

nonenes, where although the reactivity of the S_1 and T_1 states are comparable, reaction *via* the T_1 state is much more efficient.¹⁰ A recent theoretical model of photochemical reactions in fact suggests that intermolecular hydrogen abstraction should be much less efficient from alkanone S_1 states than alkanone T_1 states.²⁶ For the intermolecular case inefficiency could imply that abstraction is occurring (or partially occurring) but is rapidly followed by return of the hydrogen. Such a process would lead to fluorescence quenching without photoreduction from S_1 , *i.e.*, inefficient intermolecular hydrogen abstraction.

Thus while strong mechanistic evidence is admittedly difficult to obtain for photochemical reactions of low reactivity ($\sim 10^6 M^{-1} \text{sec}^{-1}$) arising from excited states of short lifetimes ($< 10^{-8}$ sec), it is now clear that the possibility that singlet ketones are equally reactive as triplet ketones toward intermolecular hydrogen abstraction is a real one. If this is correct, then one of the major arguments for different mechanisms for intra-

(26) J. Michl, *Mol. Photochem.*, **4**, 243, 257, 287 (1972).

molecular γ -hydrogen abstraction from S_1 and T_1 states of alkanones²⁷ is invalidated, further clearing the way for a unified theory of singlet-triplet reactivity in alkanone photochemistry.²⁸

Another implication of our work is that when inefficient quenching ($k_q\tau \leq 0.1$) of alkanones by hydrogen donors is observed, the quenching may be occurring from the alkanone singlet and/or triplet state. Thus the reported greater reactivity of triplet cyclopentanone than triplet cyclohexanone toward intermolecular hydrogen abstraction from 2-propanol⁷ may be subject to question. The triplet reactivities were derived from 2-propanol quenching of enal formation ($k_q \sim 0.04$ – 0.14).⁷ The inefficient quenching was assumed to represent only triplet quenching. If singlet quenching were also occurring the reported triplet reactivities would be incorrect.

(27) P. J. Wagner, *Accounts Chem. Res.*, **4**, 168 (1971).

(28) NOTE ADDED IN PROOF. For a recent study of quenching of acetone triplets by hydrogen donors see G. Porter, S. K. Dogra, R. O. Loutfy, S. E. Sugamori, and R. W. Yip, *J. Chem. Soc., Faraday Trans. 1*, 1462 (1973).

Nucleophilic Reactions of Sulfite Esters in Aqueous Media

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Abstract: The hydrolysis reactions of three sulfite esters, diphenyl sulfite (VIII), bis-*p*-nitrophenyl sulfite (IX), and phenyl *p*-nitrophenyl sulfite (X), in carboxylic acid buffers were examined as simple models for the corresponding pepsin-catalyzed processes. The observation of a substantial Brønsted β value, 0.85, for the monocarboxylate ion catalyzed hydrolysis of VIII, as well as the finding that the kinetic solvent isotope effect $(k_{\text{OAc}}^{\text{H}_2\text{O}}/k_{\text{OAc}}^{\text{D}_2\text{O}} = 1.32$, are consistent with the hypothesis that these reactions of VIII occur by nucleophilic catalysis. Similarly, the acetate-catalyzed solvolysis of IX and X is suggested to occur through a nucleophilic pathway. Support for the proposal that the nucleophilic attack of the carboxylate ions on the sulfites leads to the formation of mixed anhydride intermediates (eq 7) has been obtained by the detection of the acetohydroxamic acid produced when VIII, IX, and X are solvolyzed in acetate buffer in the presence of hydroxylamine. In the case of VIII measurement of the rate of acetohydroxamic acid production has indicated that under the conditions employed the rate-controlling step is mixed anhydride formation. In contrast to the solvolyses in carboxylic acid buffers, the direct kinetic detection of intermediates in the reactions of the sulfite esters VIII and X with hydroxylamine buffers has been accomplished. The rate constants for intermediate formation and decomposition were obtained by a computer-assisted kinetic analysis in the case of VIII and by observation of the reaction course at different wavelengths in the case of X. Through a combination of kinetic and synthetic experiments, the solvolysis of X in *N,O*-dimethylhydroxylamine buffer has been shown to proceed through the initial formation of phenyl methoxymethylamidodisulfite (XI). The demonstration that reactive intermediates can be detected in model solvolytic reactions of sulfite esters provides encouragement for the search for conditions under which intermediates formed by nucleophilic attack by the active site enzymatic carboxylate groups of pepsin can be detected directly.

On the basis of kinetic studies and chemical modification data, the mechanism shown in Figure 1 involving the postulated formation of covalent enzyme-substrate intermediates has been proposed for the pepsin-catalyzed hydrolysis of sulfite esters.¹ While direct evidence for the existence of intermediates like the anhydride species V during the course of these reactions is lacking, our observations on the inequality of the apparent Michaelis constant for the hydrolysis of diphenyl sulfite (VIII) and the inhibition constant for the inhibition of the hydrolysis of bis-*p*-nitrophenyl

(1) S. W. May and E. T. Kaiser, *Biochemistry*, **11**, 592 (1972).

sulfite (IX) by added VIII² besides those on the complexity of the k_{cat} vs. pH profile for the hydrolysis of IX³ are strongly suggestive of the existence of such an intermediate.

In parallel with our investigation of the action of pepsin on sulfite esters, we have examined the catalytic effects of model carboxylic acids on the hydrolysis of sulfite esters. The objective of these studies has been to ascertain whether or not carboxylate ions act as

(2) S. W. May and E. T. Kaiser, *J. Amer. Chem. Soc.*, **91**, 6491 (1969).

(3) S. W. May and E. T. Kaiser, *J. Amer. Chem. Soc.*, **93**, 5567 (1971).

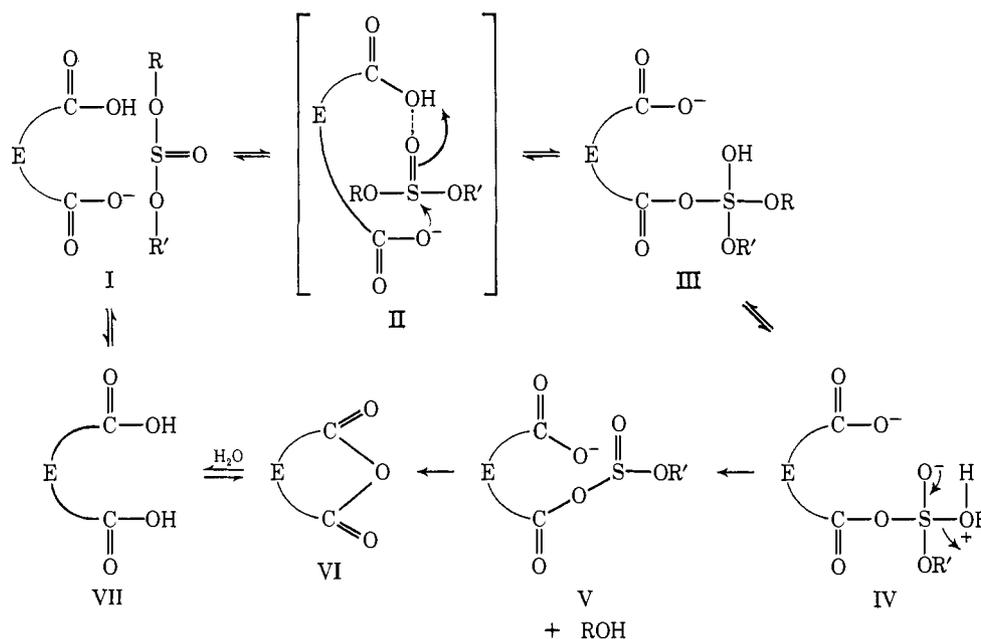


Figure 1. Proposed mechanism for the pepsin-catalyzed hydrolysis of sulfite esters.

nucleophilic catalysts, simulating, at least in part, the behavior of an enzymatic carboxylate group in pepsin's active site according to the mechanism of Figure 1. In the course of our work we resorted to the use of hydroxylamine as a trapping agent for the detection of the intermediate mixed anhydrides which might be formed during the reactions of organic carboxylate ions with sulfite esters. In the present paper our findings on the interaction of carboxylic acids and hydroxylamines with sulfite esters in aqueous solution are summarized.

