Intramolecular Electrostatic and General Acid Catalysis in the Hydrolysis of *O,S*-Thioacetals

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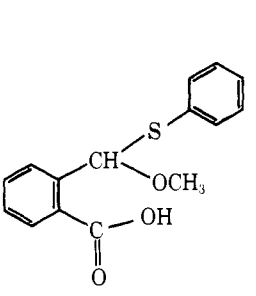
Abstract: The pH-independent release of thiophenolate ion from phthalaldehydic acid *O*-methyl *S*-phenyl thioacetal in H_2O at 50 °C and at pH values where the carboxyl group is ionized is 22 times faster than the corresponding reaction in hydrolysis of the terephthalaldehydic acid derivative. This rate difference arises because of electrostatic stabilization of the developing carbonium ion by the neighboring carboxylate ion. In view of the large amount of C–S bond breaking in the transition state the rate enhancement due to electrostatic effects must be near maximal in water for reactions in which a methoxybenzyl carbonium ion is produced. The plot of log k_{obsd} vs. pH for release of thiosalicylic acid from phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal at 50 °C in 50% dioxane–H_2O shows hydronium ion catalysis at low pH, and from pH 3 to 7 the profile is bell shaped. The value of the rate constant k_2 for hydronium ion catalyzed reaction of the dianionic species is 6×10^6 greater than the second-order rate constant k_H for hydronium ion catalyzed hydrolysis of the dimethyl ester and is 360-fold greater than the corresponding rate constant of terephthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal. The hydronium ion catalyzed neutral species reaction of phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal is retarded in 50% dioxane–H_2O as compared with H_2O, but k_2 is accelerated 50-fold. Both carboxyl groups are participating in hydrolysis of the monoanionic species, i.e., intramolecular general acid catalysis is occurring in conjunction with electrostatic stabilization effects. It is likely that intramolecular general acid catalysis also occurs in hydrolysis of benzaldehyde *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal and terephthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal, but rate enhancements are small in comparison with corresponding *O,O*-acetals. The significant electrostatic stabilization effects in the general-acid-catalyzed reaction of phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal in contrast with the absence of such effects in the intramolecular general-acid-catalyzed reaction of phthalaldehydic acid *O*-methyl *O*-salicyl acetal shows that much more bond breaking is required in the transition state in reaction of the thioacetal. The factors influencing concerted bifunctional catalysis are discussed.

There has been considerable recent interest in the mechanism of hydrolysis of thioacetals.[1-6] The hydrolysis of benzaldehyde *O*-methyl S-substituted phenyl thioacetals was shown to proceed with initial C–S bond breaking.[3,5] General acid catalysis by buffer acids was not detected in hydrolysis of those thioacetals even though hydrolysis of exactly analogous oxygen acetals is subject to pronounced general acid catalysis.[7] Likewise, large rate enhancements due to intramolecular general acid catalysis were not found in hydrolysis of benzaldehyde *O*-methyl *S*-salicyl thioacetal in contrast with benzaldehyde methyl salicyl acetal.[8] As a consequence of the very low basicity of sulfur in comparison to oxygen, these results supported the view that low basicity of the atom undergoing protonation was not the factor of primary importance in giving rise to general acid catalysis in acetal hydrolysis.[9-14]

In all cases where general acid catalysis has been observed in acetal hydrolysis, the bond-breaking process is facile[13,14] because of an extremely good leaving group (a phenol),[7,9,10] a highly stabilized carbonium ion intermediate when the leaving group is poor (an aliphatic alcohol),[11] or steric strain in the molecule which is relieved in the transition state.[12,15] Consequently, the lack of general acid catalysis in hydrolysis of benzaldehyde *O*-methyl *S*-phenyl thioacetals may be due to difficulty of breaking the C–S bond in comparison to C–O. In the concerted reactions of acetals occurring with partial proton transfer (indicated by α values of 0.5–0.7), the bond must begin to break while the proton is still at a distance. The pH-independent unimolecular breakdown of benzaldehyde *O*-ethyl *S*-phenyl thioacetal is 10^3 slower than the corresponding reaction of benzaldehyde methyl *m*-nitrophenyl acetal[5] even though *m*-nitrophenoxide is more basic than thiophenolate anion. Likewise, the E1cB elimination of thiol anions from esters is 10^3 slower than that of oxygen anions of comparable pK_a.[16] The pH-independent reactions of thioacetals are a factor of great importance since they make it impossible to search for general acid catalysis with the weak buffer acids which offer the best chance for success.[17] The above explanations[3] were meant only to apply to the benzaldehyde *O*-methyl S-substituted phenyl thioacetals; it seemed reasonable that hydrolysis of other types of thioacetals in which bond breaking is easier might indeed be general acid catalyzed.[3] Jensen and Jencks[5] have recently suggested that lack of general acid catalysis in hydrolysis of the benzaldehyde *O*-methyl S-substituted phenyl thioacetals is due to the difficulty of hydrogen bonding of the general acid to sulfur.

In the attempt to find general acid catalysis in thioacetal hydrolysis one cannot make bond breaking easier by improving the leaving group since that will also lower the pH at which the pH-independent reaction becomes important. For example, with benzaldehyde *O*-methyl *S*-(2,4-dinitrophenyl) thioacetal the reaction is pH independent over nearly the entire pH scale.[3] As Jensen and Jencks[5] have pointed out, the pH-independent reaction must occur at or before the pK_a of the leaving group. A possible approach, however, is to increase the stability of the carbonium ion intermediate beyond that of the methoxybenzyl carbonium ion. We have in fact found buffer acid catalysis in thioacetal hydrolysis in such cases.[18]

Electrostatic stabilization of the developing carbonium ion by a neighboring carboxyl group can increase the rate of acetal hydrolysis by a factor of 100–500-fold in 50% dioxane–H_2O in favorable cases where there is extensive bond breaking in the transition state.[19,20] Since in the pH-independent hydrolysis of benzaldehyde *O*-ethyl *S*-phenyl thioacetal the C–S bond is largely broken in the transition state,[5,6] electrostatic stabilization effects should be nearly maximal. To determine the magnitude of such an effect, we have studied the hydrolysis



