state. This would confirm our conclusion that it is in fact a biradicaloid, derived from the biradical by a strong through-bond interaction betwen the radical centers.

o-Benzyne was originally obtained as a reaction intermediate by dehydrochlorination of chlorobenzene by base. If the meta and para isomers are comparable in stability with *o*-benzyne, as the MINDO/3 calculations[4] and those reported here suggest, may their derivatives also be obtainable by the action of base on suitable precursors? *o*-Benzyne would of course be expected to be formed most easily in this way because the hydrogen atoms adjacent to chlorine in chlorobenzene are the most acidic and because the ortho isomer is probably the most stable. It should, however, be possible to obtain the other isomers in cases where the ortho positions are blocked by suitable substituents. To test this possibility, we calculated the energies of the three chlorophenyl anions, **15–17**, and of the transition states for their conversion to benzynes by loss of chloride ion. As Table III shows, all three isomers are predicted to be formed in this way via intermediates of not too dissimilar energy, so derivatives of all three should indeed be obtainable by the action of base on suitable precursors.

The possibility that derivatives of *m*- and *p*-benzyne might play a role as intermediates in reactions, comparable in importance with *o*-benzyne, has not been seriously considered until now because it was always assumed that the meta and para isomers would be high-energy biradical-like species, incapable of formation under the conditions used to prepare *o*-benzyne itself. Our calculations suggest that derivatives of *m*-benzyne, and perhaps also of *p*-benzyne, should be obtainable in this way, and exeriments designed to test these predictions are in progress.

Acknowledgment. This work was supported by the Air Force Office of Scientific Research (Grant AFOSR 79-0008), the Robert A. Welch Foundation (Grant F-126), and the National Science Foundation (Grant CHE78-03213).

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Kinetics of Breakdown of the Tetrahedral Intermediate of an O,S-Acyl Transfer Reaction

Linda J. Santry and Robert A. McClelland*

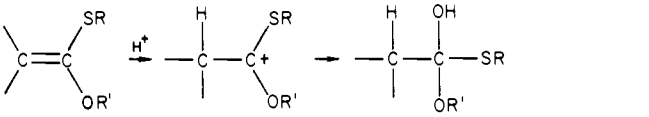
Contribution from the Department of Chemistry and Scarborough College, University of Toronto, Toronto, Ontario, M5S 1A1 Canada. *Received September 30, 1982*

Abstract: The hydrolysis of the ortho thiolester 2-methoxy-2-(4-methoxyphenyl)-1,3-oxathiolane proceeds with an initial exocyclic cleavage producing as intermediates the (4-methoxyphenyl)-1,3-oxathiolan-2-ylium ion (R^+) and the hemiorthothiolester 2-hydroxy-2-(4-methoxyphenyl)-1,3-oxathiolane (ROH). The latter species is the tetrahedral intermediate of the O,S-acyl transfer of the 4-methoxybenzoyl group from one end of 2-mercaptoethanol to the other. These two species are formed in equilibrium as transient intermediates in acid solution, and a kinetic analysis furnishes directly the rate constants for the decomposition of ROH. This occurs in a noncatalyzed reaction (k_3°) and an H^+-catalyzed reaction (k_3^H). At pH >2.5 the only product of the hydrolysis is 2-mercaptoethyl 4-methoxybenzoate (O) derived from C–S cleavage of ROH. In more acidic solutions increasing amounts of C–O cleavage product 2-hydroxyethyl 4-methoxythiolbenzoate (S) are observed. This behavior can be analyzed in terms of the noncatalyzed decomposition of ROH producing only O and the H^+-catalyzed decomposition producing only S. This analysis independently reproduces the ratio k_3°/k_3^H found in the kinetics. These results are compared with those obtained in other systems where hemiorthothiolester type tetrahedral intermediates are formed. The direct kinetic analysis available here verifies the mechanism commonly accepted to explain partitioning behavior. A comparison is also made with the analogous hemiorthoester 2-hydroxy-2-(4-methoxyphenyl)-1,3-dioxolane, the tetrahedral intermediate of an O,O-acyl transfer reaction. The hemiorthothiolester undergoes the noncatalyzed breakdown 5 times more rapidly and the H^+-catalyzed breakdown 100 times more slowly.

Evidence for the presence of a tetrahedral addition intermediate in an O,S-acyl transfer reaction was first presented by Fedor and

$$RC(=O)SEt \underset{\nu_{-1}}{\overset{\nu_1}{\rightleftharpoons}} RC(SEt)(OH)OH \xrightarrow{\nu_2} RC(=O)OH + EtSH \quad (1)$$

Bruice[1] through the observation of a break in the rate–pH profile for the hydrolysis of ethyl trifluorothiolacetate. This was explained by a change with pH in the preferred direction of breakdown of a kinetically significant intermediate, as was subsequently confirmed by Bender and Heck[2] using carbonyl oxygen exchange. The pH dependency for the partitioning of this type of tetrahedral intermediate seems to be general. It is seen in the hydrolysis of other thiolesters[3,4] and is also apparent in the products obtained in the hydrolysis of ketene *O,S*-acetals[3,5] (eq 2) and ethyl thionbenzoate[6] (eq 3). In all these cases[1–6] C–S bond cleavage occurs



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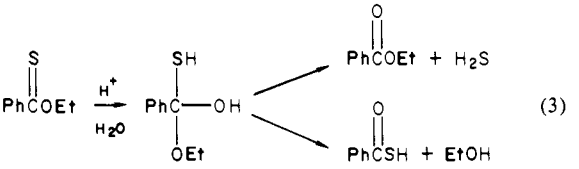