Experimental Section

Analytical reagent grade inorganic salts were used without further purification. Acetonitrile was distilled over P_2O_5 and showed no absorption in the uv region above 235 nm. Chloroacetic acid was recrystallized from CCl_4 . Maleic acid was recrystallized from acetone-petroleum ether. Methoxyacetic acid was redistilled. Hydroxylamine hydrochloride was recrystallized from methanol before use. *N,O*-Dimethylhydroxylamine hydrochloride was purified by recrystallization from ethanol-diethyl ether. Phenyl chlorosulfite was prepared according to the procedure of May,⁴ except that following the addition of thionyl chloride to diphenyl sulfite, the reaction mixture was stirred for about 4 hr. Bis-*p*-nitrophenyl sulfite (IX)² was synthesized by Mr. Scott Landfear as was phenyl *p*-nitrophenyl sulfite (X).⁵ Diphenyl sulfite (VIII) was prepared according to May.² Acetohydroxamic acid was prepared by the method of Munson and Connors.⁶ 5,5'-Dithiobis(2-nitrobenzoic acid) (DTNB) and 4,4'-dithiopyridine (4-PDS) were purchased from Aldrich and used without further purification.

The synthesis of phenyl methoxymethylamidodisulfite (XI) was accomplished as follows. Free *N,O*-dimethylhydroxylamine was obtained by adding an aqueous solution of the hydrochloride to concentrated aqueous KOH, followed by distillation at atmospheric pressure, bp 45°, uncorr (lit.⁷ bp 42.2–42.6°). Phenyl chlorosulfite (14.4 g, 0.08 mol) in 20 ml of anhydrous diethyl ether was added to *N,O*-dimethylhydroxylamine (10.0 g, 0.16 mol) in 20 ml of anhydrous diethyl ether over a period of 15 min at ice bath temperature. After the reaction mixture was allowed to come to room

temperature the white precipitate formed was removed by filtration. After the resultant ether solution was washed with dilute HCl, dilute NaOH, and water, it was dried over sodium sulfate. The solvent was evaporated and the residual oil was vacuum distilled (bp 70–73° (0.5 mm), uncorr) to give 9.5 g of the product as a colorless liquid (yield 60%, based on the starting amount of phenyl chlorosulfite). The ir and nmr spectra obtained were consistent with the structure assigned.

Anal. Calcd for $\text{C}_8\text{H}_{11}\text{NO}_3\text{S}$: C, 47.74; H, 5.51; N, 6.96. Found: C, 47.82; H, 5.60; N, 6.99.

Rate Measurements. All kinetic measurements were carried out at 25.0°. The studies on the hydrolysis of diphenyl sulfite (VIII) in various buffer solutions were performed using a Cary 15 or a Gilford Model 222 spectrophotometer as follows. The appropriate amount of acetonitrile was added to the buffer to give a final volume of 9.1% of this solvent. Reaction was initiated by the addition of an aliquot of a stock solution of VIII in acetonitrile. Phenol release was followed at 269 nm except in maleate buffer where the reaction was observed at 278 nm. The hydrolysis of VIII in hydroxylamine buffer was carried out in the presence of 10^{-4} M EDTA.

The hydrolysis of bis-*p*-nitrophenyl sulfite (IX) was followed at 320 nm using an Aminco-Morrow stopped-flow spectrophotometer. That of phenyl *p*-nitrophenyl sulfite (X) was observed with the Aminco-Morrow instrument at 320 nm or with a Cary 15 spectrophotometer at 269 nm. In typical experiments with the stopped-flow spectrophotometer, one syringe was filled with buffer solution of the appropriate concentration and allowed to equilibrate to 25.0°. The second syringe was filled with a solution prepared in the following manner: acetonitrile, distilled, deionized, and degassed water, and a stock solution of substrate in acetonitrile were mixed in appropriate proportions to give the desired final substrate concentration and percentage of acetonitrile and equilibrated at 25.0°. Experimental traces were recorded and retained on the screen of a storage oscilloscope and then photographed. All of the reactions of the sulfite esters VIII, IX, and X, except those in hydroxylamine buffer, followed apparent first-order kinetics for at least 2 half-lives.

Experiments Using Hydroxylamine as a Nucleophilic Trapping Reagent in the Acetate-Catalyzed Hydrolysis of VIII. A typical experiment on the acetate catalysis of the hydrolysis of the sulfite esters in the presence of hydroxylamine was performed as follows: 1 ml of a 9.57×10^{-4} M stock solution of diphenyl sulfite (VIII) in acetonitrile was added to 10 ml of a 0.2 M acetate buffer containing 0.002 M hydroxylamine at pH 5.6. The reaction was interrupted by adding 5 ml of 5.2% $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in 0.54 N HCl. After 5–10 min the absorbance of the resultant solution was measured at 510 nm in a 5-cm path length cell. The extinction coefficient of the acetohydroxamic acid- FeCl_3 complex was determined under the same conditions using a synthetic sample.

(4) S. W. May, Ph.D. Thesis, University of Chicago, 1970.

(5) The preparation of X will be described in a manuscript now in preparation (S. Landfear and E. T. Kaiser).

(6) J. W. Munson and K. A. Connors, *J. Amer. Chem. Soc.*, **94**, 1979 (1972).

(7) "Dictionary of Organic Compounds," 4th ed, Vol. 4, I. Heilbron, Ed., Eyre and Spottiswoode, Ltd., Oxford, 1965, p 2227.

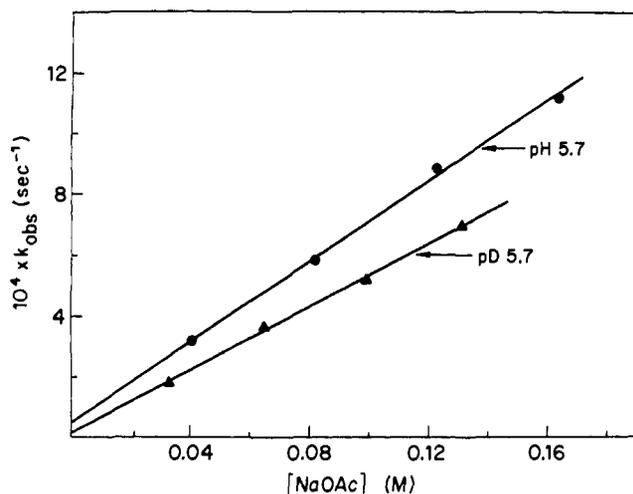


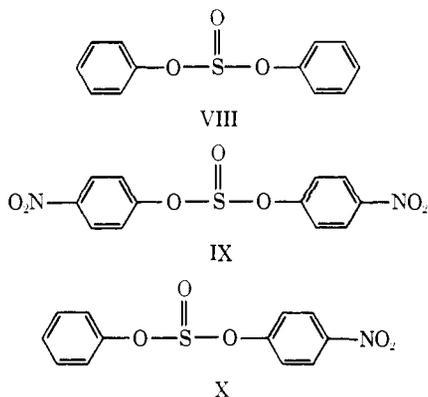
Figure 2. Plots of k_{obsd} vs. $[\text{NaOAc}]$ for the acetate-catalyzed hydrolysis of VIII in H_2O and D_2O : pH 5.7 (●); pD 5.7 (▲).

