sulfate	H_2O	1.78×10^{-1} [e]		25.1	+3.2
	D_2O	4.17×10^{-1} [d]			

[a] Calculated from eq 1. [b] Calculated from the equations $\Delta H^* = E_a - RT$; $\Delta S^* = (\Delta H^* - \Delta F^*)/T$; $\Delta F^* = -RT \ln k_r h/kT$ at 35°. See Figure 3 for plots of k_0 and k_{H^+} *vs.* $1/T$. [c] Kinetically determined pK_a' = 3.65 (35°, μ = 1.0); pK_a' by method of half-neutralization, 3.8 ± 0.2 (35°, μ = 1.0). [d] Calculated from plot of log k_{obsd} *vs.* pD; k_{obsd} = 2.43, 2.41 × 10^{-1} hr^{-1} at pD 0.23, k_{obsd} = 1.82 × 10^{-1} hr^{-1} at pD 0.35, k_{obsd} = 1.17 × 10^{-1} at pD 0.51. [e] Calculated from eq 2. [f] Estimated error in ΔH^* = ±1 kcal mole^{-1}; ΔS^* = ±3 eu.

sulfate, pH 0.20, 35°) led to the precipitation of crystalline material at t_∞ identified as salicylic acid (mp 159°) and *p*-hydroxybenzoic acid (mp 213°), respectively.

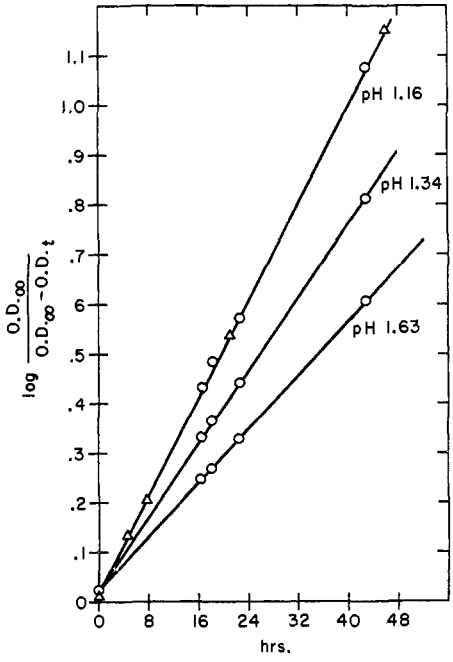


Figure 1. First-order plots of the experimental data for the hydrolysis of salicyl sulfate at various pH values (35°, μ = 1.0). The data at pH 1.16 represent duplicate runs.

Results and Discussion

The pH–rate profile for the hydrolysis of salicyl sulfate (**1**) and *p*-carboxyphenyl sulfate (**2**) are exhibited in Figure 2. Pertinent kinetic data are summarized in Table I. The pH–rate profile of **1** may be conveniently divided into two regions: (1) at pH <1, log k_{obsd} is linear with pH (slope = −1) indicative of hydronium ion catalysis; (2) at pH 2–5, log k_{obsd} is independent then dependent on pH (slope = −1) as expressed by the function $a_H/(K_a' + a_H)$, suggesting involvement of the neighboring carboxyl group. Evidence in support of this contention is furnished by the pH–rate profile of **2** where only hydronium ion catalysis is observed (slope = −1). Values of k_{obsd} for **1** may be calculated from the equation[6]

$$k_{obsd} = k_{H^+}a_H + k_0 a_H/(K_a' + a_H) \quad (1)$$

which provides a satisfactory fit of the data as shown in Figure 1. Evaluation of k_{obsd} for **2** is provided simply by

$$k_{obsd} = k_{H^+}a_H \quad (2)$$

It is convenient to divide the analysis of the results into hydronium ion and intramolecular catalysis.

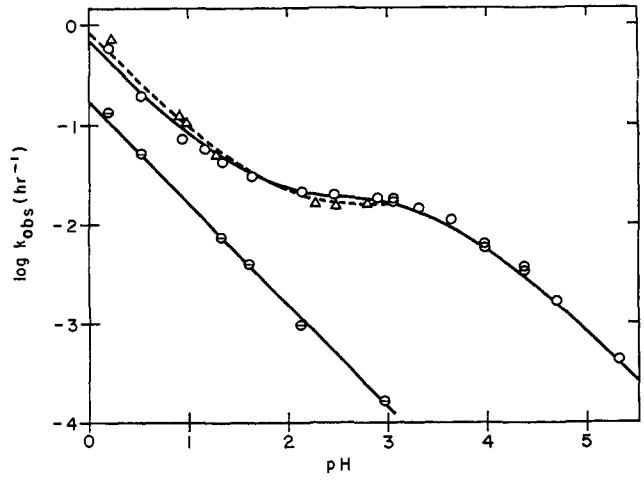


Figure 2. The pH–rate profiles (35°, μ = 1.0) for the hydrolysis of salicyl sulfate (○, H_2O; △, D_2O) and *p*-carboxyphenyl sulfate (⊖, H_2O). Solid lines (H_2O) and dashed line (D_2O) are calculated from data given in Table I.