(3)

predominantly if not exclusively in the decomposition at low acidities, while C–O bond cleavage or a mixture of C–O and C–S bond cleavages occurs at high acidities. This has been interpreted in terms of the presence of different forms of the intermediate,

(1) Fedor, L. R.; Bruice, T. C. *J. Am. Chem. Soc.* **1965**, *87*, 4138–4147.
(2) Bender, M. L.; Heck, H. d'A. *J. Am. Chem. Soc.* **1967**, *89*, 1211–1220.
(3) Hershfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 1263–1270.
(4) Hershfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1973**, *95*, 3994–4002.
(5) Hershfield, R.; Yeager, M. J.; Schmir, G. L. *J. Org. Chem.* **1975**, *40*, 2910–2916.
(6) Edward, J. T.; Wong, S. C. *J. Am. Chem. Soc.* **1977**, *99*, 7224–7228.

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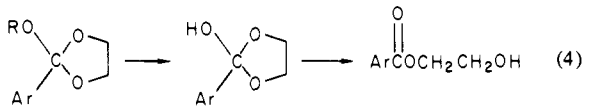
the protonated form being involved in strong acids and a neutral or anionic form being involved in weak acids.

We have recently developed ways of generating hemiorthoester type tetrahedral intermediates as transient species in the hydrolysis of suitable ortho acid derivatives,[7-11] for example, a 2-aryl-2-hydroxy-1,3-dioxolane from a 2-aryl-2-alkoxy-1,3-dioxolane. A



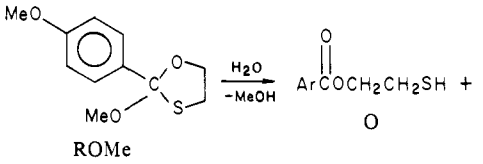
(4)

hemiorthoester is the tetrahedral intermediate of an O,O-acyl transfer reaction, in eq 4, of the degenerate intramolecular ester interchange of an aroyl group from one end of ethylene glycol to the other. Our experiments, and similar ones reported by Capon,[12] not only establish the existence of these species they also provide direct kinetic information about the decomposition process, since the intermediate is actually being observed. Such information cannot be obtained in the acyl transfer reaction itself where the intermediate is formed only in steady-state amounts.

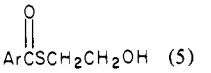
The tetrahedral intermediates in eq 1–3 are hemiorthothiolesters, and we felt it of interest to see if our approach could be applied to the study of these. One question that we wished in particular to address was whether the change in the mode of breakdown could be detected by a change in the kinetic behavior.

Results

The ortho acid derivative chosen was the ortho thiolester ROMe, 2-methoxy-2-(4-methoxyphenyl)-1,3-oxothiolane. This undergoes



ROMe



(5)

hydrolysis in neutral and dilute acid solutions to produce only the mercapto ester O and presumably methanol (less than 3% other products), while in more concentrated acids a mixture of mercapto ester and hydroxythiol ester S are obtained, as summarized in Figure 1.

Hydrolysis kinetics were investigated in acetate and phosphate buffers by following the appearance of the ester product. First-order behavior is observed, and the first-order rate constants obey the simple relationship $k_{obsd} = k_1^H[H^+]$ (Figure 2), with $k_1^H = 2.4 \times 10^3\ M^{-1}\ s^{-1}$ (ionic strength = 0.1) and $3.6 \times 10^3\ M^{-1}\ s^{-1}$ (ionic strength = 1.0). Buffer catalysis is not seen, although this aspect was not investigated in detail.

The situation in perchloric acid solutions (pH <3) is considerably different in that the formation and decay of an intermediate with λ_{max} = 350 nm is clearly evident (Figure 3). This intermediate is the 2-(4-methoxyphenyl)-1,3-oxathiolan-2-ylium ion. This cation with λ_{max} at 350 nm is formed from the oxathiolane in concentrated H_2SO_4 where it is stable and can be characterized by NMR spectroscopy (for details see Experimental Section).

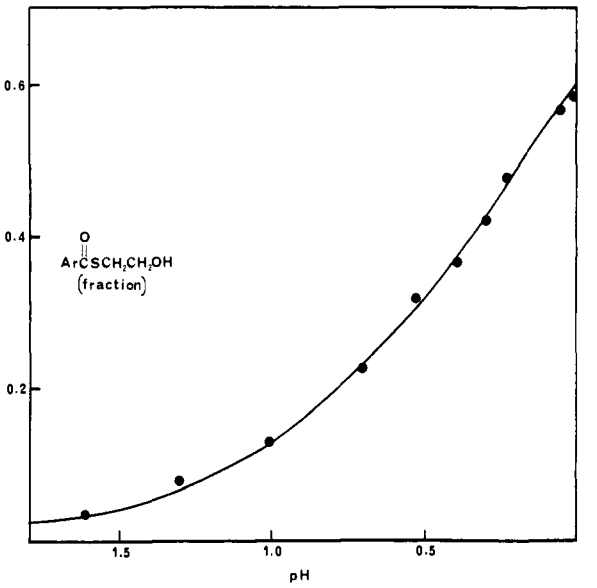


Figure 1. Fraction of 2-hydroxyethyl 4-methoxythiolbenzoate formed in the hydrolysis of 2-methoxy-2-(4-methoxyphenyl)-1,3-oxathiolane. The points are experimental. The line is drawn according to eq 9, with $P^+ = 1.00$, and $k_3^\circ/k_3^H = 0.69$. (Temperature = 25 °C; ionic strength = 1.0.)