Inorganic Sulfite Trapping Experiments. Inorganic sulfite reacts stoichiometrically with 4,4'-dithiodipyridine (4-PDS) to produce the corresponding thiol and organic thiosulfate.⁸ A similar process occurs when inorganic sulfite reacts with 5,5'-dithiobis(2-nitrobenzoic acid).⁸ The measured extinction coefficient at 324 nm for the reduced species obtained from 4-PDS in 0.182 *M* acetate buffer (9.1% CH_3CN , pH 5.7) containing 0.0018 *M* hydroxylamine was 23,750 (lit.⁸ 21,500). The measured extinction coefficient at 412 nm for the reduced species produced from DTNB is 11,400 in 0.182 *M* acetate buffer at pH 5.6 (lit.⁸ 15,500 for the thiol anion; 13,600⁹). Rates of inorganic sulfite production in the hydrolysis of the organic sulfite esters were measured by following the reduction of 4-PDS or DTNB which had been added initially to the reaction mixtures.

Results

Hydrolysis of Sulfite Esters in Carboxylate Buffers.

Measurements on the hydrolysis of VIII, IX, and X in



acetate buffers showed that the sulfite esters reacted according to a pseudo-first-order rate law. The release of both phenolic molecules from which the sulfite esters were derived appeared to occur synchronously in the course of the decomposition of VIII, IX, and X. Typically, in 0.2 *M* acetate buffer at pH 5.64 and 25.0°, the pseudo-first-order rate constant observed at 320 nm for the formation of *p*-nitrophenol in the acetate-catalyzed hydrolysis of phenyl *p*-nitrophenyl sulfite was 3.23 sec^{-1} . Measurement at 269 nm gave a rate constant of 3.5 sec^{-1} , and the final absorption was consistent with the production of equal amounts of *p*-nitro-

(8) R. E. Humphrey, M. H. Ward, and W. Hinze, *Anal. Chem.*, **42**, 698 (1970).

(9) G. L. Ellman, *Arch. Biochem. Biophys.*, **82**, 70 (1959).

phenol and phenol. Similar observations were made for the methoxyacetate, chloroacetate, and maleate-catalyzed hydrolytic reactions of VIII.

The rate of the formation of inorganic sulfite in the hydrolysis of diphenyl sulfite (VIII) was followed by the observation at 324 nm of the reduction of added 4-PDS. When 2.07×10^{-5} *M* VIII was hydrolyzed in 0.2 *M* acetate buffer at pH 5.6 and 25.0° in the presence of 1.5×10^{-4} *M* 4-PDS, the pseudo-first-order rate constant measured for inorganic sulfite production was 1.1×10^{-3} sec^{-1} and the calculated amount of inorganic sulfite formed from observation of the extent of 4-PDS reduction was 2.06×10^{-5} *M*. Reaction of 8.7×10^{-5} *M* VIII under these conditions gave an observed rate constant of 1.13×10^{-3} sec^{-1} and 7.9×10^{-5} *M* inorganic sulfite appeared to be produced. The rate constant for phenol formation measured in the same buffer system in the absence of 4-PDS, using a concentration of 2.07×10^{-5} *M* VIII, was 1.12×10^{-3} sec^{-1} , in good agreement with the values for inorganic sulfite production.

Because *p*-nitrophenol absorbs strongly in the uv region near the wavelength used for monitoring the reduction of 4-PDS, a different disulfide, DTNB, was employed to follow inorganic sulfite production in the hydrolysis of bis-*p*-nitrophenyl sulfite (IX) and phenyl *p*-nitrophenyl sulfite (X). In typical runs at 25.0° in 0.2 *M* acetate buffer at pH 5.6, by the observation of the production of the phenolic species, the half-life measured for the hydrolysis of IX was 0.07 sec and that for X was 0.2 sec. When 5.02×10^{-6} *M* inorganic sulfite was reacted in the same buffer with 5.52×10^{-4} *M* DTNB the half-life observed was approximately 20 sec. In view of these results it was not surprising that when inorganic sulfite production in the hydrolysis of IX and X was monitored with DTNB a rate constant of 2.8×10^{-2} sec^{-1} was measured, a value consistent with the reaction of the inorganic sulfite with DTNB being rate limiting. These measurements demonstrate that there is not an extremely great time lag between the production of inorganic sulfite and that of the phenolic species, but they do not establish firmly the synchronous release of these products in the decomposition of IX and X. When 4.94×10^{-6} *M* IX and 5.84×10^{-6} *M* X were hydrolyzed, the final concentrations of inorganic sulfite produced as determined by the reduction of added DTNB were 4.48×10^{-6} and 5.87×10^{-6} *M*, respectively.

The pseudo-first-order rate constants obtained in the acetate-catalyzed hydrolysis of VIII, IX, and X were analyzed in terms of eq 1, where k_0 corresponds to the

$$k_{\text{obsd}} = k_0 + k_A[\text{A}] + k_B[\text{B}] \quad (1)$$

$$= k_0 + \left(\frac{k_A[\text{H}^+]}{K_a} + k_B \right) [\text{B}]$$

apparent first-order rate constant at a given pH due to a combination of the pH-independent, H_3O^+ -catalyzed and OH^- -catalyzed hydrolytic pathways, A is the acidic form of the buffer component, B is the basic form of the buffer component, and K_a is the acid dissociation constant for the buffer. The second-order rate constants, k_A and k_B , were computed by plotting initially the values of k_{obsd} against the concentration of the basic form of the buffer, [B], at constant pH values and then the slopes of the straight lines obtained against

[H⁺]. A typical plot at constant pH is illustrated in Figure 2 for the acetate-catalyzed hydrolysis of VIII. The rate data for the methoxyacetate- and chloroacetate-catalyzed hydrolysis of VIII were analyzed by the same approach.¹⁰

The results of our studies on the hydrolysis of diphenyl sulfite (VIII) catalyzed by various carboxylate buffers and the reactions of IX and X with acetate buffers are summarized in Table I. As can be seen

Table I. Summary of the Second-Order Rate Constants for the Hydrolysis of VIII in Various Carboxylate Buffers and IX and X in Acetate Buffer

Substrate	Buffer	pK _a ^a	k _A , M ⁻¹ sec ⁻¹	k _B , M ⁻¹ sec ⁻¹
VIII	Acetate	4.77		6.2 × 10 ⁻³
	Methoxyacetate	3.50		6.35 × 10 ⁻⁴
	Chloroacetate	2.86	3.3 × 10 ⁻⁵	1.4 × 10 ⁻⁴
	Maleate	6.15		9.5 × 10 ⁻³
IX	Acetate	4.77	2.3	54.0
X	Acetate	4.77		17.4

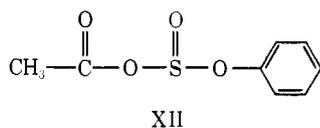
^a pK_a values were determined by titrating the acids under the same conditions as the kinetic experiments were performed.

from the table, except for maleate, the monoionized forms of the buffers were the reactive species for which rate constants were obtained. In the case of VIII only with chloroacetic acid were we able to detect catalysis of hydrolysis by the un-ionized form of the buffer. While acetate ion was far more effective, we did detect catalysis by acetic acid, however, in the hydrolysis of IX.

In Figure 3 a logarithmic plot of the rate constants k_B as a function of the pK_a values of the buffers is shown. The slope, β , of the line drawn through the points representing catalysis by the monoanion forms of the monocarboxylic acids is 0.85. The logarithm of the rate constant for catalysis by the maleate dianion shows a marked negative deviation from the line.

Figure 2 illustrates not only the acetate-catalyzed hydrolysis of VIII in H₂O but also the corresponding solvolysis in D₂O. To calculate the acetate concentrations in the D₂O containing buffers a ratio of $K_{DOAc}/K_{HOAc} = 3.3$ was employed.¹¹ From Figure 2, the ratio $(k_{OAc})_{H_2O}/(k_{OAc})_{D_2O} = 1.32$.

