Hydrolysis of Mixed O,S-Ortho Esters of *p*-Methoxybenzoic Acid. Reactivity and Partitioning of the Tetrahedral Intermediates

Tadashi Okuyama,* Masakazu Kitano, and Takayuki Fueno

Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan

Received December 4, 1986

Hydrolyses of four ortho esters of *p*-methoxybenzoic acid, $ArC(OMe)_{3-n}(SMe)_n$ (n = 0–3), have been examined at 30 °C in aqueous solution. All the hydrolyses are catalyzed by acid, rate decreasing with increasing number of methylthio groups (n). Uncatalyzed reaction was observed for the thio ortho esters (n = 1–3). Products from the mixed O,S-ortho esters (n = 1 and 2) are mixtures of the ester ArCOOMe and the thio ester ArCOSMe. Fraction of the latter increases with acidity of the medium, following a sigmoid curve (pK_{3b} = 0.8) from 0 to 0.68 in the case of n = 1 and following a biphasic sigmoid from 0 to 0.86 (pK_{1c} = 4.73) and then to 0.96 (pK_{3b} = 0.8) in the case of n = 2. These results are interpreted in terms of different partitioning in acid-catalyzed and spontaneous breakdowns of the tetrahedral intermediate as well as O,S-ortho esters.

Extensive studies on the hydrolysis of ortho esters have established a three-stage reaction mechanism which involves a carbocation and a hydrogen ortho ester as intermediates.[1,2] The latter intermediate is a tetrahedral intermediate involved in an acyl-transfer reaction.[3-5] The sulfur analogues, trithio ortho esters and mixed O,S-ortho esters, must also undergo acid-catalyzed hydrolysis through a similar three-stage reaction process as described in Scheme I.

Investigations of hydrolyses of a series of ortho esters bearing a changing number of methoxy and methylthio groups, as those illustrated in Scheme I, would provide interesting information about relative stabilities of oxo and thio carbocations as well as leaving abilities of methanol and methanethiol. Furthermore, mixed O,S-ortho esters provide a tetrahedral intermediate for an O,S-acyl transfer and give a mixture of the ester and thio ester as hydrolysis products. The ratio of these products changes with acidity of the reaction medium reflecting the partitioning of the ortho esters themselves and the tetrahedral intermediate. Such investigations are carried out with four ortho esters of *p*-methoxybenzoic acid 1 (Ar = *p*-methoxyphenyl in Scheme I), and the results are presented herein.

Results

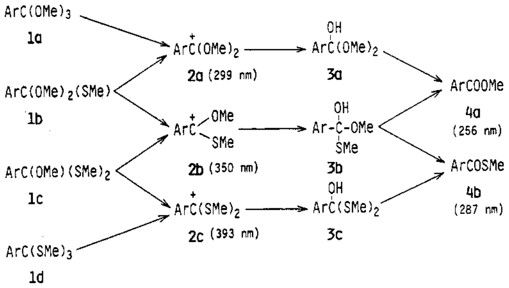
Mixed O,S-ortho esters **1b** and **1c** were prepared by reactions of the isolated carbocation salts **2a** and **2c** with methanethiol and methanol, respectively (eq 1 and 2).

$$\underset{\mathbf{2a}}{ArC^+(OMe)_2{\cdot}BF_4^-} + MeSH + Et_3N \rightarrow \underset{\mathbf{1b}}{ArC(OMe)_2(SMe)} + Et_3NHBF_4 \quad (1)$$

$$\underset{\mathbf{2c}}{ArC^+(SMe)_2{\cdot}ClO_4^-} + MeONa \rightarrow \underset{\mathbf{1c}}{ArC(OMe)(SMe)_2} + NaClO_4 \quad (2)$$

These reactions easily afford pure mixed ortho esters. There have not been prepared many mixed O,S-ortho esters previously.[6] Acid-catalyzed transesterification of an ortho ester with a thiol gives a mixture of monothio and dithio ortho esters.[6,7]

Scheme I



Hydrolyses of ortho esters 1 were mostly carried out at 30 °C in aqueous solution containing 1 vol % of acetonitrile and followed spectrophotometrically. The ionic strength of the solution of low acidity was maintained at 0.50 M with KCl.

Hydrolysis of the ortho ester **1a** in very dilute acid solutions occurs with an isosbestic point at 235 nm to form the absorption of the ester **4a** (λ_{max}, 256 nm). Pseudo-first-order rate constants k_{obsd} were measured at 10^{-4} to 10^{-3} M of HCl from the increase in the 256 nm absorbance, are given in Table S1 (supplementary material), and are plotted against pH in Figure 1.