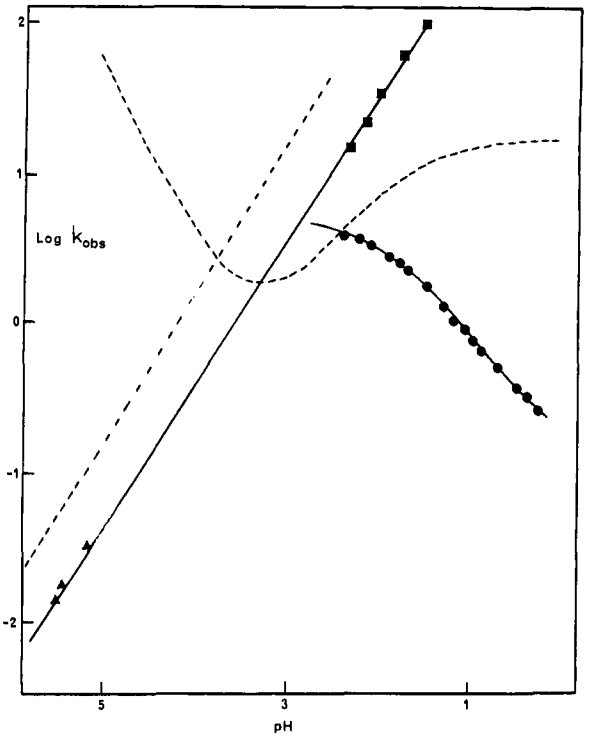


Figure 2. Observed first-order rate constants for the hydrolysis of 2-methoxy-2(4-methoxyphenyl)-1,3-oxathiolane (solid lines) and 2-methoxy-2-(4-methoxyphenyl)-1,3-dioxolane (dashed lines—data from ref 7). The straight lines refer to the first stage of the hydrolysis, the formation of the cation. The curves represent the breakdown of the equilibrating mixture of 1,3-oxathiolan-2-ylium ion and hemiorthothiolester or 1,3-dioxolan-2-ylium ion and hemiorthoester. (All lines refer to a temperature of 25 °C and ionic strength 1.0, with the exception of the straight line for the dioxolane, which refers to ionic strength 0.1.)

First-order rate constants for both the formation and decay processes were measured at an ionic strength of 1.0, and these are also shown in Figure 2. Rate constants based on product formation were within experimental error identical with those obtained for the decay process. It was also noted that the actual amount of the absorbing intermediate that was being formed decreased with increasing pH, although this was difficult to

(7) Ahmad, M.; Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *J. Am. Chem. Soc.* **1979**, *101*, 2669–2677.
(8) McClelland, R. A.; Ahmad, M.; Bohonek, J.; Gedge, S. *Can. J. Chem.* **1979**, *57*, 1531–1540.
(9) McClelland, R. A.; Ahmad, M. *J. Org. Chem.* **1979**, *44*, 1855–1860.
(10) McClelland, R. A.; Alibhai, M. *Can. J. Chem.* **1981**, *59*, 1169–1176.
(11) McClelland, R. A.; Patel, G. *J. Am. Chem. Soc.* **1981**, *103*, 6912–6915.
(12) Capon, B.; Ghosh, A. K.; Grieve, D. M. A. *Acc. Chem. Res.* **1981**, *14*, 306–312.

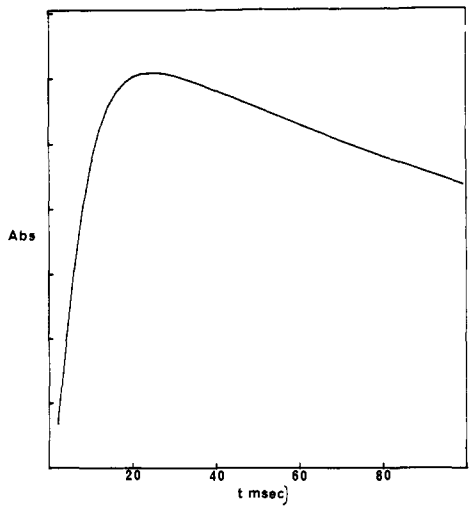
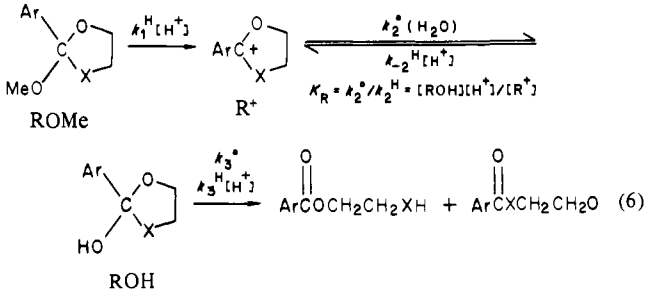


Figure 3. Formation and decay of the 2-(4-methoxyphenyl)-1,3-oxathiolan-2-ylium ion during the acid hydrolysis of 2-methoxy-2-(4-methoxyphenyl)-1,3-oxathiolane. (Wavelength 350 nm, concentration 5 × 10^{-5} M.)

quantify since in the more dilute acids the rate of formation approaches that of decay.