To test the possibility that the mixed anhydride species XII is formed in the acetate-catalyzed hydrolysis



of diphenyl sulfite (VIII), trapping experiments using hydroxylamine were performed. If XII is an intermediate, then addition of hydroxylamine to the acetate buffers used to catalyze the hydrolysis of VIII may result in the formation of acetohydroxamic acid from the attack of hydroxylamine on the carbonyl carbon of XII. In accordance with this possibility the spectra

(10) In the case of maleate catalysis of the hydrolysis of VIII the possibility exists that the un-ionized form, the monoanion, and the dianion are all catalytically active. However, our kinetic measurements (see Table I) were confined to pH values in the vicinity of the pK for the ionization of the monoanion to the dianion, and we did not attempt to determine whether catalysis by un-ionized maleic acid could be seen.

(11) S. Korman and V. K. La Mer, *J. Amer. Chem. Soc.*, **58**, 1396 (1936).

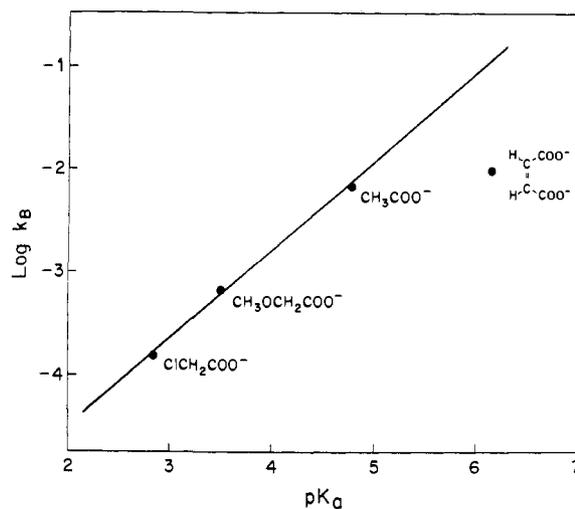


Figure 3. Brønsted plot for the hydrolysis of VIII in carboxylate buffers. No statistical correction for the presence of two carboxyl groups in the maleate species was made.

produced by quenching the acetate buffers containing VIII and hydroxylamine with acidic ferric chloride solutions agreed reasonably well with the spectra produced by the addition of authentic samples of acetohydroxamic acid to the ferric chloride solutions.¹² This is illustrated in Table II where the ratios of the

Table II. Comparison of the Spectra of Authentic Acetohydroxamic Acid-Ferric Chloride Complex (A) and the Material Produced by Reaction of VIII-Acetate-Hydroxylamine Mixtures with Ferric Chloride (B)

Sample	$A_{540\text{nm}}/A_{510\text{nm}}$, %	$A_{580\text{nm}}/A_{510\text{nm}}$, %	$A_{600\text{nm}}/A_{510\text{nm}}$, %
A	95	55	68
B	91	53	74

absorbances at 540, 580, and 600 nm to that at 510 nm are compared for authentic acetohydroxamic acid-ferric chloride complex and the material produced by reaction of the diphenyl sulfite-acetate-hydroxylamine mixtures with ferric chloride.

A representative measurement of the rate of formation of acetohydroxamic acid in 0.182 M acetate buffer, pH 5.6, containing 8.7×10^{-5} M VIII and a total concentration of 1.8×10^{-3} M hydroxylamine is shown in Figure 4. In general, as seen in this figure, the concentrations of acetohydroxamic acid formed in the presence of hydroxylamine during the initial phase of the acetate-catalyzed hydrolysis of reaction of VIII were somewhat higher than would be expected by extrapolation of the straight line drawn using the points measured later in the reaction. The reasons for this observation are not clear, but the slope of the line drawn using a least-squares procedure gave a k_{obsd} value of 1.08×10^{-3} sec⁻¹, in good agreement with the observed rate constant (1.12×10^{-3} sec⁻¹) seen in the same buffer system when phenol release was monitored in the absence of hydroxylamine. Using a value of $\epsilon_{510\text{nm}}$ 1016 for the ferric chloride-aceto-

(12) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **151**, 21 (1945); see also W. P. Jencks, *J. Amer. Chem. Soc.*, **80**, 4581 (1958).

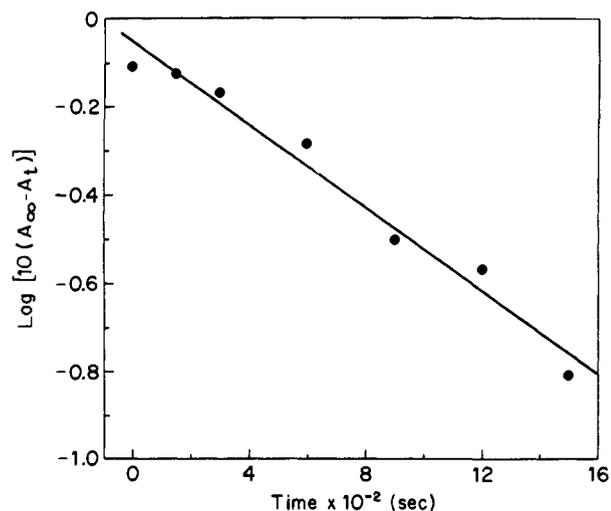


Figure 4. Plot of the rate of aceto-hydroxamic acid formation in 0.18 M acetate buffer at pH 5.6 containing 8.7×10^{-5} M VIII and 1.8×10^{-3} M hydroxylamine. The line represents a least-squares correlation of the experimental points.

hydroxamic acid complex, the yield of aceto-hydroxamic acid formed in this run was estimated to be 25.6%.

While the observed formation of aceto-hydroxamic acid is consistent with the postulate that hydroxylamine can trap the intermediate XII by attack at the carbonyl carbon, an alternative possibility which needs to be considered is that acetic anhydride is actually the intermediate being trapped.¹³ To test this alternative, 2.07×10^{-5} M VIII was solvolyzed in 0.182 M acetate buffer, pH 5.7, in the presence of 3.27×10^{-3} M aniline. The optical density change observed at 250 nm agreed well with the spectrum of the mixture produced when VIII was solvolyzed in acetate buffer in the absence of aniline. Furthermore, addition of aniline to acetate buffer at the concentrations given above had no significant catalytic effect on the solvolysis of VIII. Hydrolysis of 8.16×10^{-5} M VIII in the same acetate buffer in the presence of 1.53×10^{-3} M aniline and observation at 250 nm gave a similar result.

For purposes of comparison, 4.5×10^{-5} and 9×10^{-5} M acetic anhydride was solvolyzed in 0.182 M acetate buffer (apparent pH ~ 5.7), containing 1.53×10^{-3} M aniline and 9.1% acetonitrile. Observation at 250 nm revealed that the rate of formation of acetanilide obeyed pseudo-first-order kinetics for more than 3.5 half-lives and that about an 85% yield of acetanilide was produced.¹⁴ Division of the pseudo-first-order rate constant (0.03 sec^{-1} at 25.0°) by the aniline concentration gave a second-order rate constant of $20 \text{ M}^{-1} \text{ sec}^{-1}$ for the production of acetanilide. Although hydroxylamine is expected to be more effective than aniline in attacking the carbonyl groups in either acetic anhydride or VIII, it is clear that under the conditions discussed above the nucleophilic trapping of

(13) Of course, if acetic anhydride were the intermediate being trapped, it seems likely that it would be produced by the attack of acetate on XII. Thus, our finding that aceto-hydroxamic acid is formed in the solvolysis of VIII in acetate-hydroxylamine buffers appears to imply strongly that XII is a significant intermediate species, whether or not it is directly reacting with hydroxylamine.