Hydrolysis of the trithio ortho ester **1d** in dilute HCl solutions proceeds to form absorption of the thio ester **4b** (λ_{max}, 287 nm) with isosbestic points at 224 and 247 nm. Pseudo-first-order rate constants were obtained from the increase in the absorbance at 287 nm. Formation and decay of the S,S-cation **2c** could also be observed at 393 nm in stronger acid ($[HClO_4]$ > 2 M). The decay of **2c** accompanies formation of **4b**, and rate constants determined from the absorbance decrease at 393 nm agree well with those obtained from the increase in the 287 nm absorbance. Here, the induction period was observed, and k_{obsd} values were determined from the later stage of the reaction. The rates of appearance of **2c** were also determined. All the observed rate constants k_{obsd} are summarized in Table S1 and shown plotted logarithmically against pH or the H_0 acidity function[8] in Figure 1. On addition of **1d** in very strong acid (e.g., 70% perchloric acid), immediately developed stable absorption of **2c** at 393 nm.

---

[1] For reviews, see: Cordes, E. H. *Progr. Phys. Org. Chem.* **1967**, *4*, 1. Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581–603.

[2] 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 and ensuing papers.

[3] Capon, B.; Ghosh, A. K.; Grieve, D. M. A. *Acc. Chem. Res.* **1981**, *14*, 306–312. Capon, B.; Dosunmu, M. I.; Sanchez, M. d. N. *Adv. Phys. Org. Chem.* **1985**, *21*, 37–98.

[4] Guthrie, J. P. *Acc. Chem. Res.* **1983**, *16*, 122–129.

[5] McClelland, R. A.; Santry, L. *Acc. Chem. Res.* **1983**, *16*, 394–399.

[6] DeWolfe, R. H. *Carboxylic Ortho Acid Derivatives*; Academic: New York, 1970; Chapter 6.

[7] Feugeas, C.; Olschwang, D. *Bull. Soc. Chim. Fr.* **1969**, 325–329.

[8] Kresge, A. J.; Chen, H. J.; Capen, G. L.; Powell, M. F. *Can. J. Chem.* **1983**, *61*, 249–256.

0022-3263/87/1952-2657$01.50/0

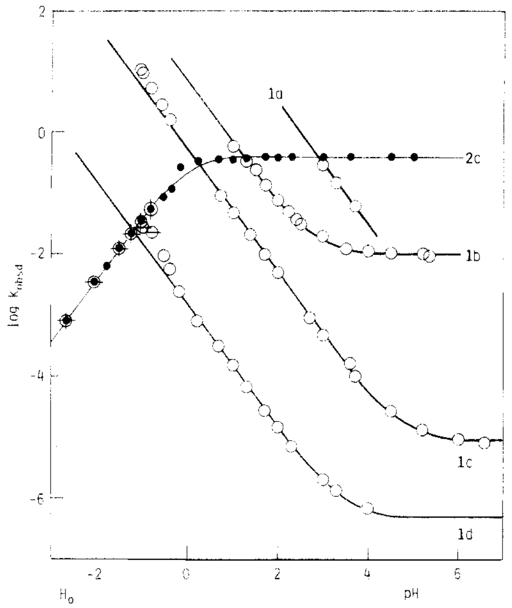


Figure 1. Observed rate constants for the hydrolyses of ortho esters 1 and the cation **2c** (●). Rate constants obtained from the 393-nm absorbance for the hydrolysis of **1c** and **1d** are indicated by vertical and horizontal bars, respectively. Solid curves are calculated with rate constants given in Table I.

The S,S-cation **2c** was prepared and isolated as perchlorate by the reaction of **1d** with $HClO_4$ in acetic anhydride. Reaction of the isolated **2c** was spectrophotometrically examined. On introducing the acetonitrile solution of **2c** into an aqueous acid solution, the absorption of **2c** disappears rapidly to form **4b** with isosbestic points at 227, 240, and 310 nm. Rate constants k_{obsd} were determined from the decrease in the 393-nm absorbance, which are equal to those obtained from the increase in the 287 nm absorbance. The reaction is very rapid ($t_{1/2} \simeq 1.8$ s) in dilute acids (pH >1), and k_{obsd} values were determined from the remaining 10% of reaction on a conventional UV spectrophotometer. The observed rate constants k_{obsd} are practically constant in HCl solutions of [HCl] = 0–0.05 M ($k_{obsd} = 0.398$ s^{-1}) and decrease with increasing acidity below pH 1. The rate constants obtained are summarized in Table S1 and plotted in Figure 1. Positive buffer effects on the rate were observed in formate and acetate buffers (Table S2, supplementary material), but further details were not examined because the effects were very weak.