Discussion

Kinetic Analysis. In the study of the dioxolane ortho esters[7] the following major points were demonstrated. The first stage of the hydrolysis involves cleavage of the bond to the exocyclic alkoxy group, producing a 2-aryl-1,3-dioxolan-2-ylium ion (see eq 6 with X = O). At high pH (>4) that stage is the slow step



(6)

in the overall hydrolysis, and observed first-order rate constants based on product formation follow the relationship $k_{obsd} = k_1^H[H^+]$. At low pH (<3) a changeover occurs and hemiorthoester decomposition becomes the slow step. This decomposition occurs in three ways, an acid-catalyzed reaction, a pH-independent or water catalyzed reaction, and a hydroxide ion catalyzed reaction, although only the first two are important at pH <3. Prior to decomposition, a pH-dependent equilibrium is established between the hemiorthoester and dioxolan-2-ylium ion, and the cation can be observed as a transient species, particularly in more acidic solutions. Observed rate constants based either on product appearance or on cation disappearance follow the relationship of eq 7.

$$k_{obsd} = \frac{k_3^\circ + k_3^H[H^+]}{1 + [H^+]/K_R} \qquad (7)$$

The situation described in the above paragraph arises because k_1^H, the rate constant for the initial stage, is greater than k_3^H, the rate constant for acid decomposition (for reasons of which we are still uncertain). In acid solutions, therefore, the hemiorthoester forms more rapidly than it decays. The changeover occurs between low acidities and high acidities because the initial stage is only acid catalyzed whereas the hemiorthoester decomposition has the other pathways available. These take over at low acidities and result in decomposition becoming more rapid than formation. The equilibration of cation and hemiorthoester is rapid relative to decomposition in acid solutions for a similar reason,

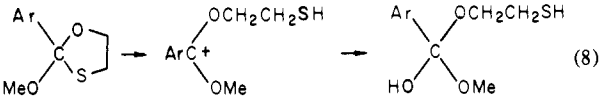
Table I. Rate and Equilibrium Constants in the Hydrolysis of 2-Methoxy-2-(4-methoxyphenyl)-1,3-dioxolane and 2-Methoxy-2-(4-methoxyphenyl)-1,3-oxathiolane

constant	dioxolane[a]	oxathiolane[b]
k_1^H, M^{-1} s^{-1}	1.9×10^4 [c]	2.4×10^3,[c] 3.6×10^3 [d]
pK_R	1.1,[c] 1.8[d]	1.8[d]
k_2°, s^{-1}	1.2×10^3 [c]	46[d]
k_{-2}^H, M^{-1} s^{-1}	1.5×10^4 [c]	2.9×10^3 [d]
k_3^H, M^{-1} s^{-1}	7.5×10^2 [c] 1.3×10^3 [d]	9.3[d]
k_3°, s^{-1}	1.4[c]	6.2[d]

[a] Reference 7. [b] This work. [c] Ionic strength 0.1. [d] Ionic strength 1.0.

$k_{-2}^H > k_3^H$. This is not unexpected since the k_{-2}^H process, the H^+-catalyzed loss of OH from hemiorthoester, is very similar to the initial reaction of the ortho ester. Rate–pH profiles obtained with 2-methoxy-2-(4-methoxyphenyl)-1,3-dioxolane are shown in Figure 2 and clearly show the crossover in kinetic behavior between low pH and high pH. Values of the individual constants are listed in Table I. The constant k_1^H is obtained from the kinetics at high pH; k_3°, k_3^H, and pK_R are obtained by fitting the low-pH kinetics to eq 7, and k_{-2}^H and k_2° were obtained by the actual observation of the equilibration process using as a precursor an amide acetal.

The same analysis can be applied to the oxathiolane. Initial exocyclic cleavage is established by the observation of the oxathiolan-2-ylium ion in concentrated acids. Arguments that the situation could be different in dilute acids are countered in the following way. An initial endocyclic C–O cleavage would not give rise to the mercapto ester O, the only product in dilute acids. Initial C–S cleavage would produce this product, but methyl benzoate should also be present, since it seems unlikely that the tetrahedral intermediate that results from C–S cleavage would break down only with loss of MeOH. Moreover, the cation that is observed as a transient intermediate below pH, 3 clearly has



(8)

sulfur at the carbocation center. The (4-methoxyphenyl)dimethoxycarbocation[13] and the 2-(4-methoxyphenyl)-1,3-dioxolan-2-ylium[7] ion both have λ_{max} near 300 nm, not 350 nm.

The kinetic analysis is also straightforward. Both the formation and decay of the oxathiolan-2-ylium ion are seen in acid solutions. The formation rates obviously must refer to the first stage of the ortho thiolester hydrolysis. By analogy to the dioxolane, rates measured at pH >4 should also refer to this stage, and indeed a common line can be drawn through these rates and those for cation formation. The rates of decay of the cation could correspond to two situations—rate-limiting hydration or, as in the dioxolane system, equilibrium hydration with rate-limiting decomposition of the hemiorthothiolester. The former is ruled out by the kinetic form taken by the decay rates; hydration should be pH independent at pH < 3, since it simply involves addition of water to the cation.[13] An excellent fit is in fact found to eq 7,[14] the kinetic expression that corresponds to the latter situation, with the values of k_3°, k_3^H, and K_R listed in Table I. As with the dioxolane k_3^H is significantly less than k_1^H. The kinetics of the actual equilibrium process cannot be measured, but we estimate $k_{-2}^H = 0.8k_1^H$ as it is in the dioxolane,[7] and calculate k_2° as $k_{-2}^H K_R$.

It is interesting to note that the overall hydrolysis rate of the ortho thiolester decreases in acid solutions (pH <3), while that of the corresponding ortho ester increases (Figure 2). The same

(13) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7027–7031.

(14) Although the rate–pH profiles for the dioxolane and the oxathiolane have significantly different forms, they both correspond to the same kinetic situation and conform to eq 7. The difference lies in the differing significance of k_3° and k_3^H in the two systems.