(14) An acetanilide yield of 86% has been reported in the literature for the solvolysis of 7×10^{-4} M acetic anhydride in a 0.45 M sodium acetate buffer containing 1×10^{-3} M free aniline and 0.2% dioxane at pH 5.0: V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc. B*, 515 (1968).

acetic anhydride by aniline competes effectively with hydrolysis.¹⁵ If the intermediate giving rise to aceto-hydroxamic acid in the solvolysis of VIII in acetate-hydroxylamine buffer at pH 5.7 were acetic anhydride, it should be possible to trap this species in the acetate-aniline buffers.¹⁶ Since we found no evidence for acetanilide formation in the solvolysis of VIII in the acetate-aniline system, it seems reasonable to conclude that acetic anhydride is not present in a significant concentration and therefore that XII is probably the species which is being trapped in the acetate-hydroxylamine system.

Due to the rapidity with which the sulfite esters IX and X solvolyze in acetate buffers, we were not able to measure the rates of aceto-hydroxamic acid production in these cases in the presence of hydroxylamine in the manner described above for diphenyl sulfite. However, by use of the ferric chloride test we estimate that when 4.2×10^{-5} M IX was hydrolyzed in 0.182 M acetate buffer, pH 5.6, containing a total concentration of 1.8×10^{-3} M hydroxylamine, a 37% yield of aceto-hydroxamic acid was formed. Solvolysis of X under the same conditions yielded approximately 35% aceto-hydroxamic acid.

While we were able to show that the rate of aceto-hydroxamic acid formation in the solvolysis of VIII measured in acetate buffer containing hydroxylamine was in reasonable agreement with the rate of phenol formation in the same buffer system in the absence of hydroxylamine, we were unsuccessful in our attempts to follow the rate of inorganic sulfite production in the presence of hydroxylamine, using 4-PDS as a trapping agent. For example, when we tried to monitor inorganic sulfite production using 2.6×10^{-4} M 4-PDS in a solution of 8.26×10^{-5} M VIII in a 0.2 M acetate buffer, pH 5.6, containing 0.002 M hydroxylamine, the absorption at 324 nm due to the reduction of 4-PDS increased, went through a maximum, and then decreased. This observation is not understood. The final concentration of inorganic sulfite formed was estimated from measurement with 4-PDS to be 4.40×10^{-5} M, about half the amount expected. When 8.26×10^{-5} M Na_2SO_3 instead of VIII was placed in the acetate-hydroxylamine buffer, measurement with 4-PDS after a 70-min incubation period showed only a 5% decrease in the inorganic sulfite content. Thus, the low yield of inorganic sulfite detected using 4-PDS in the solvolysis of VIII in acetate-hydroxylamine buffer does not seem to be due to loss of SO_2 on standing. We have found also that the other products, phenol and aceto-hydroxamic acid, have no effect on the rate of the reaction of inorganic sulfite with 4-PDS in acetate buffer.

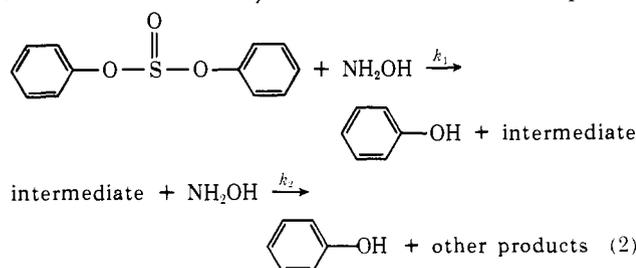
Turning from measurements of the rates of aceto-hydroxamic acid and inorganic sulfite production to the rate of formation of phenol from VIII, followed at 269 nm in acetate-hydroxylamine buffer, we have observed an acceleration in the latter rate due to the presence of hydroxylamine. For example, when 2.07

(15) In 50% aqueous acetone at 25° with an initial acetic anhydride concentration of 0.07 M, the observed rate constant for the hydrolysis of the anhydride was $9.8 \times 10^{-5} \text{ sec}^{-1}$ and $25.0 \times 10^{-5} \text{ sec}^{-1}$ in the presence of 0.1 M sodium acetate; see A. R. Emery and V. Gold, *J. Chem. Soc. B*, 1451 (1950).

(16) The important assumption underlying this statement is that the same reactive intermediate is present in the solvolysis of VIII in acetate-hydroxylamine and acetate-aniline buffers.

$\times 10^{-5} M$ VIII was hydrolyzed in 0.182 M acetate buffer, pH 5.6, containing a total concentration of $1.8 \times 10^{-3} M$ hydroxylamine, the pseudo-first-order rate constant for phenol formation was $1.6 \times 10^{-3} \text{ sec}^{-1}$ while it was $1.1 \times 10^{-3} \text{ sec}^{-1}$ in the absence of hydroxylamine. This observation suggested that direct attack of hydroxylamine on VIII, resulting in the acceleration of phenol release, was occurring.

Reactions of Sulfite Esters with Hydroxylamine Buffers. In corroboration of this hypothesis a typical run illustrating the solvolysis of VIII in hydroxylamine buffers is shown in Figure 5. It can be seen that the hydroxylamine-catalyzed formation of phenol from the decomposition of diphenyl sulfite does not follow a simple pseudo-first-order rate law. However, we have found that the rate data can be analyzed in terms of the scheme shown in eq 2. If the kinetics of phenol



formation can be measured at a wavelength where the starting material (VIII) and the intermediate absorb negligibly, then according to the scheme of eq 2, the rate expression of eq 3¹⁷ should hold. From evidence $A_\infty - A_t =$

$$\frac{A_\infty}{2} \left(\frac{2k_2' - k_1'}{k_2' - k_1'} e^{-k_1't} - \frac{k_1'}{k_2' - k_1'} e^{-k_2't} \right) \quad (3)$$

to be discussed later (the hydroxylamine-catalyzed solvolysis of phenyl *p*-nitrophenyl sulfite), it appears that this condition is met at 280 nm for the hydroxylamine-catalyzed production of phenol from VIII.

The rate constants k_1' and k_2' calculated according to eq 3¹⁸ were analyzed further by the use of eq 4 and 5,

$$k_1' = k_0 + k_1^{\text{NH}_2\text{OH}}[\text{NH}_2\text{OH}] \quad (4)$$

$$k_2' = \bar{k}_0 + k_2^{\text{NH}_2\text{OH}}[\text{NH}_2\text{OH}] \quad (5)$$

where $k_1^{\text{NH}_2\text{OH}}$ and $k_2^{\text{NH}_2\text{OH}}$ are the rate constants for the attack of the free base form of hydroxylamine on VIII and on the intermediate, respectively. Values of $k_1^{\text{NH}_2\text{OH}} = 1.68 M^{-1} \text{ sec}^{-1}$ and $k_2^{\text{NH}_2\text{OH}} = 1.46 M^{-1} \text{ sec}^{-1}$ were obtained in hydroxylamine buffers at $\mu = 0.182$ with 9.1% CH_3CN present.

When $1.71 \times 10^{-6} M$ inorganic sulfite and $3.28 \times 10^{-4} M$ DTNB were reacted in 0.005 M NH_2OH at pH 6.8 a pseudo-first-order reaction was seen with a half-life of about 8.4 sec. When $4.06 \times 10^{-6} M$ VIII and $3.8 \times 10^{-4} M$ DTNB were mixed in a pH 6.9, 0.0066 M NH_2OH buffer, not surprisingly, however, a significant deviation from pseudo-first-order kinetics was observed. A thorough analysis of the rate behavior was not attempted, but the half-life of this reaction, approximately 100 sec, indicates that a considerable lag between the formation of inorganic sulfite and that of

(17) The value of $A_0 = 0$; k_1' and k_2' are defined in eq 4 and 5. The derivation of eq 3 is closely related to that given for series first-order reactions by A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms," 2nd ed, Wiley, New York, N. Y., 1963, pp 166-167.