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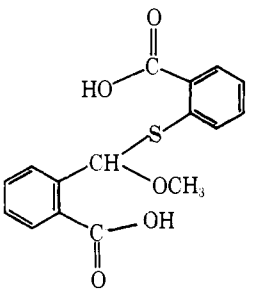

II

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Table I. Titrimetrically Determined pK_a Values in 50% Dioxane-H_2O (v/v) at 30 °C (μ = 0.1)

compd	pK_1	$^{a}pK_2$
phthalaldehydic acid *O*-methyl *S*-phenyl thioacetal	5.67	
terephthalaldehydic acid *O*-methyl *S*-phenyl thioacetal	5.76	
phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal	5.00	5.76 3.92[a]
terephthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal	5.05	5.78

[a] In H_2O at 30 °C, μ = 0.1.

of phthalaldehydic acid *O*-methyl *S*-phenyl thioacetal (I), and to determine whether electrostatic stabilization effects will allow intramolecular general acid catalysis by a neighboring carboxyl group in a concerted reaction, we have measured the rates of hydrolysis of phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal (II). For comparison purposes the corresponding terephthalaldehydic acid derivatives have also been studied.

Experimental Section

Materials. The thioacetals of phthalaldehydic acid and terephthalaldehydic acid were synthesized as previously described for analogous *O,O*-acetals.[19,20]

2-Carbomethoxybenzaldehyde *O*-methyl *S*-phenyl thioacetal had bp 130 °C (0.08 mm), $n^{21}D$ 1.5882. Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.67; H, 5.56. Found: C, 66.72; H, 5.38.

4-Carbomethoxybenzaldehyde *O*-methyl *S*-phenyl thioacetal had bp 135 °C (0.03 mm), $n^{20}D$ 1.5940. Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.67; H, 5.56. Found: C, 66.82; H, 5.53.

2-Carbomethoxybenzaldehyde *O*-methyl *S*-(2-carbomethoxyphenyl) thioacetal had bp 170 °C (0.005 mm), $n^{21}D$ 1.5950. Anal. Calcd for $C_{18}H_{18}O_5S$: C, 62.43; H, 5.20. Found: C, 62.66; H, 5.00.

4-Carbomethoxybenzaldehyde *O*-methyl *S*-(2-carbomethoxyphenyl) thioacetal had bp 180 °C (0.005 mm), $n^{21}D$ 1.6023. Anal. Calcd for $C_{18}H_{18}O_5S$: C, 62.43; H, 5.20. Found: C, 61.63; H, 4.83.

3-Methoxyphthalide was synthesized by the method of Bender et al.[21] (mp 45-46 °C, lit.[21] 42-44 °C).

The thioacetal esters were converted to thioacetal acid sodium salts by hydrolysis in NaOH-EtOH solutions. These salts were not isolated but were used directly in the kinetic studies. The dioxane used in these studies was spectral grade (Mallinckrodt) and was refluxed over sodium borohydride for at least 3 h and freshly distilled prior to use.

Kinetic Measurements. The rates of hydrolysis of the thioacetals at 30 or 50 °C in water or 50% dioxane-H_2O (v/v) were measured on a Beckman Model 25 or a Pye Unicam SP8-100 recording spectrophotometer. The ionic strength was maintained at μ = 0.1 with KCl, and all solutions contained 2×10^{-5} M EDTA to prevent trace metal ion catalyzed oxidation of the thiophenol product. In addition, the 50% dioxane-water (v/v) solutions were deoxygenated by bubbling nitrogen through them for 10 min prior to use. Buffer concentrations were 0.02 M when required.

Rates of hydrolysis of the terephthalaldehydic acetals were measured by following appearance of aldehyde at 255 nm. With phthalaldehydic acid *O*-methyl *S*-phenyl thioacetal (I), the rates from pH 1.2 to 3.9 were measured by following disappearance of thioacetal at 260 nm. From pH 4.0 to 5.0, no kinetic measurements were possible, as the rates of reaction of the thioacetal and hydrolysis of the product, 3-methoxyphthalide, are similar and have opposing absorbance changes. At pH values greater than 5, the rate of reaction of the thioacetal is much slower than that of 3-methoxyphthalide hydrolysis, so the former could be measured by monitoring the appearance of aldehyde at 260 nm. In the case of phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal (II), the rates were measured by following the disappearance of thioacetal at 266 nm from pH 1 to 4 (1-5 in dioxane-H_2O), appearance of thiosalicylate anion at 241 nm at pH values from 5 to 7, and appearance of aldehyde at 255 nm from pH 8 to 9. In the region where these absorbance changes overlapped, the kinetic measurements were independent of wavelength. Hydrolysis rates of the dimethyl ester of II were measured by following appearance of aldehyde at 255 nm.

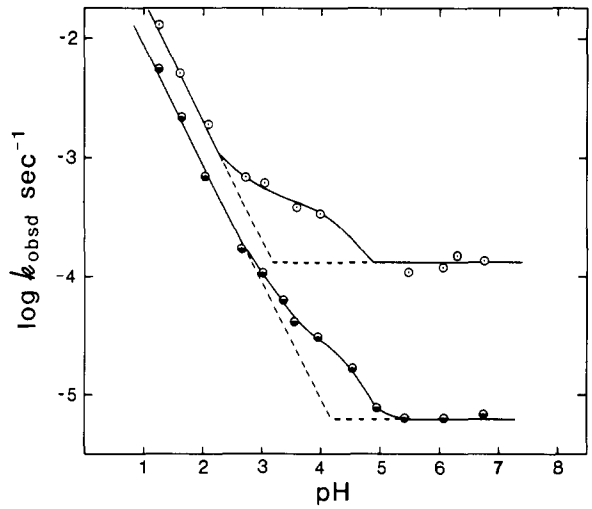


Figure 1. Plots of log k_{obsd} vs. pH for release of thiophenol from phthalaldehydic acid *O*-methyl *S*-phenyl thioacetal (⊙) and terephthalaldehydic acid *O*-methyl *S*-phenyl thioacetal (◒) in H_2O at 50 °C, μ = 0.1 (with KCl).

In a typical kinetic experiment, 5-10 μL of the thioacetal stock solution was injected into 2-3 mL of reactant solution maintained at the desired temperature. The reactions followed pseudo-first-order kinetics for at least 4 half-lives. Pseudo-first-order rate constants and subsequent kinetic parameters were evaluated using a nonlinear least-squares computer program. Reaction mixture pH values were measured with a Beckman Model 3500 digital pH meter.