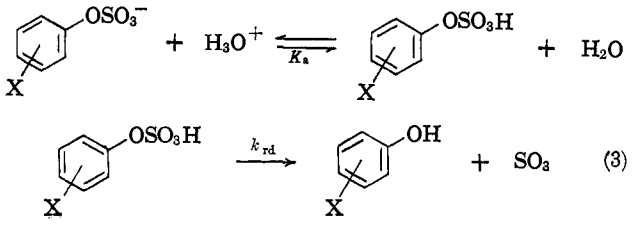
Hydronium Ion Catalysis. The hydrolysis of aromatic sulfates has long been known to be subject to hydronium ion catalysis. The extensive work of Burkhardt and co-workers[7,8] led to several results pertinent to this discussion: (1) the hydronium ion-catalyzed hydrolysis of a series of 12 *ortho*- and *para*-substituted phenyl sulfates increases with increasing electron withdrawal ($\rho \cong +0.5$); (2) the activation entropies are zero or slightly positive; and (3) large substituents (Cl, NO_2) in the *ortho* position may act to increase the rate 1.2–3-fold. The data of Table I indicate that k_{H^+} for **1** and **2** likewise possess positive entropy terms ($\Delta S^* = +3.2$ eu) and that k_{H^+} for **1** is 3.7-fold greater than for **2**.

(6) Values for k_{H^+}, k_0, and K_a' (the kinetically determined pK_a') are listed in Table I; a_H is the activity of hydrogen ion as measured by the glass electrode. A satisfactory fit of the kinetic data is also obtaiend by assuming the plateau rate is associated with a bimolecular term, $k_0' a_H K_a'/(K_a' + a_H)$, where $k_0' = 7.95 \times 10^1$ M^{-1} hr^{-1}.

(7) (a) G. N. Burkhardt, W. G. Kenneth Ford, and E. Singleton, *J. Chem. Soc.*, 17 (1936); (b) G. N. Burkhardt, A. G. Evans, and E. Warhurst, *ibid.*, 25 (1936).

(8) G. N. Burkhardt, C. Horrex, and D. I. Jenkins, *ibid.*, 1649, 1654 (1936).

The acid-catalyzed hydrolysis is faster in D_2O than H_2O, $k^{H_2O}/k^{D_2O} = 0.78$ (**1**) and $k^{H_2O}/k^{D_2O} = 0.43$ (**2**). In general, A1 mechanisms, which involve rapid pre-equilibrium protonation of substrate followed by rate-determining unimolecular decomposition, give rise to similar effects. The acid-catalyzed hydrolyses of acetals and ketals for which the accepted mechanism is A1 are characterized by ratios of $k^{H_2O}/k^{D_2O} = 0.5$ and positive ΔS^* values.[9-14] In contrast, in A2 reactions, where the protonated intermediate breaks down through rate-determining attack by water, as, for example, the acid-catalyzed hydrolysis of cyclic and aryl sulfites, the value of k^{H_2O}/k^{D_2O} ranges from 0.6–0.7 and ΔS^* is generally less than −20 eu.[15-17] The accumulated data therefore appear to be in accord with an A1 mechanism involving protonation of the ester followed by elimination of sulfur trioxide which then undergoes rapid hydrolysis. It is apparent that $k_{H^+}{}^{H_2O}/k_{H^+}{}^{D_2O}$



$$SO_3 + H_2O \xrightarrow{\text{fast}} H_2SO_4$$

$$k_{H^+} = k_{rd}/K_a \qquad (3a)$$

for salicyl sulfate falls in the range of an A2 mechanistic classification. However, the existence of slight acceleratory *ortho* effects, which for substituents incapable of hydrogen bonding are presumably steric in origin,[18] definitely implies interactions between the sulfate moiety and the *ortho* substituent. With the *o*-COOH, hydrogen-bonding effects may occur in (1) the preequilibrium step of eq 3a, lowering the pK_a' of the sulfate, thereby generally increasing the ratio of $K_a{}^{D_2O}/K_a{}^{H_2O}$;[19] and/or (2) the rate-determining step where disappearance of reorganization of hydrogen bonds may increase $k_{rd}{}^{H_2O}/k_{rd}{}^{D_2O}$.[20]