(18) We thank Dr. P. Campbell and Mr. G. Moll for the use of their computer program.

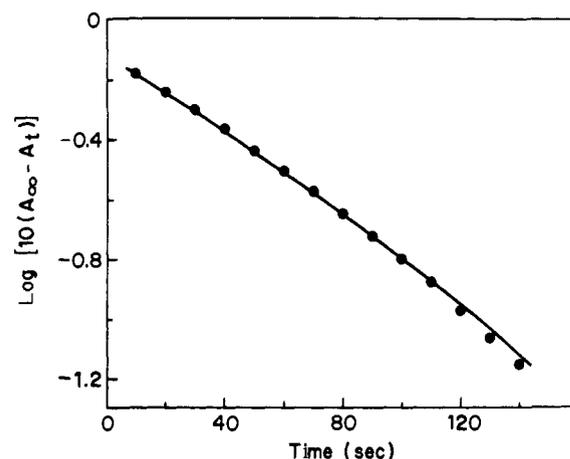
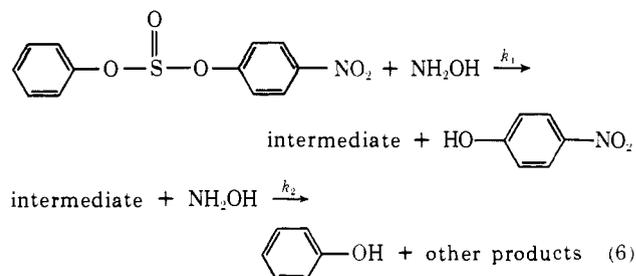


Figure 5. Plot of $\log [10(A_\infty - A_t)]$ vs. time for the hydrolysis of VIII in 0.04 M hydroxylamine buffer at pH 5.8. The curve is a computer-calculated plot based on eq 3.

phenol does not occur. The final absorption at 412 nm corresponded to a 100% yield of inorganic sulfite.

While qualitatively it appears that a reaction scheme like that in eq 2 holds for the reaction of hydroxylamine with bis-*p*-nitrophenyl sulfite (IX), because we do not know what the uv spectrum of the intermediate is in this case, we could not ascertain proper measurement conditions under which eq 3 is valid. Our crude measurements, however, suggested that the k_1 step occurred several times faster than the k_2 step and that both of these steps proceeded at least several hundred times faster than the corresponding steps in the hydroxylamine-catalyzed solvolysis of VIII.

In view of our postulation of the stepwise sequence of eq 2 for the reactions of diphenyl sulfite and bis-*p*-nitrophenyl sulfite with aqueous hydroxylamine, it was of considerable interest to examine the solvolysis of an unsymmetrical sulfite ester like phenyl *p*-nitrophenyl sulfite (X) in which there is a substantial difference in the leaving group tendencies of the product alcohol molecules. As would be anticipated if the scheme of eq 6 which is analogous to that of eq 2 holds, two steps



were observed in the hydroxylamine-catalyzed decomposition of X. The release of *p*-nitrophenol, the k_1 step, was observed at 320 nm and the formation of phenol, the k_2 step, was followed at 269 nm. From measurements over the range pH 5.2-7.0, employing hydroxylamine concentrations from 0.003 to 0.1 M , it was concluded that $^+\text{NH}_3\text{OH}$ is not a catalytically active species and that only NH_2OH is effective. Analysis of the rate data by means of eq 4 and 5 gave average values of $1140 M^{-1} \text{ sec}^{-1}$ for $k_1^{\text{NH}_2\text{OH}}$ and $1.5 M^{-1} \text{ sec}^{-1}$ for $k_2^{\text{NH}_2\text{OH}}$. From measurements in D_2O at pD 7.3, employing hydroxylamine concentrations ranging from 0.004 to 0.015 M , a $k_1^{\text{ND}_2\text{OD}}$ value of 830

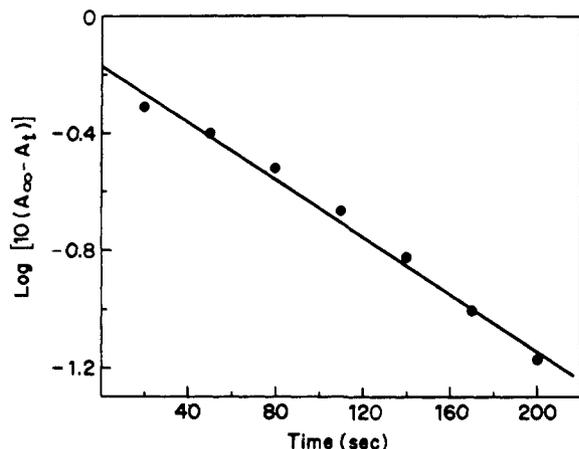


Figure 6. The rate of inorganic sulfite liberation from the solvolysis of X in 0.01 M hydroxylamine buffer at pH 6.7 using DTNB as the trapping agent: [X], 5.21×10^{-6} M, [DTNB], 4.97×10^{-4} M. The line represents a least-squares fit to the experimental points.

$M^{-1} \text{ sec}^{-1}$ was found.¹⁹ The ratio of $(k_1^{\text{NH}_2\text{OH}})_{\text{H}_2\text{O}} / (k_1^{\text{ND}_2\text{OD}})_{\text{D}_2\text{O}} = 1.37$, consistent with the hypothesis that NH_2OH acts as a nucleophile in the k_1 step. Measurements at pD 7.4, using hydroxylamine concentrations of 0.002–0.009 M, gave a $k_2^{\text{ND}_2\text{OD}}$ value of $1.2 M^{-1} \text{ sec}^{-1}$. Thus, the ratio $(k_2^{\text{NH}_2\text{OH}} / k_2^{\text{ND}_2\text{OD}})$ is 1.25 which implies that in the k_2 step, also, hydroxylamine acts as a nucleophile.

When 5.21×10^{-6} M X was solvolyzed in a 0.011 M hydroxylamine buffer at pH 6.72 in the presence of 4.97×10^{-4} M DTNB and the reduction of DTNB due to inorganic sulfite production was followed at 412 nm, the data illustrated in Figure 6 were obtained. From these data, a pseudo-first-order rate constant of 0.011 sec^{-1} was calculated for the formation of inorganic sulfite, in reasonable agreement with the pseudo-first-order rate constant expected for phenol release (0.014 sec^{-1}) based on the value of $k_2^{\text{NH}_2\text{OH}}$ given above.

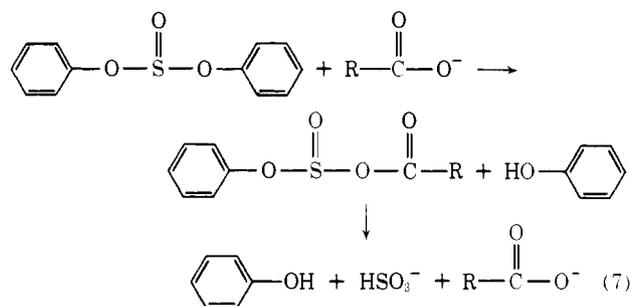
In addition to our work in hydroxylamine buffers, the solvolysis of phenyl *p*-nitrophenyl sulfite (X) in an *N,O*-dimethylhydroxylamine buffer was briefly examined. Observation at 320 nm of the formation of *p*-nitrophenol when 6.25×10^{-6} M X was reacted with 0.043 M *N,O*-dimethylhydroxylamine buffer at pH 4.6 gave a pseudo-first-order rate constant of 0.016 sec^{-1} . Because the release of phenol as measured at 269 nm was very slow under these conditions, its rate of production was not measured. When a 5-ml sample of the solution containing the species generated by the release of *p*-nitrophenol in the reaction of X with 0.009 M *N,O*-dimethylhydroxylamine was mixed with 5 ml of an acetate buffer to give a final concentration for this species of 8.2×10^{-5} M and for acetate of 0.18 M at pH 5.81, the formation of phenol was observed to occur with a pseudo-first-order rate constant of $4.1 \times 10^{-4} \text{ sec}^{-1}$. This rate constant was the same within experimental error as that seen for the solvolysis of 7.84×10^{-5} M solution of authentic phenyl methoxymethylamidodisulfite (XI) in a 0.18 M acetate buffer at pH 5.81 ($3.9 \times 10^{-4} \text{ sec}^{-1}$).