Hydrolysis of the mixed ortho esters **1b** and **1c** proceeds with clear isosbestic points in dilute HCl solutions, but the absorption spectra of the ultimate product mixtures change with pH. Products from the O,O,S-ortho ester **1b** are mostly the ester **4a** (256 nm) above pH 2, and the isosbestic point was seen at 237 nm. The absorbance at 287 nm (**4b**) increases with increasing acidity. Products from the O,S,S-ortho ester **1c** are mainly the thio ester **4b** below pH 4 (isosbestic points being at 225 and 245 nm), but the absorbance at 256 nm develops at higher pH. The observed spectra of the product mixtures are the same as those of appropriate mixtures of the authentic samples of **4a** and **4b**. The absorbances at 256 and 287 nm, A_{256} and A_{287}, of the product mixtures from **1b** and **1c** were measured after six to ten half-times of reaction at varying acidities and are summarized in Table S3 (supplementary material). Neither **4a** nor **4b** showed any spectral change under the reaction conditions.

The fraction of **4b** (x) can be evaluated from the absorbances A_{256} and A_{287} and molar extinction coefficients of **4a** and **4b**. The extinction coefficients were determined with the authentic samples of **4a** and **4b**. The apparent extinction coefficients of the mixture at 256 and 287 nm are then described by eq 3 and 4. The observed absorbances give the total product concentrations, [P] = [**4a**] + [**4b**], as well as the fraction x. The product concentrations, [P], calculated were found to be equal to the initial substrate concentrations added within ±1.7%. The fractions of **4b** are plotted against pH or H_0 in Figure 2.

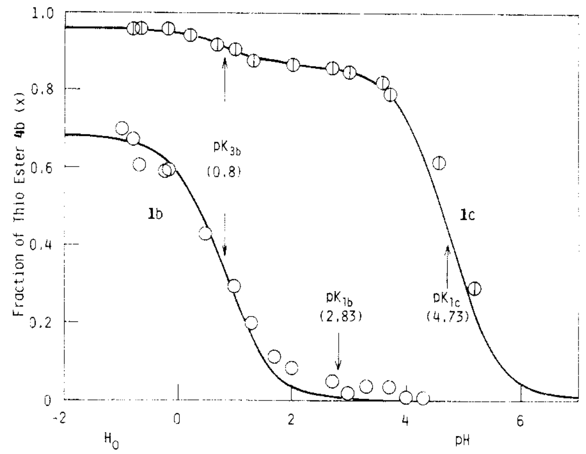


Figure 2. Fractions of the thio ester **4b** in the products of hydrolysis of mixed ortho esters, **1b** (○) and **1c** (⦶). Solid curves are calculated according to eq 5 and 6 with parameters given in text.

$$\epsilon_{256} = 16250(1 - x) + 7990x = 16250 - 8260x \quad (3)$$

$$\epsilon_{287} = 15530x + 840(1 - x) = 840 + 14690x \quad (4)$$

Rate constants k_{obsd} for the hydrolysis of **1b** and **1c** were determined from the absorbance increase either at 256 or 287 nm depending on the product distribution (Figure 1 and Table S1). Rate constants were measured also in buffer solutions (Table S2). The rates were found essentially to be independent of buffer concentration at higher pH (<3) but to increase with increasing buffer concentration at pH 2.4 (chloroacetate buffer) both for **1b** and **1c**. In the reaction of **1c** in $HClO_4$ solutions ([$HClO_4$] > 1 M), both the formation and disappearance of **2c** could be monitored. The rates of disappearance of **2c** agree well with those obtained with the isolated salt of **2c**. The appearance of **2c** was followed by stopped-flow spectrophotometry and rates increase with acidity (Figure 1 and Table S1).