Determinations of the pK_a values of the thioacetals at 30 °C, μ = 0.1 (with KCl), in 50% dioxane-H_2O (v/v) were made using a Radiometer Type SBR2c/TTT1c titration assembly which has previously been described.[22] With the exception of II, the thioacetals were not sufficiently soluble in H_2O to permit accurate pK_a determinations in that medium. The titrimetrically determined pK_a values are given in Table I.

Product Analysis. 3-Methoxyphthalide was shown to be a product of the reactions in the following manner. The dimethyl ester of II (0.5 g) was dissolved in 10 mL of 80/20 EtOH-H_2O containing 1 M NaOH and was allowed to stand for 1 h at room temperature. This solution was poured into 100 mL of 0.2 M acetate buffer solution which had previously been equilibrated in a 50 °C bath. The final pH of the reaction mixture was 4.65. After 8 min, the solution was removed from the 50 °C bath and quickly extracted with four 125-mL portions of hexane. The hexane extracts were combined and dried with sodium sulfate, and the solvent was removed by rotary evaporation. The white residue which remained had an infrared spectrum very similar to that of 3-methoxyphthalide. Recrystallization of the residue from hexane yielded white crystals whose melting point (42-43 °C) and infrared spectrum were identical with those of 3-methoxyphthalide (42-44 °C).[21]

Results

In Figure 1 is shown a plot of log k_{obsd} vs. pH for release of thiophenol from phthalaldehydic acid *O*-methyl *S*-phenyl thioacetal (I) in H_2O at 50 °C, μ = 0.1, with KCl. Hydronium ion catalysis is observed, k_H = 0.20 M^{-1} s^{-1}, and at pH values greater than 5 the reaction is pH independent, $k_0 = 1.25 \times 10^{-4}$ s^{-1}. Also included in Figure 1 is a plot of log k_{obsd} vs. pH for hydrolysis of terephthalaldehydic acid *O*-methyl *S*-phenyl thioacetal in H_2O at 50 °C. The rate constant for the pH-independent reaction, $k_0 = 5.8 \times 10^{-6}$ s^{-1}, is 22-fold less than the corresponding rate constant for reaction of I. The observed rate constants should follow the equation

$$k_{obsd} = \frac{k_H a_H^2 + k_1 K_1 a_H + k_0 K_1}{K_1 + a_H} \quad (1)$$

where k_1 is the rate constant for hydronium ion catalyzed reaction of the anionic species and K_1 is the apparent dissociation

Table II. Rate Constants for Reaction of Carboxyl Substituted Thioacetals at 50 °C in H_2O or 50% Dioxane-H_2O (v/v), μ = 0.1 (with KCl), and Kinetically Determined pK_a Values

compd	solvent	$k_H \times 10^2$, $M^{-1} s^{-1}$	$k_0 \times 10^4$, s^{-1}	k_1, $M^{-1} s^{-1}$	k_2, $M^{-1} s^{-1}$	pK_1	pK_2
phthalaldehydic acid *O*-methyl *S*-phenyl thioacetal	H_2O	20.2	1.25	3.7		3.8	
	50% dioxane-H_2O	0.3					
terephthalaldehydic acid *O*-methyl *S*-phenyl thioacetal	H_2O	8.41	0.058	0.38		4.0	
phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal	H_2O	129	0.32	*a*	713	3.22	4.09
	50% dioxane-H_2O	4.17		31.4	37800	5.26	5.86
terephthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal	H_2O	35.6		*a*	44		4.42
	50% dioxane-H_2O	1.20		3.86	105	5.13	5.77

[a] Values of k_1 in H_2O were indeterminate.

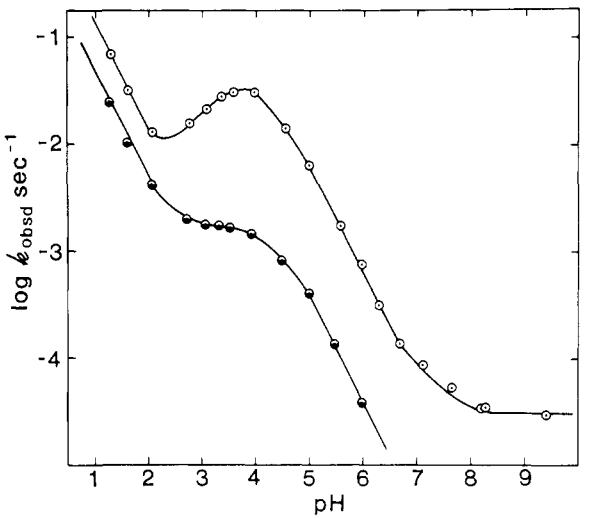


Figure 2. Plots of log k_{obsd} vs. pH for release of thiosalicylic acid from phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal (⊙) and terephthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal (◒) in H_2O at 50 °C, μ = 0.1 (with KCl).

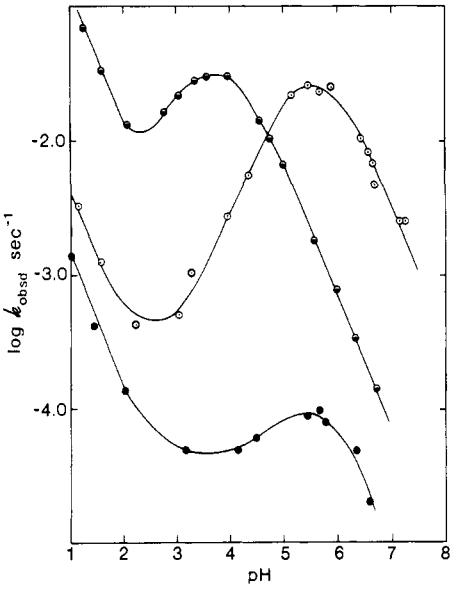


Figure 3. Plots of log k_{obsd} vs. pH for release of thiosalicylic acid from phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal in 50% dioxane-H_2O (v/v) (⊙) and in H_2O (◒) and from terephthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal in 50% dioxane-H_2O (v/v) ●) at 50 °C, μ = 0.1 (with KCl).

constant of the carboxyl group. In 50% dioxane-H_2O as the solvent the hydronium ion catalyzed reaction of I is retarded by a factor of 67, $k_H = 3 \times 10^{-3}$ $M^{-1} s^{-1}$, as compared with H_2O. The value of k_0 could not be determined in 50% dioxane-H_2O since the acylal product of the reaction hydrolyzes in the required pH range (pH 4.4-6.6, $k_0 = 6.61 \times 10^{-4}$ s^{-1} in H_2O at 50 °C) and thereby complicates the kinetic measurements at 260 nm. Computer best fit rate constants for these reactions are tabulated in Table II. Values of k_1 and K_1 are not highly precise, standard deviations for these constants are larger than desired because of the small deviation of k_{obsd} from the equation in which these constants are omitted.