Discussion

Our results for the catalysis of the hydrolysis of di-

(19) In these calculations values of $(pK_a)_{\text{NH}_2\text{OH}\cdot\text{HCl}} = 6.0$ and $(pK_a)_{\text{ND}_2\text{OD}\cdot\text{DCl}} = 6.6$ were used.

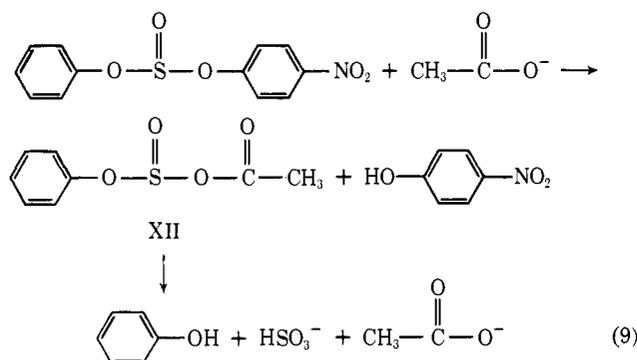
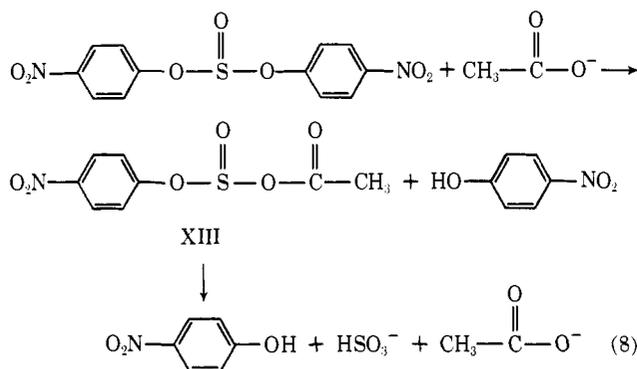
phenyl sulfite (VIII) by monocarboxylate ion species are consistent with the reaction scheme of eq 7 in which



nucleophilic attack of the carboxylate anions on the sulfite sulfur occurs in the rate-determining step, under the conditions we employed. The marked negative deviation of the logarithm of the rate constant for the maleate dianion from the line drawn in Figure 3 may be due at least in part to electrostatic repulsion in the transition state between the negative charge on one carboxylate group and the developing negative charge on the sulfite group which is being attacked by the other carboxylate function. Also, the slow rate of the reaction of the maleate dianion may reflect steric crowding in the transition state due to the presence of the *cis* carboxylate groups.

Our observation that the Brønsted coefficient β for the catalysis of the hydrolysis of VIII by simple monocarboxylate ions is 0.85, a rather substantial value, is consistent with the postulation that under our reaction conditions the first step of eq 7 is rate determining. The same is true for our finding that the ratio $(k_{\text{OAc}})_{\text{H}_2\text{O}} / (k_{\text{OAc}})_{\text{D}_2\text{O}} = 1.32$ and for our demonstration that in the reaction of acetate with VIII the measured rate constants for inorganic sulfite and phenol production agree satisfactorily. Evidence that the mixed anhydride XII is produced as an intermediate comes from our determination that a significant yield of acetohydroxamic acid is formed when added hydroxylamine is present. Although we have not detected a substantial accumulation of the anhydride XII in our reaction mixtures, it is clear that hydroxylamine can compete effectively with water in its nucleophilic attack on the carbonyl carbon of this fleeting intermediate. The correspondence in our trapping experiments employing hydroxylamine between the rate of acetohydroxamic acid formation and those for phenol and inorganic sulfite release in the absence of hydroxylamine again supports the argument that under our conditions the first step of eq 7 is rate controlling.

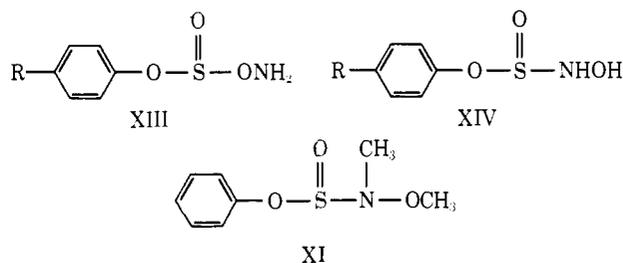
While our data on the monocarboxylate ion catalyzed hydrolysis of IX and X are confined to studies with acetate ion, the detection of acetohydroxamic acid in the solvolysis of these sulfite esters in acetate-hydroxylamine buffers supports the hypothesis that mixed anhydride species intervene in these reactions also as illustrated in eq 8 and 9. Although we were unable to measure the rates of acetohydroxamic acid generation in these cases, the observation that both molecules of *p*-nitrophenol and that phenol and *p*-nitrophenol are released synchronously in the reactions of IX and X, respectively, with acetate ion is in accord with the hypothesis that we are observing the first step in eq 8 and 9 as the rate-determining one. Unfortunately, although we did show that no great lag exists between



the rate of inorganic sulfite production in these reactions and the rate of formation of the phenolic species, we were not able to demonstrate experimentally the identity of these rates.

When the rate of phenol release from the solvolysis of VIII was measured in the acetate-hydroxylamine buffer employed to trap XII, we found that the formation of phenol was clearly accelerated by the addition of hydroxylamine. In other words, not only did hydroxylamine act to trap XII, but it also attacked VIII. Because of this observation and to broaden our knowledge of the aqueous reactions of sulfite esters with nucleophiles, we have carefully examined the solvolysis of VIII and X in hydroxylamine buffers. In contrast to our observations on the carboxylate ion catalyzed hydrolysis of these compounds, under the conditions we used, the intermediates formed by nucleophilic attack of hydroxylamine at the sulfite sulfur in VIII and X accumulate sufficiently to be detectable kinetically. The pathways for the hydroxylamine-catalyzed solvolysis of VIII and X involving these intermediates have been illustrated in eq 2 and 6 above. As expected from these equations which suggest that the intermediates formed from the reactions of VIII and X are identical, the $k_2^{\text{NH}_2\text{OH}}$ rate constants measured in the solvolysis of VIII and X are the same within experimental error. Because the value of $k_1^{\text{NH}_2\text{OH}}$ was much larger than that of $k_2^{\text{NH}_2\text{OH}}$ for the solvolysis of X, it was possible to show in this case that the intermediate did not absorb significantly at 280 nm. The identity of the intermediates postulated for the reactions of VIII and X provided thus a justification for analyzing the data measured at 280 nm for the hydroxylamine-catalyzed hydrolysis of VIII by means of eq 3 (*vide ante*) since diphenyl sulfite does not have an important absorption at that wavelength either.

While the reaction of bis-*p*-nitrophenyl sulfite with aqueous hydroxylamine was not investigated as thoroughly as those of VIII and X, the results obtained with IX are at last qualitatively in accord with the hypothesis that solvolysis occurs by a pathway similar to those shown in eq 2 and 6. Although the evidence is strong that intermediates are formed in the solvolysis of the sulfite esters in hydroxylamine buffers, the structures of the intermediates have not been determined. Either of the structures illustrated by formulas XIII and XIV appears to be possible. While



at first glance it might seem that if the intermediate had the structure shown in formula XV, containing a sulfur-nitrogen bond, it would not be very labile, the probability appears high that it could rapidly react *via* hydroxylamine catalysis to give phenol by an elimination process involving the ionizable proton on its nitrogen atom.