In very strong acids like concentrated sulfuric acid and 70% perchloric acid, stable absorptions of the carbocations were observed above 300 nm. Addition of the ortho ester **1a** in concentrated H_2SO_4 resulted in a spectrum of maximum absorption at 299 nm, which must correspond to the O,O-cation **2a**, while **1d** showed the spectrum of the S,S-cation **2c** (393 nm). The acid solution of **1b** in both $HClO_4$ and H_2SO_4 showed the absorption at 350 nm probably due to the O,S-cation **2b**. The spectrum of **1c** was dependent on the acid employed. In 70% $HClO_4$, the broad absorption of a trapezoid form was seen in the range 330–390 nm, which may be attributed to a mixture of **2b** and **2c**. The absorbance at shorter wavelength increased in concentrated H_2SO_4. In a weaker acid like 30% $HClO_4$, the absorption was mostly due to **2c**, which gradually changed into the thio ester absorption (287 nm) with clear isosbestic points (227, 240, and 310 nm) in the same way as the preformed cation **2c** or the trithio ortho ester **1d**.

Discussion

Product Distribution. Fractions of the thio ester **4b** formed in the hydrolysis of mixed O,S-ortho esters **1b** and

1c change with pH as seen in Figure 2. This is interpreted according to the reaction sequences given in Scheme I. Acid-catalyzed reactions of the tetrahedral intermediate **3b** as well as **1b** and **1c** result in cleavages of both C–O and C–S bonds, while the spontaneous reaction may solely give rise to C–S bond cleavage. The latter assumption is based on the observed absence of the uncatalyzed reaction of the ortho ester **1a**[9] and previous findings[10–13] that O,S-tetrahedral intermediates give essentially only the ester products in the spontaneous reaction.

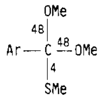
Fractions of **4b**, x, can be described by eq 5 and 6 for **1b** and **1c**, respectively, according to Scheme I, where P_{1b}, P_{1c}, and P_{3b} are fractions of C–O bond cleavage in the acid-catalyzed reactions of **1b**, **1c**, and **3b**, respectively, and

$$x = \left(\frac{P_{1b}[H^+]}{[H^+] + K_{1b}}\right)\left(\frac{P_{3b}[H^+]}{[H^+] + K_{3b}}\right) \tag{5}$$

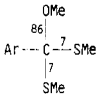
$$x = \frac{P_{1c}[H^+]}{[H^+] + K_{1c}} + \left(1 - \frac{P_{1c}[H^+]}{[H^+] + K_{1c}}\right)\left(\frac{P_{3b}[H^+]}{[H^+] + K_{3b}}\right) \tag{6}$$

K_{1b}, K_{1c}, and K_{3b} are relative rate constants for the uncatalyzed and acid-catalyzed reactions of the respective species, k_0/k_{H^+}. Values $pK_{1b} = 2.83$ and $pK_{1c} = 4.73$ can be evaluated from the kinetic results. Limiting values of x in Figure 2 give $P_{1b}P_{3b} = 0.68$, $P_{1c} = 0.86$, and $P_{1c} + (1 - P_{1c})P_{3b} = 0.96$, which lead to values $P_{1b} = 0.96$ and $P_{3b} = 0.71$. With these values and $pK_{3b} = 0.8$, solid curves of Figure 2 are calculated, which reasonably fit the experimental points.

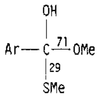
From the partitioning parameters used above, the relative ease of bond cleavage in the acid-catalyzed reaction is illustrated as follows:



1b



1c



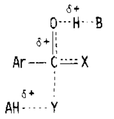
3b

The numbers show percent of the respective bond cleavages. Preferable cleavage of the C–O bond over the C–S bond must be primarily due to preferable protonation at the oxygen atom; pK_a of dialkyl ether and sulfide are about −2.5 and −7.0, respectively.[14] The tetrahedral intermediate **3b** gives away thiol relatively more readily than the thio ortho esters **1b** and **1c**. Both of the partitioning parameters P_{1b} and P_{1c} give relative leaving ability of methanol and methanethiol in the acid-catalyzed reaction of thio ortho esters to be about 12/1, while a similar value for **3b** is 2.4/1. This difference in relative ease in the bond cleavage between ortho ester and hydrogen ortho ester may reflect the difference in the reaction mechanism. Although the detailed mechanism of hydrogen ortho ester **3** has not been established,[5] a proton is very likely being removed from the hydroxyl group simultaneously with departure of the leaving group Y. By contrast, the carbocation is

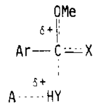
Table I. Rate Constants for the Hydrolyses[a]

substrate	k_{H^+}, M^{-1} s^{-1}	k_0, s^{-1}
1a	295	
1b	6.69	1.0×10^{-2}
1c	0.485	0.9×10^{-5}
1d	1.39×10^{-3}	0.5×10^{-6}
2c		0.398[b]

[a] Measured at 30 °C and 0.50 M ionic strength. [b] 0.279 s^{-1} at 25 °C.