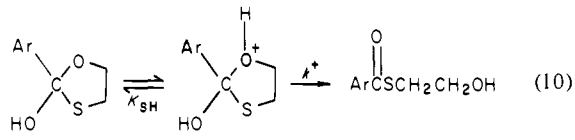
mechanism and same kinetic equation (eq 7) can however be applied. The differing forms of the rate–pH profiles arise because of the different magnitudes of the constants. In particular the cation–hemiorthothiolester equilibrium shifts toward the cation while the hemiorthothiolester breakdown is still noncatalyzed, and this shows up as acid inhibition. With the dioxolane system, acid-catalyzed breakdown becomes important before the equilibrium starts shifting, and acid catalysis is therefore observed. Both systems would eventually level off in rate in concentrated acids (the dioxolane almost does).

Like those in eq 1–3, the hemiorthothiolester cleaves the C–S bond in dilute acids, with increasing amounts of C–O cleavage in more acidic solutions. This can be interpreted by having the pH-independent pathway for intermediate decomposition proceed only with C–S cleavage, while the H^+-catalyzed pathway can do both. If the fraction of C–O cleavage in the latter is defined as P^+, eq 9 expressing the product–pH dependency is written. The

$$\frac{[ArCOSCH_2CH_2OH]}{[ArCOOCH_2CH_2SH] + [ArCOSCH_2CH_2OH]} = \frac{P^+[H^+]}{(k_3^\circ/k_3^H) + [H^+]} \quad (9)$$

experimental data are fit to this equation to give $P^+ = 1.004$ and $k_3^\circ/k_3^H = 0.69$. The former indicates that there is only C–O cleavage in the H^+-catalyzed decomposition. The latter value is within experimental error identical with the value (0.67) obtained directly for these two rate constants in the kinetics. In other words, the kinetic analysis and the product analysis independently generate the same ratio of k_3°/k_3^H.

Our approach, therefore, verifies the conclusions of Schmir and co-workers[3-5] regarding hemiorthothiolester decomposition in acid solutions. These workers write the acid-catalyzed reaction as proceeding via a protonated intermediate, but this simply means that the constant k_3^H of our mechanism would be written as k^+/K_{SH} (eq 10). The actual involvement of the protonated species

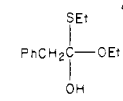
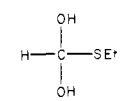
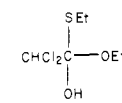
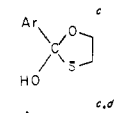
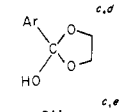
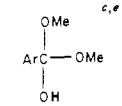
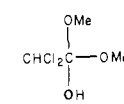


(10)

is questionable. Although mechanistic details are not conclusively established, H^+-catalyzed hemiorthoester decomposition appears not to involve an equilibrium protonation.[11,15]

Our quantity P^+ is the same as that of Schmir and co-workers[3,5] and our ratio k_3°/k_3^H is identical with their K'. This latter term represents the changeover point from one mechanism to the other, actually the H^+ concentration where the two reactions equally contribute. Values for several hemiorthothiolesters are summarized in Table II. (The term P° is the fraction of C–S cleavage in the noncatalyzed reaction). A trend can be noted in the P^+ ratios, namely that electron-donating groups on the pro-acyl carbon favor C–O cleavage. This tendency has also been seen in the H^+-catalyzed hydrolysis of benzaldehyde *O,S*-acetals,[16] where electron-donating substituents on the benzene ring also increase the amount of C–O cleavage. In general quite strongly acidic solutions are required for the H^+-catalyzed reaction to become important. The higher pK' values associated with the acyclic hemiorthothiolester probably reflect increased values of k_3^H. When cyclic and acyclic hemiorthoesters (entries five and six in Table II) are compared, little change is seen in the k_3° values while a considerable difference occurs in k_3^H. The decreased pK' in the dichloromethyl derivative (entry three) is probably also more associated with a change in k_3^H rather than k_3°, as can be seen in numbers for a corresponding hemiorthoester (entry seven).

Table II. Decomposition Parameters for Hemiorthothiolesters and Hemiorthoesters

compound	P^+	P°	$pK' - \log(k_3^\circ/k_3^H)$	k_3°, s^{-1}	k_3^H, $M^{-1}\ s^{-1}$
 [a]	0.79	0.009	1.66		
 [a]	0.48	0.02	1.23		
 [b]	0.35	0	−0.55		
 [c]	1.0	<0.03	0.16	6.2	9.3
 [c,d]			2.73	1.4	7.5×10^2
 [c,e]			4.81	0.7	4.5×10^4
 [f]			−0.4	0.5	0.2

[a] Reference 3. [b] Reference 5. [c] Ar = 4-methoxyphenyl. [d] Reference 7. [e] Reference 11. [f] Reference 17, numbers have been extrapolated to pure aqueous solution following the procedure in ref 15.

Sulfur vs. Oxygen. (a) Cation-Forming Reactions. Contrasting reports[18] can be found on the relative ability of oxygen and sulfur to stabilize an adjacent positive charge. Gas-phase measurements[19] and ab initio calculations[20] indicate that sulfur is the more effective electron donor. Results in solution are based on rates of reactions that form cations and generally support the opposite view, although there is a considerable variation in the magnitude of the effect,[21] and even one case[18] where sulfur is slightly better. These results have been explained[18] by differing degrees of carbocation character in the transition states, with sulfur having the greater ability to stabilize a fully developed carbocation, and hence a product-like transition state, and oxygen having a greater ability to stabilize a reactant-like transition state.