The above entropies of activation and solvent deuterium isotope effects do not distinguish between the conventional A1 mechanism of eq 3 and one involving rate-limiting proton transfer.[21-23] But in the present situation the rate constant for protonation of the sulfate moiety may be calculated from

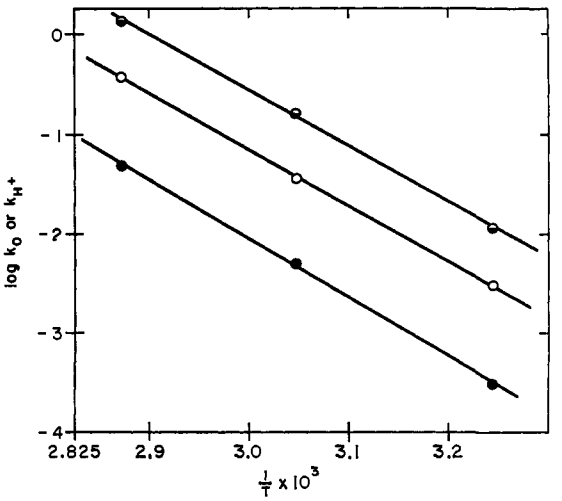


Figure 3. Plots of the logarithms of k_{H^+} (M^{-1} min^{-1}) and k_0 (min^{-1}) *vs.* $1/T$ (35, 55, 75°): salicyl sulfate (k_{H^+}, ◒) and (k_0, ●); *p*-carboxyphenyl sulfate (k_{H^+}, ○). Values of k_{H^+} and k_0 (55, 75°) for salicyl sulfate determined from duplicate runs at pH 0.54 and 2.46, respectively. Values of k_{H^+} (55, 75°) for *p*-carboxyphenyl sulfate determined from runs at two pH values.

$$ROSO_3^- + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ROSO_3H + H_2O \qquad (4)$$

where $k_1 = k_{-1}/K_a'$. Assuming k_{-1} to be diffusion controlled, 10^{11} sec^{-1} (this order of magnitude is observed for proton transfers involving strong acids in aqueous solution[24,25]), an untenable value of K_a' must be employed in order for k_1 to approach k_{H^+}. Moreover the negative ρ may only be rationalized in terms of the kinetic importance of the second step in eq 3. Thus we exclude k_1 as being rate-determining and favor operation of the conventional A1 mechanism in aromatic sulfate ester hydrolysis. Similar conclusions have been reached for the acid-catalyzed hydrolysis of alkyl sulfates which proceed *via* S–O bond cleavage.[26a] The A1 mechanism is also in accord with arguments based on microscopic reversibility[26b] since there is some evidence that sulfur trioxide may be the reactive species in aromatic sulfation.[27,28]

It is of interest to attempt to locate the site of protonation of the sulfate moiety. Studies on the rates of solvolysis of steroid sulfates and sulfamic acid in mixed aqueous solvents reveal a striking acceleration in systems of low water content.[29-31] Recently Batts[26a] has reported that the rate of acid-catalyzed hydrolysis of methyl sulfate is increased 1.63×10^7-fold in changing from pure water to 1.9% H_2O–98.1% dioxane. This unusual solvent effect has been rationalized in terms of a zwitterionic protonated intermediate which undergoes charge neutralization in the transition state.[26a] From the above solvent effect and the kinetic evidence it appears that the transition state in the hydronium ion catalyzed hydrolysis of aromatic sulfates may be zwit-