A plot is presented in Figure 2 of log k_{obsd} vs. pH for release of thiosalicylic acid from phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal (II) in H_2O at 50 °C, μ = 0.1, with KCl. At low pH hydronium ion catalysis occurs, k_H = 1.29 $M^{-1} s^{-1}$. At pH values greater than 2.5 the profile is bell shaped. The observed rate constants give a good fit to the equation

$$k_{obsd} = \frac{k_H a_H^3 + k_1 K_1 a_H^2 + k_2 K_1 K_2 a_H + k_0 K_1 K_2}{a_H^2 + K_1 a_H + K_1 K_2} \quad (2)$$

in which k_1 is the rate constant for hydronium ion catalyzed reaction of the monoionized species, k_2 is the rate constant for hydronium ion catalyzed reaction of the dianion, and K_1 and K_2 are the first and second acid dissociation constants of the thioacetal. The equation for the kinetically equivalent intramolecular general-acid-catalyzed reaction of the neutral and monoanionic species is

$$k_{obsd} = \frac{k_H a_H^3 + k_{H_2A} a_H^2 + k_{H_1A} K_1 a_H + k_0 K_1 K_2}{a_H^2 + K_1 a_H + K_1 K_2} \quad (3)$$

where k_{H_2A} is the rate constant for intramolecular general catalysis in the neutral species and k_{H_1A} is the rate constant for reaction of the monoanion. Note that the kinetic equivalencies

$$k_{H_2A} = k_1 K_1 \qquad k_{H_1A} = k_2 K_2 \quad (4)$$

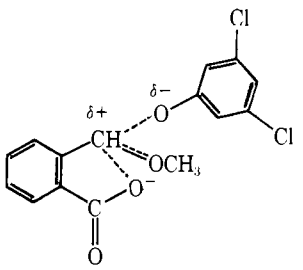
hold. A plot is also given in Figure 2 of log k_{obsd} vs. pH for hydrolysis of terephthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal in H_2O at 50 °C, μ = 0.1, with KCl. Rate constants for these reactions are also tabulated in Table II.

In Figure 3 a plot is shown of log k_{obsd} vs. pH for release of

thiosalicylic acid from II at 50 °C in 50% dioxane-H_2O, μ = 0.1, with KCl. For comparison purposes the profile for reaction in water is also included. It can be seen that k_H is greatly retarded in 50% dioxane-H_2O; the value of k_{obsd} at pH 2.5 is 30-fold less than in H_2O. However, k_2 is 50-fold greater in 50% dioxane-H_2O. A plot of log k_{obsd} vs. pH is also shown in Figure 3 for hydrolysis of terephthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal in 50% dioxane-H_2O at 50 °C. The hydrolysis of the dimethyl ester of II in 50% dioxane-H_2O at 50 °C, μ = 0.1, is hydronium ion catalyzed with $k_H = 6 \times 10^{-3}$ M^{-1} s^{-1}.

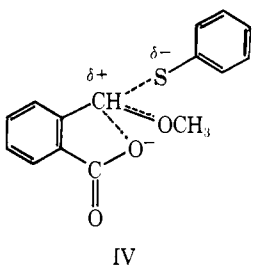
Discussion

The pH-independent rate of reaction of phthalaldehydic acid 3,5-dichlorophenyl methyl acetal in 50% dioxane-H_2O is 100-fold faster than that of the corresponding *p*-carboxyl substituted compound,[19] indicating that electrostatic stabilization of the developing carbonium ion by the neighboring carboxylate anion is important (III). In this reaction there must



III

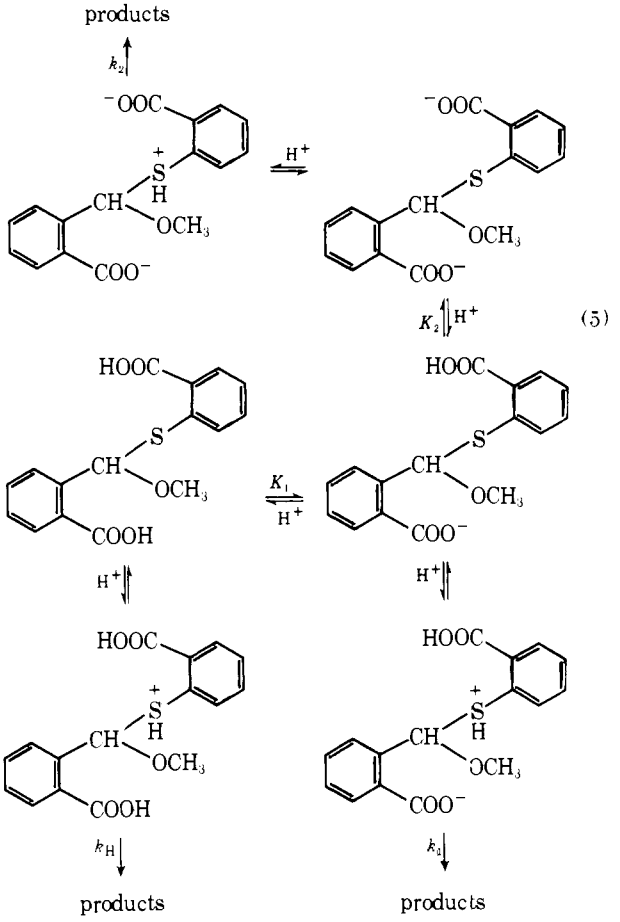
be considerable C-O bond breaking in the transition state. Since there is evidently almost complete C-S bond breaking in the transition state in the pH-independent breakdown of benzaldehyde *O*-ethyl *S*-phenyl thioacetal,[5,6] near maximum electrostatic stabilization effects by a neighboring carboxyl group should be obtained. In H_2O at 50 °C the pH-independent reaction of phthalaldehydic acid *O*-methyl *S*-phenyl thioacetal (I) is 22-fold faster than that of the terephthalaldehydic acid derivative, and mechanism IV is undoubtedly