In this study rates of formation of the cation R^+ from the ortho ester also imply a greater donation by oxygen, k_H^1 for the dioxolane being 8 times greater than k_H^1 for the oxathiolane. An equilibrium comparison is also available in the pK_R values, which measure the thermodynamic stability of the cation relative to its OH adduct or pseudo base. These values are, within experimental error,

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(16) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476–1488.
(17) Capon, B.; Dosunmu, M. I. *J. Am. Chem. Soc.*, submitted for publication.
(18) Modena, G.; Scorrano, G.; Venturello, P. *J. Chem. Soc., Perkin Trans. 2*, **1979**, 1–6.
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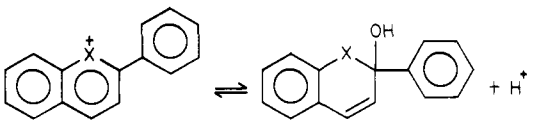
(20) Bernardi, F.; Csizmadia, I. G.; Schlegel, H. B.; Wolfe, S. *Can. J. Chem.* **1975**, *53*, 1144–1153. Bernardi, F.; Mangini, A.; Epiotis, N. D.; Larson, J. R.; Shaik, S. *J. Am. Chem. Soc.* **1977**, *99*, 7465–7470.
(21) (a) The following rate ratios k(oxygen)/k(sulfur) have been reported: CH_3XCH_2Cl, solvolysis,[18,21b] 1.1×10^2; CH_3XCH_2OAc, H^+-catalyzed loss of HOAc,[21c,d] 1.7; $CH_3XCH{=}CH_2$,[21e] H^+-catalyzed hydration, 34; $CH_3XC{\equiv}CH$, H^+-catalyzed hydration,[21f,g] 4.4×10^2; $CH_3XCH_2OCH_3$, H^+-catalyzed expulsion of CH_3OH,[18] 0.1; $CH_3CH_2XCHPhOCH_2CH_3$, H^+-catalyzed expulsion of CH_3CH_2OH,[16] 1.5×10^2. (b) Jones, T. C.; Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 4863–4867. (c) McClelland, R. A. *Can. J. Chem.* **1975**, *53*, 2763–2771; (d) *Ibid.* **1975**, *53*, 2772–2780; (e) *Ibid.* **1977**, *55*, 548–551. (f) Stamhuis, E. J.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 797–809. (g) Hogeveen, H.; Drenth, W. *Ibid.* **1963**, *82*, 375–384.

identical for the two cations; that is, there is no difference between oxygen and sulfur. In the kinetics of the equilibration, however, the rate of formation of the sulfur-stabilized cation is lower, but this is equally balanced by a slower rate of hydration.[22] In other words, the relative energies of the reagents and products are the same, but the relative position of the transition state is higher in the sulfur system.

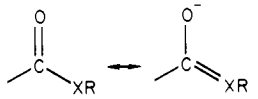
At the moment we can think of no clear explanation. As seen in the measurements of basicity of sulfur- and oxygen-containing compounds,[23] solvation likely is important. The oxathiolan-2-ylium ion may be inherently more stable but more poorly solvated. There is a related example where sulfur is more effective, the equilibrium hydration of the flavylium ion (pK_R = 3.0)[24] and thioflavylium ion (pK_R = 5.9).[25]



It is possible here that the highly delocalized nature of these cations makes solvation less important.

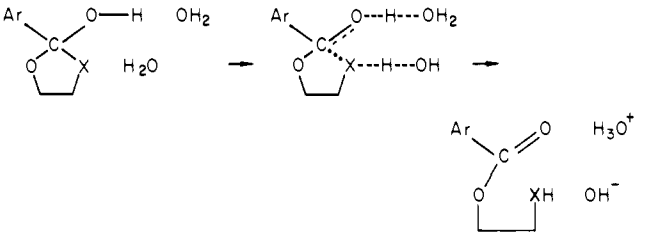
In any event the previous proposal[18] that sulfur more effectively stabilizes a fully developed cation is clearly not valid in the present case. It can also be pointed out that the majority of the other examples studied to date[21] produce cations that probably do not exist as free ions in water;[26] there must be some solvent assistance or S_N2 character in the transition state. The cation of this study obviously does exist, since it can be observed.

(b) Tetrahedral Intermediate Decomposition. There are two areas of concern here–the factors that determine whether C–O or C–S cleavage occurs in the hemiorthothiolester and the rate comparison of this compound with its hemiorthoester analogue. The direction of bond cleavage can be analyzed[16] in terms of the *pull* exerted by the leaving group and the *push* provided by the remaining group and other substituents. In the present case the sulfur is undoubtedly the better leaving group when departing as an anion, but is it probably considerably worse as a neutral group departing after protonation. This occurs not only because the sulfur is less basic[23] but also because the neutral group is an inherently poorer leaving group.[18,27] When the remaining group effect is analyzed, it can be noted that the mercapto ester O is more stable, probably by several kilocalories, than the hydroxy thiol ester S.[28,29] This has been explained[28] by a greater resonance of the carbonyl with the oxygen.



If the transition state has ester character, the oxygen should therefore provide a better push. The other possibility, particularly for the acid-catalyzed reactions, is that protonated esters are being produced. This situation then becomes similar to that discussed in the previous section since analogous cations are involved, and on a kinetic basis oxygen should again provide the better push.

The neutral reaction of the hemiorthothiolester cleaves only the C–S bond, and it does so about 10 times[30] more effectively than the C–O cleavage in the corresponding hemiorthoester. This reaction is currently viewed[11,15] as a concerted process, with water molecules acting as acid and base.[31] Such a mechanism would



account for the observations, particularly if there is some anionic character on the X leaving group or more C–X bond cleavage than X protonation. Thus C–S cleavage would be favored in the hemiorthothiolester because of the combination of a better leaving group and the production of a more stable product. The former also explains the increased rate of decomposition over that of the hemiorthoester.