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(11) M. M. Kreevoy and R. W. Taft, Jr., *ibid.*, 77, 3146 (1955).
(12) W. J. C. Orr and J. A. V. Butler, *J. Chem. Soc.*, 330 (1937).
(13) M. Kilpatrick, *J. Am. Chem. Soc.*, 85, 1036 (1963).
(14) M. L. Bender and M. S. Silver, *ibid.*, 85, 3006 (1963).
(15) C. A. Bunton, P. B. D. de la Mare, and J. G. Tillett, *J. Chem. Soc.*, 4754 (1958).
(16) F. A. Long, *Ann. N. Y. Acad. Sci.*, 84, 596 (1960).
(17) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Am. Chem. Soc.*, 79, 2362 (1957).
(18) R. W. Taft, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 3.
(19) E. Hogfeldt and J. Bigeleisen, *J. Am. Chem. Soc.*, 82, 15 (1960).
(20) M. F. Hawthorne, *ibid.*, 76, 6358 (1954).
(21) J. G. Fullington and E. H. Cordes, *J. Org. Chem.*, 29, 970 (1964).
(22) A. J. Kresge and R. J. Preto, *J. Am. Chem. Soc.*, 87, 4593 (1965).
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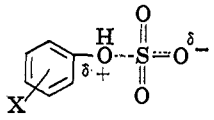
(25) M. Eigen, *Angew. Chem. Intern. Ed., Engl.*, 3, 1 (1964).
(26) (a) B. D. Batts, *J. Chem. Soc.*, 547, 551 (1966), and references therein; (b) E. T. Kaiser, M. Panar, and F. H. Westheimer, *J. Am. Chem. Soc.*, 85, 602 (1963).
(27) V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, 1635 (1956).
(28) R. L. Burwell, *J. Am. Chem. Soc.*, 74, 1462 (1952).
(29) S. Burstein and S. Lieberman, *ibid.*, 80, 5235 (1958).
(30) J. McKenna and J. K. Norymberski, *J. Chem. Soc.*, 3889 (1957).
(31) B. E. Fleischfresser and I. Lauder, *Australian J. Chem.*, 15, 242 (1962).

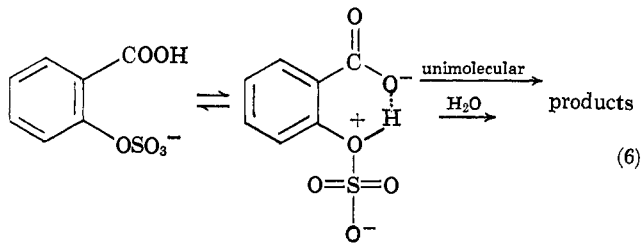
terionic, although further experimental evidence is



(5)

desirable.

Intramolecular Catalysis. The observation of carboxyl group participation represents the first example of anchimeric assistance in sulfate ester hydrolysis. The ratio of k_0' (assuming the plateau rate is kinetically bimolecular, $[a_H][o\text{-}{}^{-}O_3SOC_6H_4COO^-]$) to k_{H^+} is 67.5 and 12.1 for **2** and **1**, respectively. In view of the positive ρ and $\sigma_{COOH} > \sigma_{COO^-}$, the plateau phenomenon cannot be ascribed to electronic effects created by ionization of the carboxyl group, since $k_{H^+} < k_0'$.



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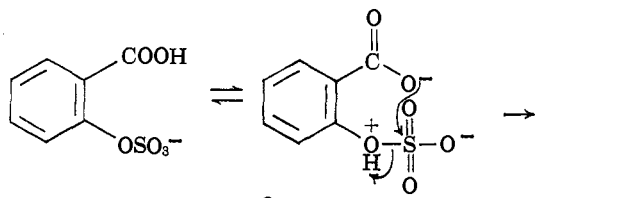

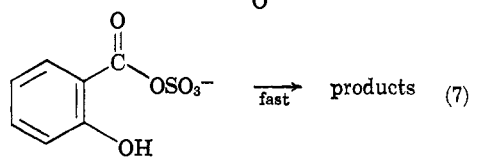

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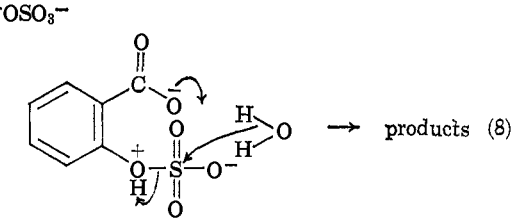

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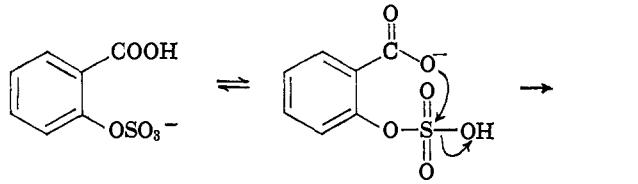