IV

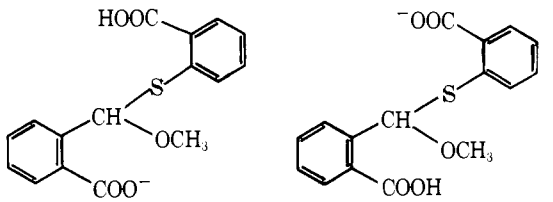
occurring. It has been shown previously that the thiophenol group of benzaldehyde *O*-methyl *S*-phenyl thioacetals is the initial leaving group.[3,5] This is confirmed in the present work by the fact that 3-methoxyphthalide is a reaction product. The rate enhancement will increase as the dielectric constant of the solvent decreases. The hydrolyses of I and the reference thioacetal were much too slow to follow conveniently in 50% dioxane-H_2O at the required pH values, but reasonable estimates of the enhancement would place it in the range 10^2–10^3 which has previously been observed in acetal hydrolysis in 50% dioxane-H_2O.[19,20] A rate enhancement of that magnitude is very likely near maximal for carboxylate ion stabilization of a developing alkoxybenzyl carbonium ion in 50% dioxane-H_2O. If the pH-independent breakdown of thioacetals involves rate-determining diffusion-controlled separation of an oxocarbonium ion and thiophenolate ion as suggested,[5,6] then apparent electrostatic catalysis by a neighboring carboxyl group could be due to carbonium ion capture which would prevent reversal of the reaction.

The reaction of the dicarboxyl substituted thioacetal II involves hydronium ion catalyzed hydrolysis of the neutral, monoanionic, and dianionic species (eq 5) or the kinetically



(5)

equivalent intramolecular general-acid-catalyzed reactions of the neutral and monoanionic species. There are two possible monoanionic species (V and VI). It would be expected that an



V VI

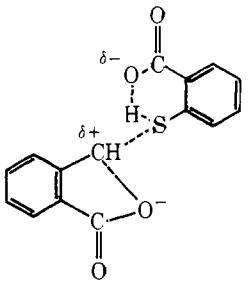
intramolecular general-acid-catalyzed reaction would proceed through species V, since the leaving group would then be better and the developing carbonium ion in the transition state would be more highly stabilized.

The thioacetal II has a bell-shaped pH–rate constant profile for release of thiosalicylic acid in common with that of the corresponding oxygen acetal. The value of k_2, the rate constant for hydronium ion catalyzed reaction of the dianion, in 50% dioxane-H_2O is 6×10^6 larger than k_H for hydrolysis of the corresponding dimethyl ester. This comparison is, of course, not exact because of the different electronic effects exerted by carboxyl and carbomethoxy groups. Small differences in electronic effects in the leaving group would not be significant in view of the small ρ value (−1.0) for hydronium ion catalyzed hydrolysis of benzaldehyde *O*-methyl *S*-substituted phenyl thioacetals,[3] but differences in ease of carbonium ion stabilization from the aldehyde portion of the molecule would also exist. Nevertheless, the magnitude of the rate difference shows convincingly that carboxyl group participation is occurring in

the reaction of II. In H_2O k_2 for II is 2×10^3 greater than k_1, the rate constant for hydronium ion catalyzed hydrolysis of the ionized species of the electronically similar terephthalaldehydic acid methyl *S*-phenyl thioacetal.

The phthalaldehydic acid carboxyl group has an important electrostatic influence on the monoanion reaction. In Figure 3 it can be seen that in the reaction of II k_H is retarded in 50% dioxane-H_2O, but k_2 is markedly enhanced (50-fold). The rate retardation encountered in hydronium ion catalyzed reaction of the neutral species most likely reflects the increased difficulty of formation of the conjugate acid and carbonium ion intermediates (eq 5). The marked rate acceleration of the k_2 step in 50% dioxane-H_2O as compared with H_2O must indicate that the transition state is less highly charged than reactant, i.e., that charge is being destroyed by electrostatic interaction of the carboxylate anion and the incipient carbonium ion. For this to occur there must be considerable bond breaking in the transition state so that electrostatic interactions can be significant. The rate constant k_2 in reaction of II is 16-fold greater in H_2O and 360-fold greater in 50% dioxane-H_2O than the corresponding rate constant for the analogous terephthalaldehydic acid thioacetal.

The key question in regard to the thioacetal II is whether electrostatic stabilization effects by the phthalaldehydic acid carboxylate anion will alter the transition state sufficiently that the salicyl carboxyl group can function effectively as an intramolecular general acid. The rate increase in comparison with the dimethyl ester is clearly beyond that expected solely on the basis of an electrostatic effect, and it is apparent that both carboxyl groups of II are participating.[23] The ratio of k_{H_1A} for reaction of II in H_2O to k_0 for I is a factor of 465. This comparison shows directly the effect of substitution of a carboxyl group which can function as a general acid into the ortho position of the leaving group.[24] At the top of the bell-shaped region in the pH–rate constant profile of II k_{obsd} is 100-fold greater than in the reaction of I, and k_2 for II is 200-fold larger than the k_1 of I. Thus, the thiosalicyl carboxyl is contributing a factor of $\sim 10^2$ to the rate constants, and mechanism VII is likely.[23] It might be noted that a pH-independent reaction of



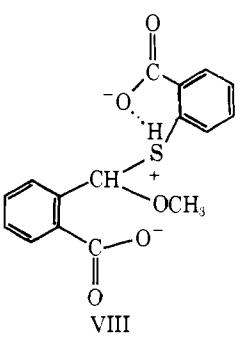
VII

the dianionic species is only observed in the reaction of II at pH >7. This is a reflection of the higher basicity of the thiosalicyl leaving group (pK_a = 7.79)[25] as compared with thiophenol (pK_a = 6.43)[26] and the rate-enhancing effect of the un-ionized thiosalicyl carboxyl group.