The acid reaction of the hemiorthothiolester proceeds with only C–O cleavage, at a rate about 100 times slower than that of the hemiorthoester. The mechanism of this reaction is not conclusively established, although it would appear as if neither the protonated hemiorthoester nor the protonated ester product is formed as a discrete intermediate.[11,15] Interestingly, the above observations exactly parallel those made in benzaldehyde *O,S*-acetal hydrolysis.[16] Here the explanation has been in terms of the better leaving ability of protonated oxygen outweighing the poorer push of sulfur, so that C–O cleavage predominates. The latter factor, however, results in rates that are considerably slower than those of corresponding acetals. The analogy can in fact be carried one step further. As noted previously some C–S cleavage is observed in both *O,S*-acetals and hemiorthothiolesters with poorer electron donors. With the acetals this was explained by the push on the sulfur being modified by other substituents.

There is therefore a definite similarity between the two systems, although this need not extend to the detailed mechanism. It is likely, for example, that in the hemiorthothiolester decomposition the acid is transferring a proton to the leaving group in the transition state. This obviously also happens with the *O,S*-acetals, but the timing of this process with others in the two systems need not be the same. Moreover, as discussed previously, the sulfur will provide a poorer push regardless of whether a protonated or neutral ester is being formed.

Experimental Section

2-Methoxy-2-(4-methoxyphenyl)-1,3-oxathiolane. 2-Mercaptoethyl ether was converted into its bis(4-methoxybenzoyl) ester by adding 4-methoxybenzoyl chloride (0.3 mol) to a solution of the ether (0.15 mol) and KOH (0.3 mol) in 50:50 ethanol:water (200 mL). After 1 h of heating at 50 °C the dithiol ester precipitate was filtered and recrystallized from water.

This product was converted into 2-(4-methoxyphenyl)-1,3-oxathiolan-2-ylium tetrafluoroborate by using the procedure of Raber and Guida[32] for the preparation of 1,3-dioxolan-2-ylium ions, taking into account that two cations form from each molecule of dithiol ester. The dithiol ester (0.05 mol) and triethyloxonium tetraflauoroborate (0.2 mol) were refluxed in dry $CHCl_2$ (100 mL) for 24 h. The NMR spectrum of this solution showed complete destruction of the original ester and the formation of material consistent with the cation structure.

No attempt was made to isolate the cation. The above solution was transferred to a dry separatory funnel and added to a cooled stirred

(22) (a) A similar effect is seen in the hydration of Ph_2C^+XMe; the rate for the sulfur compound is smaller.[22b] (b) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7031–7036.

(23) Bonvicini, P.; Levi, A.; Lucchini, V.; Scorrano, G. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2267–2269. Bonvicini, P.; Levi, A.; Lucchini, V.; Modena, G.; Scorrano, G. *J. Am. Chem. Soc.* **1973**, *95*, 5960–5964; Edward, J. T.; Lantos, I.; Derdall, G. D.; Wong, S. C. *Can. J. Chem.* **1977**, *55*, 812–821.

(24) McClelland, R. A.; Gedge, S. *J. Am. Chem. Soc.* **1980**, *102*, 5838–5848.

(25) Degani, I.; Fochi, R.; Spunta, G. *Ann. Chim. (Rome)* **1973**, *53*, 527–540.

(26) Knier, B. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6789–6798.

(27) (a) For example, protonated methyl *tert*-butyl sulfide is stable at −60 °C in FSO_3H–SbF_5–SO_2 and cleaves only very slowly to CH_3SH and *tert*-butyl cation at −15 °C,[27b] while the corresponding protonated ether decomposes rapidly at −70 °C.[27c] (b) Olah, G. A.; White, A. M.; Pittman, C. U. *J. Am. Chem. Soc.* **1967**, *89*, 2996–3001. (c) Olah, G. A.; O'Brien, D. H. *Ibid.* **1967**, *89*, 1725–1728.

(28) Hayes, D. M.; Kenyon, G. L.; Kollman, P. A. *J. Am. Chem. Soc.* **1978**, *100*, 4331–4340.

(29) Santry, L.; Csizmadia, I. G.; McClelland, R. A.; Poirier, R. A. *J. Chem. Soc., Perkin Trans. 2*, submitted for publication.

(30) This number is obtained by dividing the hemiorthoester rate by 2 because there are two C–O bonds to cleave.

(31) Possibly in a cyclic fashion through a water bridge, so that the production of charged species is avoided.

(32) Raber, D. J.; Guida, W. C. *Synthesis* **1974**, 808–809.

solution of sodium (0.3 mol) in dry methanol (100 mL). The methanol was removed on a rotary evaporator, ether (100 mL) and water (100 mL) were added, and the ether layer was dried (K_2CO_3). After removal of the ether the ortho thiolester was purified by fractional distillation. The product had bp 108–110 °C (0.05 mmHg); NMR ($CDCl_3$) δ 7.47 (d, 2 H, J = 9 Hz), 6.88 (d, 2 H, J = 9 Hz), 4.40 (distorted t, 2 H, J = 6 Hz), 3.83 (s, 3 H), 3.27 (s, + t, 5 H).

Product Analysis. (a) NMR. The ortho thiolester was added to an acid solution and immediately extracted with carbon tetrachloride. After evaporation of this solvent the NMR spectra were recorded in $CDCl_3$. The mercapto ester O had an NMR with triplets at δ 4.42 ($-CH_2OOC-$) and 2.86 ($-CH_2SH$), while the thiol ester S had triplets at δ 3.87 ($-CH_2OH$) and 3.28 ($-CH_2SOC-$). The relative amounts of these two was obtained from the integrations at δ 2.86 and 3.28.