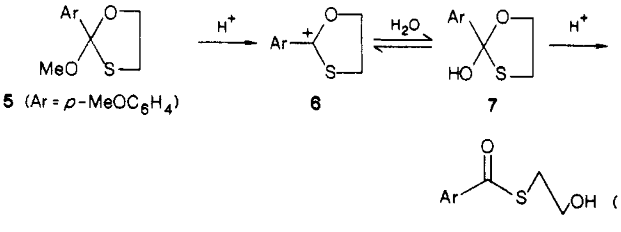
3



1

being formed from the ortho ester **1** on departure of the (protonated) leaving group Y. Since the conjugative stabilization arising from the remaining group X may be greater for the methoxy group than for the methylthio group, this argument predicts easier leaving of thiol in the ortho ester breakdown where the conjugation would be more effective. This expectation is contrary to the above observation. Another possible factor may be the nature of acid-assistance on the leaving group Y. The general acid catalysis that was observed in ortho ester hydrolysis was fairly weak, and the Brønsted coefficient is generally high ($\alpha > 0.7$),[1,9,15] while the general acid catalysis in the breakdown of hydrogen ortho ester is more significant, the Brønsted coefficient α for $PhC(OMe)_2(OH)$ being 0.46.[16] Bonding between proton and Y at the transition state would be more advanced in the ortho ester hydrolysis than in the breakdown of tetrahedral intermediates. Basicity of the oxygen atom would thus be more influential in the former reaction, making methanol be a relatively better leaving group in this reaction.

Santry and McClelland[13] have recently examined hydrolysis of a cyclic O,O,S-ortho ester **5** (eq 7) and showed that acid-catalyzed breakdown of the tetrahedral intermediate **7** occurred exclusively through the C–O bond cleavage. The acyclic intermediate **3b** was found to undergo only 71% of C–O bond cleavage. The reason for this difference is not clear at present, but the former results were based on rather long extrapolation and the partitioning ratio for **7** could be somewhat smaller. The rate for the acid-catalyzed hydrolysis of **5** is about 10^3 times greater than that of **1b**. The incipient carbocation **6** of cyclic structure is more readily formed than the acyclic one **2b**, probably owing to the conjugative stabilization enhanced by the enforced coplanarity.



(7)

Hydrolysis Rates. The acidity–rate profiles in Figure 1 show that thio ortho esters undergo uncatalyzed (water-catalyzed) hydrolysis as well as acid-catalyzed re-

---

[9] For kinetic details of hydrolysis of **1a** see: Okuyama, T.; Fueno, T. *J. Org. Chem.* **1986**, *51*, 5433–5434.

[10] Hershfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 1263–1270.

[11] Hershfield, R.; Yeager, M. J.; Schmir, G. L. *J. Org. Chem.* **1975**, *40*, 2910–2916.

[12] Edward, J. T.; Wong, S. C. *J. Am. Chem. Soc.* **1977**, *99*, 7224–7228.

[13] Santry, L. J.; McClelland, R. A. *J. Am. Chem. Soc.* **1983**, *105*, 3167–3172.

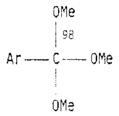
[14] Bonvicini, P.; Levi, A.; Lucchini, V.; Scorrano, G. *J. Chem. Soc. Perkin Trans. 2* **1972**, 2267–2269. Bonvicini, P.; Levi, A.; Lucchini, V.; Modena, G.; Scorrano, G. *J. Am. Chem. Soc.* **1973**, *95*, 5960–5964. Perdoncin, G.; Scorrano, G. *Ibid.* **1977**, *99*, 6983–6986.

[15] Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264–272.

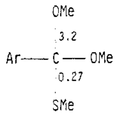
[16] McClelland, R. A.; Patel, G. *J. Am. Chem. Soc.* **1981**, *103*, 6912–6915.

action. Catalytic constants are summarized in Table I. Rate constants k_0 for the uncatalyzed reaction are only approximate and theoretical curves calculated with these rate constants are shown by solid curves in Figure 1. In the acid-catalyzed reaction, the ortho ester **1a** is the most reactive, and the reactivity decreases with increasing number of thio groups. However, the uncatalyzed reaction was only observed for thio ortho esters but not for **1a**.[9] This may be due to poor leaving ability of alkoxide as compared with thiolate ion. Relative ease of (spontaneous) formation of carbocations **2a**, **2b**, and **2c** respectively from **1b**, **1c**, and **1d** by giving away the methanethiolate ion is reflected in k_0: $6 \times 10^4/27/1$ (after statistical corrections). Formation of the O,O-cation is much easier than those of the O,S- and S,S-cations. This tendency that α-oxo carbocations are more readily formed than the corresponding thio cations in aqueous solution has generally been recognized.[17]