Large rate enhancements are observed in the reaction of phthalaldehydic acid *O*-methyl *O*-salicyl acetal where the salicyl carboxyl group functions as an intramolecular general acid,[20] but in that case the phthalaldehydic acid carboxyl group does not participate in the reaction. This lack of electrostatic stabilization effects is due to the transition state being attained before the C–O bond is extensively broken, i.e., there is little carbonium ion character in the transition state. Bond breaking must be facile in the general-acid-catalyzed reaction of the *O,O*-acetal resulting in a transition state with little bond breaking. However, for electrostatic stabilization effects to be significant there must be pronounced bond breaking. With the thioacetal II the large electrostatic stabilization effects in the monoanion reaction indicate that a transition state with significant carbonium ion character is being formed. A transition state with more carbonium ion character than in the case of the corresponding *O,O*-acetal must reflect more difficulty in bond breaking in the thioacetal reaction.

In the monoanion reaction of II the alternative that proton transfer from the thiosalicyl carboxyl group does not occur, i.e., the reaction is a unimolecular breakdown of the monoanionic species, is highly unlikely. Such a mechanism would demand that the monoanionic species with an un-ionized thiosalicylic acid carboxyl have a rate constant for unimolecular breakdown 1800-fold greater than that of the dianionic species (see Figure 2). In contrast, in reaction of phthalaldehydic acid *O*-methyl *S*-(*p*-carboxyphenyl) thioacetal[23] in H_2O, the ratio of the pH-independent rate constants for the monoanionic and dianionic species is only a factor of 5. The difference in the rate constants of 11 is too large to be explained by electronic effects considering the fairly small difference in electron-withdrawing ability of ionized and un-ionized carboxyl ($\Delta\sigma_{para} \sim 0.3$–$0.4$). The Hammett ρ value for pH-independent breakdown of benzaldehyde *O*-methyl *S*-(*p*-substituted phenyl) thioacetals in 20% dioxane-H_2O is 2.8,[28] and the ρ value is only 2.4 for pH-independent solvolysis of 2-aryloxytetrahydrofurans,[29] which give a carbonium ion intermediate much less stable than that derived from II.

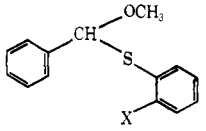
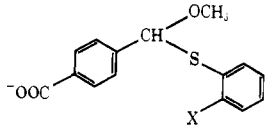
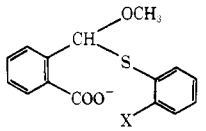
Mechanism VII has been shown as a concerted process in which C–O bond breaking and proton transfer occur simultaneously. Bimolecular general acid catalysis in acetal hydrolysis proceeds by a concerted process in view of Brønsted coefficients in the range 0.5–0.7.[7,10,12,30] It is reasonable that this is also the case in intramolecular reactions. In the hydrolysis of benzaldehyde methyl salicyl acetal[8] and *o*-carboxybenzaldehyde methyl salicyl acetal[20] proton transfer is only partial in the transition state since any mechanism involving a conjugate acid intermediate (A-1) can be ruled out. Complete proton transfer to the leaving group in those cases would demand that the rate constant for transfer of a proton from the conjugate acid to H_2O would be much greater than a rate constant for a diffusion-controlled reaction, i.e., $>10^{10}$ M^{-1} s^{-1}. However, in reactions of II formation of a conjugate acid intermediate cannot be rigorously excluded if the dissociation constant of the conjugate acid is less than 10^{11} M. Catalysis could then conceivably result from carboxylate ion stabilization of a proton on the leaving group (VIII), thereby



VIII

lowering the dissociation constant of the conjugate acid. Such a mechanism was suggested by Dunn and Bruice[31] to explain the rate enhancements (less than 10^3) found in hydrolysis of methoxymethoxybenzoic acid where the intermediate carbonium ion is quite unstable. Phenolic acetals must have dissociation constants of $\sim 10^9$ M,[8] and analogous thioacetals should be much less basic. Therefore, a dissociation constant for II of 10^{11} M or greater would not be unreasonable. While mechanism VIII cannot be rigorously excluded, it must be considered unlikely. If a proton were completely transferred to sulfur then little C–S bond breaking would occur[5,6] in the

Table III. The Effect of Substitution of a Carboxyl Group into the Ortho Position of the Leaving Group of Thioacetals

compd	X	T, °C	k_H, M^{-1} s^{-1}	k_1, M^{-1} s^{-1}	k_2, M^{-1} s^{-1}	k_{rel} (k_2/k_1 or k_1/k_H)
	H	30	0.019[a]			
	COOH	30		9.32[b]		122[c]
	H	50		0.38[b]		
	COOH	50			44[b]	116
	H	50		3.72[b]		
	COOH	50			713[b]	192

[a] In 20% dioxane-H_2O (ref 3). [b] In H_2O. [c] Making a reasonable allowance for differences in solvent (fourfold)[5] in k_H.

Table IV. Comparison of Rate Constants for Hydrolysis of Salicyl and Thiosalicyl Acetals in H_2O and 50% Dioxane-H_2O

compd	temp, °C	solvent	k_1, M^{-1} s^{-1}	k_2, M^{-1} s^{-1}	k_{H_1A},[a] s^{-1}
benzaldehyde methyl salicyl acetal[b]	30	H_2O	2.94×10^7		
	30	50% dioxane-H_2O	5.55×10^7		110[c]
phthalaldehydic acid methyl salicyl acetal[b]	30	H_2O		8.86×10^6	
	30	50% dioxane-H_2O		1.68×10^8	140[d]
	15	50% dioxane-H_2O	3.12×10^5	5.44×10^7	45.2
benzaldehyde *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal[e]	30	H_2O	9.32		3×10^{-3}
phthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl)thioacetal	30	H_2O	2.14	37.1	7.5×10^{-3}
	50	H_2O		713	5.8×10^{-2}
	50	50% dioxane-H_2O	31.4	3.8×10^4	5.2×10^{-2}
2-(*o*-carboxyphenoxy)tetrahydropyran[e]	15	50% dioxane-H_2O	1.4×10^4		2.7×10^{-2}
	15	H_2O	3.4×10^3		