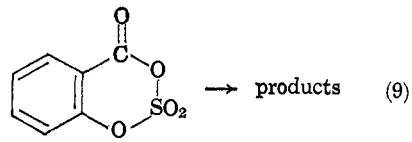

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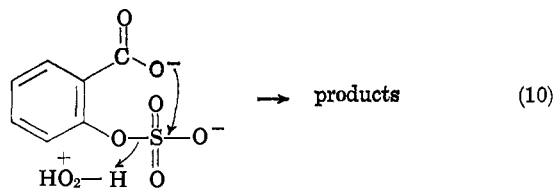

(10)

A number of mechanisms may be invoked to describe this hydrolytic behavior.[32] (See reactions 6–10.) Mechanisms 6–9 feature preequilibrium protonation of the sulfate moiety. In (6), conversion to products may proceed by unimolecular decomposition to SO_3 and salicylic acid or *via* bimolecular nucleophilic attack by water. In mechanisms 7 and 9 the carboxylate functions as a nucleophile, expelling phenol to form an acyl sulfate or hydroxide to form a cyclic sulfate; it may also act as a general base in (8). Mechanism 10 is analogous to eq 7 and 9 except that hydronium ion is the proton donor.

The kinetic evidence indicates that several mechanisms should be discarded. The solvent deuterium isotope effect, $k_0^{H_2O}/k_0^{D_2O} = 1.2$, is not consistent with mechanism 8 where ratios of $k_0^{H_2O}/k_0^{D_2O} > 2$ have been encountered for similar processes.[33] The positive entropy of activation favors a unimolecular process rather than participation of water as a nucleophilic species.[34] Mechanism 9 appears unlikely on chemical grounds since it is doubtful that the weakly basic carboxyl anion can expel hydroxide.[35]

The remaining pathways fall into two categories with the carboxyl group functioning either as a general acid or nucleophilic species. Intramolecular general acid catalysis followed by rate-limiting decomposition as depicted in mechanism 6 has been favored in the hydrolyses of certain acetals and ketals[36,37] containing suitably oriented carboxyl groups and in the hydrolysis of salicyl phosphate.[38] It is also of possible importance in the hydrolysis of alkyl esters of phthalic acid.[39,40] For salicyl sulfate the solvent deuterium isotope effect imposes a mechanistic limitation if (6) is operative. In order to accomodate the small isotope effect it is necessary to postulate nearly complete proton transfer prior to or during the transition state.[41] The mechanism is then completely analogous to that postulated for salicyl phosphate.

Many examples exist in the literature of intramolecular nucleophilic attack by carboxylate anion, especially in systems possessing good leaving groups.[38] The deuterium kinetic isotope effect or activation entropies calculated in terms of k_0 or k_0' (0.3)[42] do not rule out such mechanisms. Experimental attempts to detect intermediates *via* spectroscopic techniques or to demonstrate bimolecular catalysis were unsuccessful.

(32) Possible pentacovalent intermediates have not been included for reasons of simplicity.

(33) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1.

(34) Dividing k_0 by 55.5 and recalculating ΔS^* in terms of mechanism 6 involving attack by water yields a value of -4.9 eu.

(35) Formation of the cyclic sulfate *via* intramolecular attack by sulfate anion on the carboxyl-displacing hydroxide is considered unlikely for similar reasons.

(36) (a) B. Capon and M. C. Smith, *Chem. Commun.*, 523 (1965); (b) B. Capon, *Tetrahedron Letters*, 911 (1963).

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(42) (a) $k_0'^{H_2O}/k_0'^{D_2O} = (k_0^{H_2O}/k_0^{D_2O})(K_a'^{D_2O}/K_a'^{H_2O})$ where $K_a'^{D_2O}/K_a'^{H_2O} = 0.244$, employing the data of Korman and LaMer for salicylic acid: S. Korman and V. K. LaMer, *J. Am. Chem. Soc.*, **58**, 1396 (1936). (b) Calculated $\Delta S^* = +14.5$ eu (35°) for k_0'.

Hence an unequivocal choice between mechanisms 6 or 7 and 10 is not presently possible.[43]

The finding of carboxyl group catalysis which increases the rate 200-fold over that due to hydronium ion at pH 3–4 is of possible biochemical significance in the mechanism of action of sulfatases. Moreover, the gross mechanistic features are similar to those exhibited by salicyl phosphate; thus the analogy to phosphate ester chemistry may continue. Kaiser, *et al.*,[44,45] have recently reported the unusual alkaline lability of cyclic five-membered sulfates, whose behavior appears to closely resemble the cyclic phosphates. Investigations aimed at elucidating the actual mechanism of salicyl sulfate hydrolysis and the nature of catalytic effects by metal ions are currently in progress.[46]

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(43) It may be argued that the similarity in activation parameters for k_{H^+} and k_0 are indicative of mechanistic continuity and, therefore, that the carboxyl serves as in 6 to stabilize either electrostatically or *via* hydrogen bonding a reactive zwitterionic species. This should be viewed only as a working hypothesis.