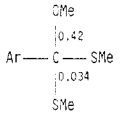
Acid-catalytic constants in Table I may not simply be compared since the leaving group is not the same for all the reactions, either methanol or methanethiol. The partitioning of the mixed ortho esters, **1b** and **1c**, should be taken into consideration. Rate constants for the acid-catalyzed cleavage of respective bonds are calculated from overall rate constants k_{H^+} and partitioning parameters P and are shown in the following illustrations:



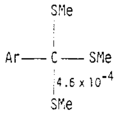
1a



1b



1c



1d

The numbers in the structures show acid-catalytic constants for the respective bond breaking and make various comparisons possible. Relative eases of carbocation formations are **2a**/**2b**/**2c** = 230:7.6:1 and 580:73:1 when methanol and methanethiol are leaving groups, respectively. On the other hand, relative leaving abilities of methanol vs. methanethiol are 360, 95, and 900 when the cations **2a**, **2b**, and **2c** are being formed, respectively. Implications of small differences in these relative values are not clear, but tendencies that methanol is a better leaving group and oxo cations are more easily formed are consistent.

On the other hand, thiol was found to be a better leaving group than alcohol in very strong acids. Spectra of **1c** in strong acids showed formation of a mixture of carbocations **2b** and **2c**. In a very strong acid (concentrated H_2SO_4, $H_0 \simeq -10$), **2b** was mainly formed by the C–S bond cleavage, while in a weaker acid (30% $HClO_4$, $H_0 \simeq -1.6$) **2c** was a main cation observed in consistent with the product analysis. Both cations were formed in a moderately strong acid (70% $HClO_4$, $H_0 \simeq -7.7$). These observations must be ascribed to different acidity dependences of protonation of sulfur and oxygen atoms. Although the pK_a values are ca. 4 units more positive for ethers than for sulfides, the ionization ratio of the latter is greater than that of the former at higher acidities, owing to the greater acidity dependence of sulfur protonation.[14] This makes the leaving ability of thiol greater than that of alcohol at higher acidities although the latter is a better leaving group than the former at lower acidities.

Rate of Breakdown of the S,S-Carbocation 2c. Rate constants for the breakdown of **2c** are constant at higher pH but decreases with increasing acidity. This behavior is similar to that observed for the dithiolanylium ion.[18] The rate constant at high pH must be that for addition of water to **2c** (k_2 in eq 8). In this pH region, the rate

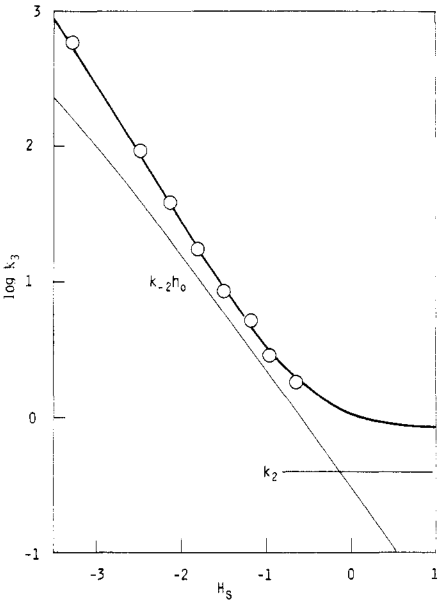


Figure 3. Acidity–rate profile for the breakdown of the tetrahedral intermediate **3c**.

$$\mathbf{2c} + H_2O \underset{k_{-2}[H^+]}{\overset{k_2}{\rightleftharpoons}} \mathbf{3c} \xrightarrow{k_3} \mathbf{4b} \qquad (8)$$

constant for the reverse of the first step, $k_{-2}[H^+]$, is smaller than that for the decay of the tetrahedral intermediate **3c**, k_3: the first step is rate determining. This occurs because the latter step is catalyzed by both acid and base while the former only by acid. At low pH, $k_{-2}[H^+]$ and k_3 may become closer, and in the region where $k_{-2}[H^+] \gg k_2$, k_{obsd} can be approximately described by eq 9.[19] Then, the rate

