mmol) of 7 N KOH (aqueous) in 1.5 mL of EtOH was stirred at room temperature for 30 min and at reflux for 5 h. After the mixture was allowed to cool to room temperature, the solvent was removed by evaporation at reduced pressure, and the residue was partitioned between Et_2O and H_2O. The aqueous phase was acidified (concentrated HCl) and extracted twice with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated at reduced pressure to afford 220 mg (100%) of **3a** as a pale yellow crystalline solid identical with an authentic sample of **3a** by mp, ^1H NMR, and IR.

Registry No. **3a**, 59042-49-8; **5**, 78137-45-8; **6**, 64501-94-6; **8**, 78984-88-0; **9**, 7796-72-7; **10**, 7796-73-8; **11**, 88819-78-7; **12**, 95470-21-6; **13**, 95470-22-7; **14**, 95470-23-8; **15**, 95470-19-2; $MeC(OMe)_2NMe_2$, 18871-66-4; $CBrCl_3$, 75-62-7; $MeC(OEt)_3$, 122-51-0; $Fe(CO)_5$, 13463-40-6; CCl_4, 56-23-5; 3-methyl-2-buten-1-ol, 556-82-1; 2-oxazolidinone, 497-25-6; methyl *cis*-2,2-dimethyl-3-(2,2,2-trichloroethyl)cyclopropanecarboxylate, 64879-04-5.

Hydrolysis of Orthoisobutyrates. Rate-Determining Step and Effects of β-Methyl Substitution on Reactivity

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The acid-catalyzed hydrolysis of ortho esters is a three-stage process (eq 1–3), with the formation of an

$$RC(OR)_3 + HA \xrightarrow{k_1} RC^+(OR)_2 + ROH + A^- \quad (1)$$

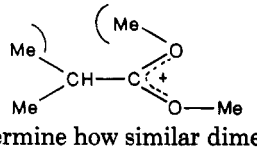
$$RC^+(OR)_2 + H_2O \rightleftharpoons RC(OH)(OR)_2 + H^+ \quad (2)$$

$$RC(OH)(OR)_2 \xrightarrow{k_3} RCO_2H + ROH \quad (3)$$

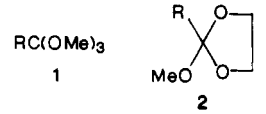
alkoxy carbocation (eq 1) being generally rate determining.[1] The formation of a similar carbocation intermediate is also the rate-determining step in the acid-catalyzed hydrolysis of ketene acetals (eq 4).[2-5] In the latter reaction, di-

$$R_1(R_2)C{=}C(OR)_2 + HA \rightarrow RC^+(OR)_2 + A^- \quad (4)$$

methylketene dimethyl acetal was found to be less reactive than the unsubstituted ketene acetal by a factor of 9×10^5.[5] This large reduction in reactivity was ascribed to steric interaction between the β-methyl and the methoxy groups in the dimethoxy carbocation, which inhibits resonance stabilization of the cation and hence its formation.



In order to determine how similar dimethyl substitution affected the reactivity of ortho esters, we have studied the kinetics of the acid-catalyzed hydrolysis of orthoisobutyrates **1b** and **2b**.



a, R = Me; **b**, R = Me_2CH; **c**, R = Me_3C; **d**, R = *p*-$MeOC_6H_4$

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Table I. Kinetic Results for the Hydrolysis of Ortho Esters

substrate	range of 10^3[HCl], M	$10^{-3}k_{H^+}$,[a] M^{-1} s^{-1}	$10^{-3}k_{H^+}$,[b] M^{-1} s^{-1}
1a[c]	1–2.5	12.0 (0.4)	
1b[c]	1–10	38.9 (0.5)	44.5 (1.6)
1c[c]	1–10	13.1 (0.2)[d]	12.9 (1.4)
1d[e]	0.45–50	0.307 (0.002)	0.325 (0.017)
2b[c]	5–50	0.858 (0.004)	22.0 (1.5)

[a] Calculated from k_{obsd} obtained in HCl solutions; standard deviations given in parentheses. [b] Calculated from data obtained at pH about 6.3 and 6.8 in biphosphate buffer solutions. The average of the two is given with the difference from the calculated k_{H^+}. [c] At 25 °C and 0.10 M ionic strength (KCl) in 1–1.5 vol % CH_3CN–H_2O. [d] $k_{D^+} = 2.20 \times 10^4$ M^{-1} s^{-1} in DCl solution; $k_{D^+}/k_{H^+} = 1.68$. [e] At 30 °C and 0.45 M ionic strength (KCl) in 10 vol % CH_3CN–H_2O.