In the reaction of phenyl *p*-nitrophenyl sulfite (X) with aqueous *N,O*-dimethylhydroxylamine, as in the solvolysis of X in hydroxylamine buffers, phenol release has been found to occur at a much slower rate than that at which *p*-nitrophenol appears.²⁰ However, in the case of the *N,O*-dimethylhydroxylamine reaction, a corresponding ambiguity in the structure of the intermediate does not exist. The proposed structure for the intermediate is shown in formula XI. We have independently synthesized XI from the reaction of phenyl chlorosulfite with *N,O*-dimethylhydroxylamine and characterized this compound. Its solvolytic behavior in an aqueous acetate buffer corresponds to that of the intermediate formed from the aqueous reaction of *N,O*-dimethylhydroxylamine with X.

Our findings that reactive intermediates formed in the solvolysis reactions of sulfite esters can be detected readily, either by nucleophile trapping experiments as in the carboxylate ion catalyzed processes or by kinetic measurements as in the hydroxylamine-catalyzed reactions, have encouraged us to search further for conditions under which intermediates formed by nucleophilic attack by the active site enzymatic carboxylate groups of pepsin can be detected directly. The results of studies along these lines will be reported in due course.

Acknowledgments. Support of this research by National Science Foundation Grant GB13208 and by an Alfred P. Sloan Foundation Fellowship held by E. T. K. is gratefully acknowledged.

(20) It should be noted that both the steps leading to *p*-nitrophenol and phenol formation proceed considerably slower with *N,O*-dimethylhydroxylamine than with hydroxylamine.

Relative Reactivities of Methanol and Methoxide Ion as Hydrogen Atom Donors to the *p*-Nitrophenyl Radical¹

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Received August 18, 1973

Abstract: The relative hydrogen atom donor reactivities of CH₃OH and CH₃O⁻ toward the *p*-nitrophenyl radical are measured by the method of *ad eundem* competition. *p*-Nitrophenyl radical is generated, by the decomposition of methyl *p*-nitrophenylazo ether, in methanolic NaOCH₃ solutions in the presence of iodobenzene or neopentyl iodide, and the ratio of nitrobenzene to *p*-nitroiodobenzene yields is measured as a function of NaOCH₃ concentration. From the data, the hydrogen donor reactivity of CH₃O⁻ is reckoned to be 45 ± 10 times greater than that of CH₃OH. The data also furnish estimates of the hydrogen donor reactivities of these species relative to the iodine donor reactivities of the iodo compounds used.

Although the relative reactivities of numerous hydrogen atom donors toward reactive radicals have been measured,² such measurements appear not to have encompassed conjugate pairs of hydrogen donors comprising an alcohol and the corresponding alkoxide ion.

Most relative reactivity data have been obtained from direct competition experiments. The radical is generated in the presence of the hydrogen atom donor and a standard halogen atom donor (often CCl₄), and the relative rates of hydrogen and halogen atom abstraction are reckoned from the yields of the respective products with attention to the concentrations of the donor species.³ For example, relative hydrogen donor reactivities toward the phenyl radical were measured by Bridger and Russell⁴ and toward the *p*-nitrophenyl radical by Pryor and coworkers.⁵

The experimental method used in the cited studies^{4,5} requires solubility of the hydrogen donor species in CCl₄ or other halogen donor. Although it could be and was applied to study of the hydrogen donor activity of methanol, extension of it to methoxide ion would encounter obvious difficulties. Even if a methoxide salt soluble in CCl₄ could be found, with a cation devoid of hydrogen donor reactivity, interpretation would be complicated by ion association effects. Furthermore, it is in methanol solution that knowledge of the hydrogen donor reactivity of methoxide ion would be most useful. However, direct competition between methoxide ion and a halogen donor in methanol solution would not be feasible because methanol is itself a good hydrogen atom donor.

On the other hand, the problem can be dealt with by the method of *ad eundem* competition.

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. This research was supported in part by the National Science Foundation.

(2) G. A. Russell in "Free Radicals," Vol. I, J. K. Kochi, Ed., Wiley, New York, N. Y., 1973, pp 275-331.

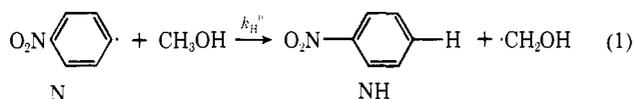
(3) The method of direct competition is discussed by G. A. Russell in "Investigation of Rates and Mechanisms of Reactions," 2nd ed, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience, New York, N. Y., 1961, p 344; L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, p 91.

(4) R. F. Bridger and G. A. Russell, *J. Amer. Chem. Soc.*, **85**, 3754 (1963).

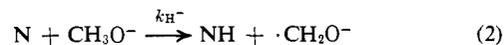
(5) W. A. Pryor, J. T. Echols, Jr., and K. Smith, *J. Amer. Chem. Soc.*, **88**, 1189 (1966); W. A. Pryor, K. Smith, J. T. Echols, Jr., and D. L. Fuller, *J. Org. Chem.*, **37**, 1753 (1972).

Method of *ad eundem* Competition.⁶ This method is useful when the competing reactions of a reactive intermediate with two species give the same product. To our knowledge, the method was first employed (in another type of system) by Mack and Huisgen.^{7a} Also, the use of a similar principle is implied by Pryor and coworkers.^{7b} One places the two reactions that give the same product in competition with a third reaction that gives a different product, and then measures the product ratio as a function of reactant concentration ratios.

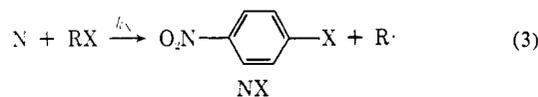
In the case of immediate interest, *p*-nitrophenyl radical (N) may react with methanol (eq 1) or meth-



oxide ion (eq 2) to form nitrobenzene (NH). Placed



in competition with these two is reaction with a halogen donor (RX)⁸ to form a *p*-nitrohalobenzene (NX), as in eq 3.



Assuming that these reactions are all second order, we write

$$d[\text{NH}]/dt = k_{\text{H}^{\cdot}}[\text{N}][\text{CH}_3\text{OH}] + k_{\text{H}^-}[\text{N}][\text{CH}_3\text{O}^-] \quad (4)$$

$$d[\text{NX}]/dt = k_{\text{X}}[\text{N}][\text{RX}] \quad (5)$$

(6) From the Latin *ad eundem fructus*, to the same product.

(7) (a) W. Mack and R. Huisgen, *Chem. Ber.*, **93**, 608 (1960); (b) W. A. Pryor, U. Tonellato, D. L. Fuller, and S. Jumonville, *J. Org. Chem.*, **34**, 2018 (1969).

(8) As a general principle the third, comparison reaction does not have to be halogen atom abstraction. J. A. Zoltewicz and T. M. Oestreich have shown that the 4-isoquinolyl radical in methanolic solutions containing both NaOCH₃ and NaSC₆H₅ undergoes competing hydrogen abstraction, from CH₃OH and CH₃O⁻, and combination with thiophenoxide as a nucleophile. Their observations of the dependence of the isoquinoline/4-thiophenoxyisoquinoline yield ratio on NaOCH₃ concentration indicate that methoxide ion is a much better hydrogen atom donor than methanol. Indeed, they formulated an equation equivalent to our eq 6 and constructed a plot of their data analogous to our Figure 1. However, the uncertainties of the slope and intercept were too great to enable evaluation of the CH₃O⁻/CH₃OH reactivity ratio; see T. M. Oestreich, Dissertation, University of Florida, 1973; J. A. Zoltewicz and T. M. Oestreich, *J. Amer. Chem. Soc.*, **95**, 6863 (1973).