$$k_{obsd} = k_2k_3/(k_2 + k_{-2}[H^+] + k_3) \qquad (9)$$

constant k_3 can be calculated according to eq 10, where K_2

$$k_3 = (K_2 + h_R)k_{obsd}/(K_2 - k_{obsd}/k_{-2}) \qquad (10)$$

is the equilibrium constant for the first step, i.e., k_2/k_{-2}, and the acidity function H_R[8] is used for acidity since the equilibrium follows this function.[20-23] Since the acid-catalytic constant for the C–O bond cleavage of **1c** is 0.417 M^{-1} s^{-1} and substitution of a hydroxyl for the methoxyl group reduces the catalytic constant by about 20%,[13] 0.334 M^{-1} s^{-1} is estimated for k_{-2}. Then, K_2 is 1.2 ($pK_2 = -0.08$). With these values for k_{-2} and K_2, k_3 values are calculated and shown plotted logarithmically against the H_S acidity function (defined for sulfur protonation[20]) in Figure 3.

The logarithms of k_3 are linearly correlated with H_S with a slope of −1. The acid-catalytic constant for the breakdown of **3c** is 0.27 M^{-1} s^{-1}, which is on the same order of magnitude as those found for 2-alkyl-2-hydroxy-1,3-dithiolanes.[20-23] Since the first step seems to be mostly rate

---

[17] See, e. g.: Modena, G.; Scorrano, G.; Venturello, P. *J. Chem. Soc. Perkin Trans. 2* **1979**, 1–6.

[18] Okuyama, T.; Fujiwara, W.; Fueno, T. *J. Am. Chem. Soc.* **1984**, *106*, 657–662.

[19] Moore, J. W.; Pearson, R. G. *Kinetics and Mechanism*, 3rd ed.; Wiley: New York, 1981; pp 313–314.

[20] Okuyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 7134–7139.

[21] Okuyama, T.; Fueno, T. *J. Am. Chem. Soc.* **1985**, *107*, 4224–4229.

[22] Okuyama, T.; Toyoda, M.; Fueno, T. *Can. J. Chem.* **1986**, *64*, 1116–1123.

[23] Okuyama, T.; Fujiwara, W.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 453–456.

determining above pH 1 as judged from the pH–logk_{obsd} profile (Figure 1), k_3 should level off or increase above pH 0. Water- and/or base-catalyzed reactions must show up in this acidity region. The curve in Figure 1 is drawn with the water-catalyzed rate constant $k_0 = 0.8\ s^{-1}$.

Conclusion

Thio ortho esters undergo spontaneous hydrolysis as well as acid-catalyzed hydrolysis, while the ortho ester without any thio group undergoes only acid-catalyzed hydrolysis. Methanol was found to be a better leaving group in the acid-catalyzed reaction of ortho esters than methanethiol by factors of 10^2–10^3. Oxo carbocations are more easily formed than the thio cations in aqueous solution. As a consequence of these factors, hydrolysis of mixed O,S-ortho esters gives exclusively the ester as product at high pH while mainly the thio ester at low pH, the fractional product compositions changing sigmoidally between high and low acidities. However, in very strong acids, thiol can become a better leaving group than alcohol. The equilibrium constant for hydration of the S,S-carbocation **2c** and the rate constant for acid-catalyzed breakdown of the tetrahedral intermediate **3c** were evaluated.

Experimental Section

Materials. Trimethyl *p*-methoxyorthobenzoate (**1a**) was obtained as described previously.[23] Methyl *p*-methoxybenzoate (**4a**) was of the best grade commercially available.

O,O,S-Trimethyl *p*-methoxythioorthobenzoate (**1b**) was prepared by the reaction of (*p*-methoxyphenyl)dimethoxycarbenium (**2a**) tetrafluoroborate with methanethiol. The fluoroborate of **2a** prepared from 3 g of **1a** by the method of Meerwein[24] was dissolved in dry acetonitrile and added to an acetonitrile solution containing an equivalent amount of methanethiol[25] and excess triethylamine. The resulting mixture was concentrated under vacuum, taken up in ether, washed with aqueous sodium carbonate, and dried over $MgSO_4$. The ether was then removed, and the residues were distilled in a Kugelrohr at 5 mmHg. A fraction (0.6 g) obtained at an oven temperature of about 120 °C was a mixture of **1b** and **4a** in a ratio of 9/1 as judged from a ^1H NMR spectrum. A pure sample was obtained by preparative chromatography: ^1H NMR (CCl_4) δ 1.53 (s, 3 H), 3.13 (s, 6 H), 3.74 (s, 3 H), 6.72 (d, 2 H), 7.45 (d, 2 H, J = 8.4 Hz).