It has recently been shown that the rate-determining step in the hydrolysis of cyclic ortho esters becomes the breakdown of the tetrahedral intermediate (eq 3) at low pH.[6-10] However, acyclic ortho esters, except for trimethyl orthocyclopropanecarboxylate, do not undergo this change.[10,11] This exception was attributed to the hydrophobicity of the cyclopropyl group.[10] We determined whether this change in the rate-determining step occurred with acyclic ortho esters **1** that have a bulky substituent.

Results

Rates of hydrolysis of **1** and **2** were measured in dilute HCl and in biphosphate buffer solutions. Pseudo-first-order rate constants k_{obsd} in 0.00005–0.05 M HCl were proportional to the acid concentration.[12] Catalytic constants k_{H^+} were determined by least-squares analysis and are given in Table I. The rate of the uncatalyzed reaction was essentially zero.

Buffer catalysis was observed for all the substrates, consistent with the general-acid catalysis usually observed for ortho ester hydrolysis.[1,12] The rate constants extrapolated to zero buffer concentration by least-squares treatment represent the hydronium ion contribution to the observed rates, $k_{H^+}[H^+]$, and were converted to k_{H^+} by using the pH of the buffer. The averages of the catalytic constants are given in Table I.

Discussion

The data in Table I show that the constants k_{H^+} for the hydrolysis of **1** are essentially equal to those determined at higher pH in biphosphate buffers. The rate constants in the two different pH regions should reflect the same reaction step (eq 1), indicating that the rate-determining step does not change with pH. In contrast, the catalytic constant for the cyclic ortho ester **2b** in HCl at pH 1.3–2.3 is about $^1/_{25}$ that in biphosphate buffers. Thus, the rate-determining step changes from that of eq 1 at high

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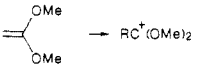
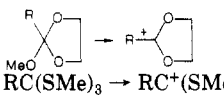
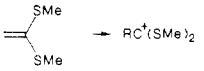
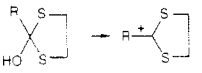
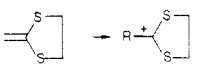
(12) Tables of observed rate constants are available as supplementary material.

0022-3263/86/1951-5433$01.50/0

Table II. Effects of β,β-Dimethyl Substitution on the Reactivity of Carbocation-Forming Reactions

entry	reaction	rel rate[a]	ref
1	$RC(OMe)_3 \rightarrow RC^+(OMe)_2$	0.31	this work
2		9×10^5	5
3		1.0	this work, 10
4	$RC(SMe)_3 \rightarrow RC^+(SMe)_2$	0.043	13
5		8.8×10^5	13, 14
6		0.33	15
7		400	15

[a] Relative rate constants of R = $CH_3/(CH_3)_2CH$ for acid-catalyzed hydrolysis at 25 or 30 °C.

pH to that of eq 3 at low pH, as was found for other cyclic ortho esters.[6-10] This change has been ascribed to an unfavorable entropy effect in the third step.[10]

Another factor in the change of rate-determining step of trimethyl orthocyclopropanecarboxylate was considered to be the solvent effect that stabilizes the hydrogen ortho ester intermediate and thus retards the third step.[10] This solvent effect should be relatively more important for hydrogen ortho esters with large hydrophobic substitutents such as aryl or cyclopropyl. However, we did not observe a change in the rate-determining step for **1b–d**, which bear isopropyl, *tert*-butyl, and aryl groups, respectively, and conclude that there is no solvent effect in the hydrolyses of these ortho esters.