(b) UV. The mercapto ester O has λ_{max} 254 nm, while the thiolester S has λ_{max} 290 nm where O has very little absorbance. A curve was therefore obtained of the absorbance at 290 nm as a function of acidity. The actual proportion of the two products in 1 M $HClO_4$ was determined by using the NMR method, and from the 290-nm absorbance in this acid the extinction coefficient of the thiol ester was calculated. This extinction coefficient was then used to determine the fraction of thiol ester in the other acids. This was checked in a couple of cases by using the NMR method.

(c) 96% H_2SO_4. The ortho thiolester was added slowly to a stirred cooled solution of 96% H_2SO_4, and the NMR spectrum was directly recorded with an external Me_4Si reference. This showed δ 8.07 (d, 2 H, J = 8 Hz), 7.07 (d, 2 H, J = 8 Hz), 5.43 (t, 2 H, J = 8 Hz), 4.07 (s), 4.04 (s), and 4.05 (t?), the latter three peaks integrating to 7 H. This spectrum is consistent with the formation of methanol and the 2-(4-methoxyphenyl)-1,3-oxathiolan-2-ylium ion.

Kinetic Analysis. Procedures were identical with those described previously.[7] The high-pH kinetics were studied by following the appearance of mercapto ester O at 254 nm. Low-pH kinetics were studied by following the appearance and disappearance of 1,3-oxathiolan-2-ylium ion at 350 nm. Appearance rates were determined by using the Guggenheim method. (These were only considered reliable when the rate so obtained was at least 10 times the decay rate.) Decay rates were obtained by using the infinity method, taking points only after a time corresponding to 10 half-lives of the formation process.

Acknowledgment. Continued financial support of the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Registry No. ROMe, 85168-64-5; 2-hydroxy-2-(4-methoxyphenyl)-1,3-oxathiolane, 85168-65-6; 2-mercaptoethyl ether, 2150-02-9; 4-methoxybenzoyl chloride, 100-07-2; 2-(4-methoxyphenyl)-1,3-oxathiolan-2-ylium ion, 85168-66-7.

Supplementary Material Available: Tables S1 and S2, observed rate constants for the hydrolysis of 2-methoxy-2-(4-methoxyphenyl)-1,3-oxathiolane in perchloric acid solutions and in acetic acid buffers (1 page). Ordering information is given on any current masthead page.

Structural Studies of Sodium Channel Neurotoxins. 2. Crystal Structure and Absolute Configuration of Veratridine Perchlorate[1]

Penelope W. Codding

Contribution from the Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4. *Received August 30, 1982*

Abstract: Crystal structure analysis has been carried out for the perchlorate salt of veratridine, a *Veratrum* alkaloid with neurotoxic and hypotensive properties. The crystals have space group symmetry $P2_12_12_1$ with a = 7.551 (1), b = 10.521 (1), and c = 44.361 (10) Å at −100 (5) °C. The absolute configuration as determined by anomalous dispersion is consistent with that determined chemically for cevine[7] and crystallographically for zygacine.[6] A β-configuration for the hydroxyl group at C20 is also confirmed by this analysis. Comparison of the structures of veratridine, aconitine, and batrachotoxin, all agonists of the sodium channel receptor, yield a model for their interaction with the receptor.

Extracts of *Veratrum* plants have been used for hundreds of years as medicinal compounds. The pharmacology of the *Veratrum* ester alkaloids has been extensively studied, especially the hypotensive action of certain members of this class. Unfortunately, the toxic side effects of these compounds has limited their clinical utility. Recently, however, one toxic aspect of veratridine activity has been utilized as a pharmacological tool in the study of the mechanism of action of ion channels.

Veratridine is one of a group of four types of lipid-soluble polycyclic compounds that have similar action on the sodium ion channels that mediate the electrical excitability of nerve, heart, and skeletal muscle. These lipid-soluble neurotoxins have been shown to bind to a single receptor site associated with the sodium channels but not to the ion pore itself.[2] Their effect is to shift activation of the channels to more negative membrane potentials and to block inactivation, thereby producing a lasting depolarization of the excitable membrane. Experiments with neuroblastoma cells[3] demonstrate competitive binding to the "activating" receptor among all four neurotoxins, and, as well, concentration dependences indicate that binding a single toxin molecule activates a single sodium channel. These ion flux studies prove batrachotoxin (**1**, Chart I) to be a full agonist of the receptor while veratridine (**2**), aconitine (**3**), and grayanotoxin (**4**) are partial agonists. Therefore, these neuorotoxins bind with different efficacies to a chemically sensitive site associated with sodium channels; occupation of this site causes persistent activation of the channels. It has been proposed[3] that the lipid-soluble neurotoxins bind with greater affinity to the active state of the channel so that their effectiveness is dependent on their selectivity for the active conformation of the receptor.

Because of the disparate chemical structures of the four neurotoxins being employed in pharmacological studies, it has proved difficult to ascertain the structural requirements for activity by the usual method of chemical modification. One attempt has been

(1) Part 1 of this series: Codding, P. W. *Acta Crystallogr., Sect. B* **1982**, *B38*, 2519–2522.

(2) Three recent reviews of the pharmacology of sodium channels have appeared: (a) Catterall, W. A.; Hartshorne, R. P.; Beneski, D. A. *Toxicon* **1982**, *20*, 27–40. (b) Catterall, W. A. *Ann. Rev. Pharmacol. Toxicol.* **1980**, *20*, 15–43. (c) Narahashi, T. *Adv. Cytopharm.* **1979**, *3*, 293–303.

(3) Catterall, W. A. *J. Biol. Chem.* **1977**, *252*, 8669–8676.

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