(44) E. T. Kaiser, I. R. Katz, and T. F. Wulfers, *J. Am. Chem. Soc.*, 87, 3781 (1963).

(45) O. R. Zaborsky and E. T. Kaiser, *ibid.*, 88, 3084 (1966).

(46) F. Huege, unpublished work.

Elimination Reactions. VI. Rearrangement and Elimination Reaction of Benzylcyclopropyldimethylammonium Bromide[1]

Carl L. Bumgardner[2]

Contribution from the Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27607, and the Gorgas Laboratory, Rohm & Haas Company, Redstone Arsenal Research Division, Huntsville, Alabama.

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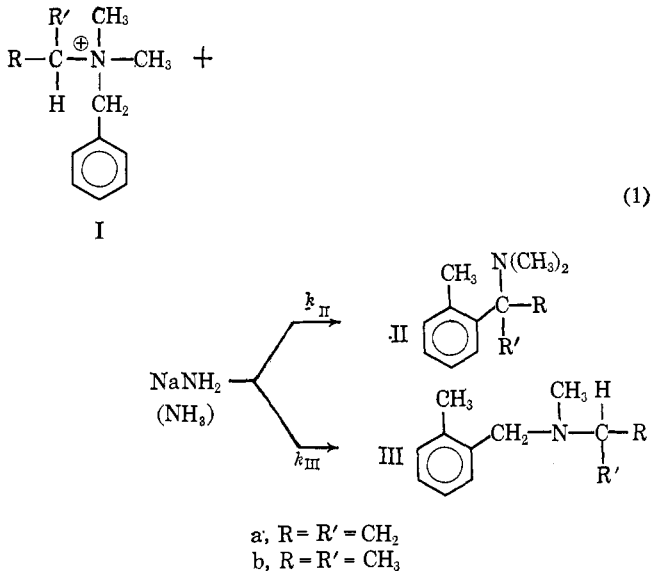
Abstract: Benzylcyclopropyldimethylammonium bromide was treated with sodium amide in liquid ammonia to learn more of the effect of the cyclopropane ring on the course of the Sommelet–Hauser rearrangement. Rearrangement to α-(N-methyl-N-cyclopropylamino)-*o*-xylene was accompanied by an unexpected elimination reaction which gave cyclopropene and benzyldimethylamine. An explanation for the formation of only one of the two possible Sommelet–Hauser products is suggested and some factors affecting the ease of elimination in this system are discussed.

Treatment of an alkylbenzyldimethylammonium halide (I) with sodium or potassium amide in liquid ammonia leads to the *ortho* substitution or Sommelet–Hauser rearrangement,[3] diagram 1. As shown in diagram 1, *ortho* substitution may occur *via* two pathways which lead to isomers II and III. When R is an alkyl group and R′ = H, the reaction gives mainly isomer III (k_{II}/k_{III} = 0.28).[4] However, when R is an unsaturated moiety, *e.g.*, R = phenyl or vinyl and R′ = H, then isomer II is produced almost exclusively.[4]



a; R = R′ = CH_2
b, R = R′ = CH_3

An interesting contrast exists between the saturated cases where R′ = H, R = isopropyl in I and R′ = H, R = cyclopropyl. In the latter example, isomer II predominates (k_{II}/k_{III} = 4.0) whereas, in the former, isomer III is favored (k_{II}/k_{III} = 0.2).[3,4]

To learn more of the effect of the small ring on the course of the Sommelet–Hauser rearrangement, we prepared benzylcyclopropyldimethylammonium bromide (Ia) and subjected it to sodium amide in liquid ammonia. The results from similar treatment of benzyldimethylisopropylammonium bromide (Ib) were available from an earlier study.[3]

Results

Exposure of bromide Ia to sodium amide in liquid ammonia for 3 hr produced two amines which were separated by fractional distillation. According to evidence presented below, the less volatile amine, isolated in 40% yield, is α-(N-methyl-N-cyclopropylamino)-*o*-xylene (IIIa). Combustion analyses and boiling point established the formula as $C_{12}H_{17}N$. In the

(1) Presented in part at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(2) North Carolina State University, Raleigh, N. C. 27607.

(3) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, 27, 1542 (1962).

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