The rate constant for the β,β-dimethyl-substituted ester **1b** is 3 times greater than that of its unsubstituted analogue **1a**, in marked contrast to the large rate-retarding effect induced by a similar substitution of the ketene acetal.[5] Although both reactions generate the same dimethoxy carbocation, the contrasting reactivity cannot be interpreted by factors operating in the product cation. The effects of dimethyl substitution in some related cation-forming acid-catalyzed reactions are summarized in Table II for comparison. The effects we have observed with ketene acetals and ortho esters are paralleled in their sulfur analogues (entries 4 and 5).[13,14] For cyclic ortho esters, dimethyl substitution has no or little effect on the relative rates (entries 3 and 6),[15] and the rate-retarding effect found for ketene acetal derivatives is less (entry 7).[15]

Factors that might affect these reactivities include (1) ground-state stabilization, (2) steric hindrance against the attacking hydronium ion, (3) electronic effects of substituents in the transition state, (4) vicinal interactions in both the ground and transition states, and (5) solvation effects. The effects of β,β-dimethyl substitution on the reactivities of ketene acetals and ortho esters will be considered by these factors operating in the rate-determining step.

One methyl group stabilizes a carbon–carbon double bond by 3.2 kcal/mol[16] in the ground state, but this effect must be much less in the transition state. The difference in stabilization energies in the ground and transition states causes a reduction in reactivity. This factor is considered to be mainly responsible for the retardation observed for the cyclic ketene thioacetals (entry 7).[15] During hydrolysis, protonation occurs at the β-carbon of a ketene acetal but at the oxygen of an ortho ester. Accordingly, steric hindrance to protonation by the β-substituent may operate in ketene acetal hydrolysis, as deduced from kinetic isotope effects[5] but should be negligible in ortho ester hydrolysis. Electronic effects of the β-methyl group in the transition state are probably small and essentially the same for both series of substrates.

Vicinal interactions between the β-methyl and the methoxy groups must, however, be much different for the two substrate classes. Ketene acetals have a C–C double bond that becomes a single bond on protonation. This bond must still retain a partial double-bond character and be incapable of rotation in the transition state. This rigidity exerts a cis methyl–methoxy interaction and forces the methoxy CH_3 group out of plane, resulting in reduced resonance stabilization of the developing carbocation. Similar vicinal interactions may be much smaller for cyclic derivatives (entry 7). On the other hand, the α,β bond in an ortho ester is single and can rotate at any time from the ground to the product state. The transition state thus assumes the most favored conformation, and the inhibition of resonance stabilization must be smaller than in the ketene acetal. Furthermore, in the rate-determining step of ortho ester hydrolysis, a methoxy group is leaving to form a carbocation, and the vicinal interactions must be reduced on going from the ground to the transition state. These factors coupled with different solvation effects give rise to the observed difference in the reactivities of the dimethyl-substituted ketene acetals and ortho esters. Although the carbocation formed in the rate-determining step is the same for both reactions, the structures of the transition states are quite different. The effects of ground-state stabilization also greatly affect the reactivity.

Experimental Section

Materials. Trimethyl orthoisobutyrate (**1b**) was prepared according to the literature;[17] bp 134 °C (lit.[17] bp 135–136 °C). Trimethyl orthopivalate (**1c**) and trimethyl *p*-methoxyorthobenzoate (**1d**) were obtained as described previously.[18] 2-Isopropyl-2-methoxy-1,3-dioxolane (**2b**) was prepared by alcohol exchange from **1b**;[19] bp 84–86 °C (50 mmHg) [lit.[20] bp 160.5 °C (744 mmHg)]. Trimethyl orthoacetate (**1a**) and other chemicals were the best available commercial grades and were used as such.

Kinetics. Rates were measured spectrophotometrically at 25.0 ± 0.1 °C by monitoring the appearance of absorption in the region 210–220 nm. A Shimadzu UV 140 spectrometer was used for slow runs in buffer solutions, and a Union RA 1100 or RA 401 stopped-flow spectrometer was used for the faster runs in HCl solution. Detailed procedures were the same as described before.[13-15]

Acknowledgment. We thank Professor M. Sawada for the use of the RA 401 stopped-flow spectrometer.

Registry No. **1a**, 1445-45-0; **1b**, 52698-46-1; **1c**, 97419-16-4; **1d**, 4316-33-0; **2b**, 66822-98-8.

Supplementary Material Available: Tables of observed rate constants (2 pages). Ordering information is given on any current masthead page.

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