S,S,S-Trimethyl *p*-methoxythioorthobenzoate (**1d**) was synthesized from *p*-methoxybenzoyl chloride and methanethiol according to the literature.[26] The products were distilled under reduced pressure. A small amount of a forerun obtained at about 100 °C and 2 mmHg was solidified. Recrystallization from petroleum ether gave white plates, which melted at 41–42 °C and was identified as *S*-methyl *p*-methoxythiobenzoate (**4b**): UV (H_2O) λ_{max} 287 nm (ϵ 15 530); ^1H NMR (CCl_4) δ 2.40 (s, 3 H), 3.82 (s, 3 H), 6.87 (d, 2 H), 7.92 (d, 2 H, J = 8.4 Hz). Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53; S, 17.59. Found: C, 59.40; H, 5.49; S, 17.24. The main fraction was collected at 138–140 °C (2 mmHg): ^1H NMR (CCl_4) δ 1.96 (s, 9 H), 3.78 (s, 3 H), 6.74 (d, 2 H), 7.61 (d, 2 H, J = 8.4 Hz). Anal. Calcd for $C_{11}H_{16}OS_3$: C, 50.73; H, 6.19; S, 36.93. Found: C, 51.03; H, 6.13; S, 36.47.

(*p*-Methoxyphenyl)bis(methylthio)carbenium (2c) Perchlorate. To an ice-cooled solution of **1c** (2 g) in acetic anhydride (30 mL) was added dropwise 70% perchloric acid (2 mL) under magnetic stirring. After 30 min of reaction on an ice bath, dry ether (80 mL) was added, and the upper layer was removed by decantation. The remaining oil was triturated with ether to give yellow plates, which were collected on a sintered-glass filter, washed with ether, and dried under reduced pressure: UV ($HClO_4$) λ_{max} 393 nm (ϵ 14 500).

***O,S,S*-Trimethyl *p*-Methoxythioorthobenzoate (1c).** A solution of perchlorate of **2c** in acetonitrile was added dropwise to methanol containing excess sodium methoxide. After the usual workup, the fraction boiling at 119–120 °C (2 mmHg) was collected: ^1H NMR (CCl_4) δ 1.60 (s, 6 H), 3.43 (s, 3 H), 3.73 (s, 3 H), 6.72 (2, 2 H), 7.53 (d, 2 H, J = 8.4 Hz). Anal. Calcd for $C_{11}H_{16}O_2S_2$: C, 54.07; H, 6.60; S, 26.24. Found: C, 54.11; H, 6.56; S, 25.98.

Rate and Product Determinations. UV spectra were recorded on a Shimadzu UV 200 spectrophotometer. A sample of 30 μL of the stock solution of a substrate in acetonitrile of an appropriate concentration was introduced from a microsyringe into 3.0 mL of an aqueous reaction solution equilibrated at 30.0 ± 0.1 °C in a quartz cuvette. After thorough mixing, the absorbance changes were followed for kinetic measurements, and/or the infinite absorbances at six to ten half-times were recorded for product determinations. Rapid reactions of **1c** in moderately strong acids were followed by a Union RA 1100 stopped-flow spectrometer as before.[20]

Acknowledgment. We thank Wataru Fujiwara for preliminary experiments. Financial support by the Ministry of Education, Science and Culture (Grant-in-Aid for Scientific Research 60470094) and Ajinomoto Co., Inc. is gratefully acknowledged.

Registry No. **1a**, 4316-33-0; **1b**, 108269-85-8; **1c**, 108269-86-9; **1d**, 108269-87-0; **2a**·BF_4^-, 108269-88-1; **2c**·ClO_4^-, 108269-90-5; **4b**, 5925-72-4; MeSH, 74-93-1.

Supplementary Material Available: Rate constants (Tables S1 and S2) and product absorbances (Tables S3 and S4) (4 pages). Ordering information is given on any current masthead page.

---

[24] Meerwein, H.; Bodenbenner, K.; Borner, P.; Kunert, F.; Wunderlich, K. *Justus Liebigs Ann. Chem.* **1960**, *632*, 38–55. Kovacs, O. K. J.; Schneider, Gy.; Lang, L. K.; Apjok, J. *Tetrahedron* **1967**, *23*, 4181–4196.

[25] Shildneck, P. R.; Windus, W. *Organic Synthesis*; Wiley: New York, 1943 Collect Vol. 2, pp 345–346, 411–412.

[26] Rinzema, L. C.; Stoffelsma, J.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 354–363.