[a] Rate constant for intramolecular general acid catalysis by the salicyl carboxyl group. [b] Reference 20. [c] Calculated with the assumption that the pK_a of the salicyl carboxyl group is the same as determined for 2-(*o*-carboxyphenoxy)tetrahydropyran (5.7) at 15 °C. [d] Calculated with the assumption that the pK_a of the salicyl carboxyl group is the same as determined for phthalaldehydic acid methyl salicyl acetal at 15 °C (6.08). [e] Reference 8.

transition state, and consequently, electrostatic stabilization by the phthalaldehydic acid carboxylate anion would not be significant, which is contrary to the evidence. Thus, it is probable that a conjugate acid intermediate is not being formed in the monoanion reaction of II. In an intramolecular general-acid-catalyzed reaction (VII) proton transfer is only partial in the transition state and, as a consequence, the amount of bond breaking required is greater than in a corresponding hydronium ion catalyzed reaction where the proton is completely transferred to the leaving group. In the monoanion reaction of II the amount of bond breaking in the transition state must be sufficiently balanced so that both carboxyl groups can participate.

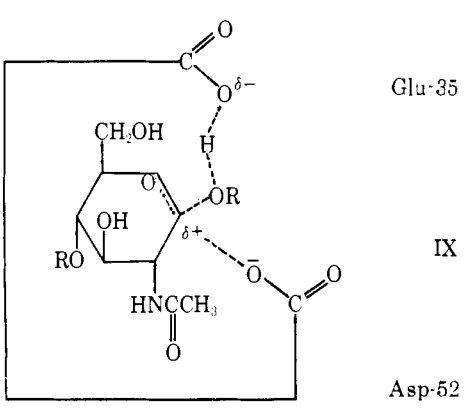
A comparison of the effect of replacing H by carboxyl in the ortho position of the thiophenol leaving group in various thioacetals is presented in Table III. It can be seen that the relative increase in rate produced by carboxyl group substitution is very similar for benzaldehyde, phthalaldehydic acid, and terephthalaldehydic acid *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal ($k_{rel} \sim 10^2$). The electronic effect of an ionized carboxyl is small ($\sigma \sim 0$). Therefore, the magnitude of the rate enhancements produced by the neighboring carboxyl group clearly does not derive from polar substituent effects but indicates direct participation in all three cases. The fact that the k_{rel} values in Table III are similar for the phthalaldehydic acid and terephthalaldehydic acid thioacetals shows that electrostatic stabilization effects have only a small enhancing effect in H_2O (twofold) on intramolecular general acid catalysis by the thiosalicyl carboxyl group. On the other hand, the pronounced electrostatic stabilization effects by the phthalaldehydic acid carboxylate anion in the concerted reaction VII result in a large overall rate enhancement which increases greatly as the dielectric constant of the solvent is lowered. Thus, the ratio of k_2/k_H (Table II) for the terephthalaldehydic acid derivative goes from 120 in H_2O to 9000 in 50% dioxane-H_2O, whereas the same ratio for II goes from 550 to 910 000 as the solvent is changed and electrostatic stabilization effects become of greater significance.

In Table IV a comparison of rate constants is given for the thioacetals and the exactly analogous oxygen acetals. The rate constants of the oxygen acetals are much greater, and rate enhancements from intramolecular general acid catalysis by the salicyl carboxyl group are all of the order 10^5–10^6,[8,20] calculated as the ratio of the rate constant for hydronium ion catalyzed hydrolysis of the ionized species to the rate constant for hydronium ion catalyzed hydrolysis of suitable reference compounds.[32] The rate constants for intramolecular general acid catalysis (k_{H_1A}) are 10^4 less for the thiosalicyl acetals as might be expected considering the much lower basicity of sulfur than oxygen and the greater difficulty of unimolecular cleavage of the C-S bond. The ratio of k_1/k_H for hydrolysis of 2-(*o*-carboxyphenoxy)tetrahydropyran in H_2O[8] is 10^3

whereas that ratio for benzaldehyde *O*-methyl *S*-(*o*-carboxyphenyl) thioacetal[8] is 30, a factor of 33 less. The much smaller rate enhancements with the thioacetals must be due to the fact that more bond breaking is required to attain the transition state in general-acid-catalyzed thioacetal hydrolysis. The ratio of k_1/k_H should then be smaller than with analogous oxygen acetals with which less bond breaking can occur in the transition state. This then accounts for the lack of detectable bimolecular general acid catalysis in thioacetal hydrolysis[3,5] in contrast with analogous oxygen acetals, i.e., the rate increases are simply not large enough with the relatively strong buffer acids that must be employed. However, in intramolecular general-acid-catalyzed reactions of acetals the effective molarity of a neighboring carboxyl group can be 10^4 M or greater.[8,33] Thus, general acid catalysis can be detected in intramolecular reactions of thioacetals.

The evidence is clear that intramolecular carboxyl group participation is occurring in the reactions of I and II. Electrostatic stabilization of the developing carbonium ion gives rate enhancements that are comparable to those that have been obtained in reactions of acetals. It is also apparent in view of the magnitude of k_2 in H_2O and 50% dioxane–H_2O that both carboxyl groups of II are participating in the reaction of that thioacetal. Thus, if the carbonium ion is sufficiently stabilized, general acid catalysis can occur in an intramolecular reaction when the leaving group is thiosalicyl.

Concerted Bifunctional Catalysis. A number of mechanisms have been proposed for action of the glycosidic enzyme lysozyme all of which involve intracomplex general acid catalysis by glutamic acid-35.[34,35] The mechanism that has received the most attention utilizes concerted general acid catalysis by Glu-35 and electrostatic stabilization of the developing carbonium ion by Asp-52 (IX). Recently the possible electrostatic



stabilization effects by Asp-52 have been stressed.[36,37] The rate enhancements of 100–500 due to this effect by a neighboring carboxyl group in acetal hydrolysis reactions in 50% dioxane–water[19,20] and the factor of 22 found for hydrolysis of I in H_2O should be nearly maximal because of the large amount of bond breaking required to attain the transition states of the respective reactions. The magnitude of the electrostatic stabilization effect will, of course, increase as the dielectric constant of the solvent is decreased. Capon and Anderson[38] reported that in 82% dioxane–H_2O the carboxyl group of phthalaldehydic acid diethyl acetal acts as a nucleophile. However, in 82% dioxane–H_2O the pK_a of the carboxyl group is approximately 11. Thus, decreasing greatly the dielectric constant of the solvent beyond that of 50% dioxane–H_2O may have little relevance for the lysozyme reaction. In the free enzyme a pK_a of 4.5 has been reported for Asp-52,[39] and the pK_a of 5.9 for Glu-35[39] corresponds to the pK_a of acetic acid in 50% dioxane–H_2O (6.1). Exclusion of H_2O from the active site in the enzyme–substrate complex should have a drastic effect on the pK_a values and would inhibit the efficiency of the hydrolytic reaction, but pK_a values are not greatly different in complexes of the enzyme.[39]

A fundamental problem with the concerted mechanism IX is that the structural features that will allow general acid catalysis and electrostatic catalysis are in opposition. For maximum occurrence of general acid catalysis bond breaking must be facile,[13,14] resulting in a transition state with little bond breaking. Significant electrostatic catalysis, on the other hand, requires a transition state in which there is considerable carbonium ion development, i.e., extensive bond breaking. A concerted mechanism (IX) then requires a precise balancing of effects which is reflected in the amount of bond breaking in the transition state. This condition is met in the hydrolysis of benzaldehyde di(*cis*-2-carboxycyclohexyl) acetal[20] and in reaction of II in the present work.

The concerted mechanism demands a compromise in that the catalytic effect of neither carboxyl group will be maximal in comparison with structurally favorable systems. The advantage of the concerted mechanism is manifested when the leaving group is poor in that the effect of one functional group then makes possible greater participation by the other. Thus, in contrast with benzaldehyde di(*cis*-2-carboxycyclohexyl) acetal, carboxyl participation is not detected in hydrolysis of benzaldehyde *cis*-2-carboxycyclohexyl methyl acetal.[20] Rate enhancements due to the concerted mechanism, although significant (10^4–10^5), are not extraordinarily large.[20] The enhancements in k_{obsd} provided by general acid catalysis alone in cases where the leaving group is phenolic range from 10^5 to 10^6 with 2-(*o*-carboxyphenoxy)tetrahydropyran and benzaldehyde methyl salicyl acetal[8] in comparison with hydronium ion catalyzed hydrolysis of the ester, unsubstituted acetal, or *p*-carboxyl substituted derivative.[32] This rate enhancement is 3×10^9 in the case of benzaldehyde disalicyl acetal in comparison with hydronium ion catalyzed hydrolysis of the dimethyl ester.[32,33] As a consequence, in the lysozyme-catalyzed hydrolysis of substrates where the leaving group is poor and the intermediate carbonium ion is normally quite unstable, additional features may be involved to account for the rates of the enzymatic reaction.

Concerted bifunctional intracomplex mechanisms have often been postulated for enzymatic reactions. There are numerous examples of external general base catalysis in the intramolecular nucleophilic reactions of esters and amides,[14] but these are generally cases where the external catalyst assists breakdown of the tetrahedral intermediate formed in the nucleophilic reaction.[14,40-42] Examples of concerted bifunctional catalysis in intramolecular reactions have been rare or nonexistent.[43] Explanations have been given for the apparent difficulty of concerted bifunctional catalysis,[44,45] stressing the difficulty of meeting at two sites the requirement that basicity of the catalyst be intermediate between reactant and product,[44] and the unfavorable effect of precise orientation of the second functional group. This results in a more negative $\Delta S^{\ddagger}$ which at least partially offsets any favorable effect on $\Delta H^{\ddagger}$.[45] Although the ease of alignment of the two functional groups is undoubtedly of importance, it is now clear that other factors can be of predominant significance; the transition state required for maximum effectiveness of participation by one functional group may make participation by a second group impossible. Concerted bifunctional catalysis may become important in those cases where neither functional group will participate effectively alone.

Acknowledgment. This work was supported by a research grant from the National Institutes of Health. We also express our appreciation to Professor William P. Jencks for a copy of his manuscript (ref 5) prior to its publication.

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On the Electron-Donating Properties of Oxygen vs. Sulfur. Redox Potentials for Some Pyrylium and Thiapyrylium Salts

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Received January 29, 1979

Abstract: The redox levels for two series of pyrylium and thiapyrylium salts were measured by cyclic voltammetry. This information was utilized to provide a quantitative comparison of the highest occupied (HOMO) and lowest unoccupied molecular orbitals (LUMO) which is a measure of the thermodynamic stabilities to electron transfer of oxygen vs. sulfur adjacent to carbon cation, radical, and anionic centers in a single system. In one of the series [i.e., 4-(4′-diethylaminophenyl)-2,6-diphenylpyrylium (thiapyrylium) system] dicationic, cationic, radical, and anionic centers were compared. The ionic and radical species were found to be thermodynamically more stable in the sulfur analogue (less stable in oxygen analogue) in every case except when the HOMO and/or LUMO level is localized on the diethylaminophenyl moiety. The order of the greatest sulfur preference or least oxygen preference is the following: anion > radical and radical > cation for the HOMO and LUMO levels, respectively. The wavelength of the intramolecular charge transfer band and the electrochemical reduction potentials indicate that the thiapyrylium moiety is more electron withdrawing than pyrylium.

Introduction

There has been considerable interest in the relative electron-donating behavior of oxygen and sulfur and their effect on stabilizing adjacent carbon ions (cation and anion) and radical centers.[1] Caserio et al.[1] have recently provided an excellent assessment of the current view of sulfur vs. oxygen stabilization. The fundamental variations between the electron-donating and -withdrawing ability of oxygen and sulfur relate to differences in their π and σ donor properties. CNDO/2 calculations[2] have indicated that the higher carbanion stabilization effect of sulfur in comparison to oxygen is related to the greater capability of the σ-bivalent sulfur to take up excess charge into the sp-valence shell. This explanation does not take into consideration sulfur d orbitals. However, stabilization of adjacent carbocations by sulfur relative to oxygen from CNDO/2 calculations,[3] on the other hand, requires the involvement of sulfur d orbitals. There are then a number of factors, including the π-donating ability of oxygen vs. sulfur, that are involved in determining the stabilizing and destabilizing effects of the two atoms. Most experimental studies designed to probe the electronic properties of oxygen

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0002-7863/80/1502-0299$01.00/0