physical-organic chemistry and would complement the equilibrium studies presented here.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research. We also gratefully acknowledge partial support of this work by grants from the National Science Foundation and the National Institutes of Health of the U.S. Public Health Service, J.C.C. thanks the Chevron Corp. for a fellowship and the Graduate School for a scholarship.

Alkyl Group Effects on the Rate Constants and Equilibrium Constants for Formation of Cyclic Tetrahedral Intermediates

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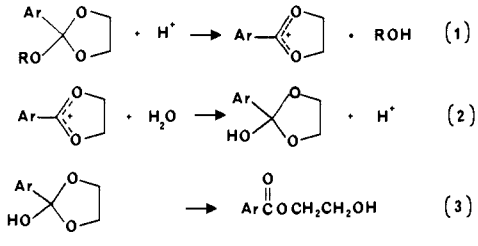
Abstract: 2-Hydroxy-2-alkyl-1,3-dioxolanes T are the cyclic tetrahedral intermediates of the degenerate intramolecular ester interchange reactions of ethylene glycol monoalkanoates A, in which alkanoyl groups transfer from one end of ethylene glycol to the other. This study reports equilibrium constants for the cyclization A ⇄ T to the tetrahedral intermediate stage with 10 alkanoate derivatives. These equilibrium constants, which when written as [A]/[T] are all large (10^7–10^9) in favor of the ring-opened form, were obtained as the ratio of rate constants for equilibration occurring with H^+ catalysis. Rate constants for the ring opening of T were directly measured through a study of the kinetics of the hydrolysis of 2-methoxy-2-alkyl-1,3-dioxolane ortho esters. These hydrolyses proceed via T, and under acid conditions the breakdown of this intermediate is rate-limiting. Rate constants in the ring-closing direction were obtained by preparing $HOCH_2CD_2OOCR$ and, with the use of ^1H NMR spectroscopy, measuring the kinetics of isomerization to an equilibrium mixture with $RCOOCH_2CD_2OH$. The reaction under investigation is an intramolecular analogue of H^+-catalyzed alkanoate ester hydrolysis, whose rate constants define the steric substituent parameter E_s. The ring-closure rate constants for A → T do show an excellent correlation with E_s. However, the rate constants for ring-opening T → A and the overall equilibrium constants are badly correlated, showing quite different behavior for series with α and β branching in the alkyl group. Thus, for this system the E_s parameter does not correlate free energy differences between the acyl derivative and tetrahedral intermediate. It is only the free energy differences between the acyl form and the transition state leading to the intermediate that fit E_s.

A three-stage reaction mechanism is now well established for the H^+-catalyzed hydrolysis of ortho esters.[1,2] Until recently, kinetic studies were generally carried out under conditions with the first stage (eq 1), generation of the dialkoxycarbocation in-



termediate, rate-limiting. However, there have now been encountered a number of ortho esters that have stage 1 rate-limiting at high pH, with a changeover at low pH to rate-limiting stage 3, the breakdown of the hydrogen ortho ester intermediate to products. This situation arises for those ortho esters that have a rate constant for H^+ catalysis of stage 3 which is smaller than that of stage 1. Thus, providing that the solution is acidic, stage 3 is a slower process than stage 1. Stage 3 is also efficiently catalyzed by OH^-. This causes stage 3 to be faster than stage 1 at high pH, with a resultant change in rate-limiting step.

A hydrogen ortho ester is also the tetrahedral intermediate of an ester alcoholysis reaction and is obviously also closely related to the tetrahedral intermediate of ester hydrolysis. The kinetic procedure usually employed in studies of ortho ester hydrolysis involves the monitoring of the appearance of the ester product, taking advantage of its carbonyl chromophore. This means that under the conditions where stage 3 is rate-limiting, the observed rate constants measure directly the breakdown of a tetrahedral intermediate.[2-5] Such rate constants cannot be obtained in investigations of the corresponding ester alcoholysis, where the tetrahedral intermediate is present only in very small stationary-state amounts. Moreover, by coupling these breakdown rate constants with rate constants for formation from appropriate acyl precursors, it has been possible to directly measure equilibrium constants for tetrahedral intermediate formation.[3a,f,4e] These equilibria substantially favor the acyl derivative, and thus the

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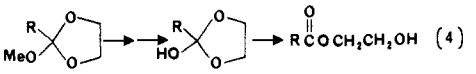
equilibrium constants cannot be measured in the normal fashion as concentration ratios.[6]

The change in rate-limiting step was first recognized with a series of 2-aryl-2-alkoxy-1,3-dioxolanes (eq 1).[2] It was later realized that a similar behavior is exhibited by 2-methyl-2-methoxy-1,3-dioxolane (eq 4).[2c,3g]



We report here a study of 10 2-alkyl derivatives, all of which follow this common behavior and in consequence undergo hydrolysis under acid conditions with rate-limiting breakdown of the hydrogen ortho ester intermediate, a 2-hydroxy-2-alkyl-1,3-dioxolane. This species is the tetrahedral intermediate of a degenerate intramolecular ester interchange involving the transfer of an alkanoyl group from one end of ethylene glycol to the other. By appropriate isotopic labeling, which removes the degeneracy, it has been possible to obtain rate constants for the formation of the tetrahedral intermediate in this process and then, by coupling formation and breakdown rate constants, the equilibrium constants.

A principal goal of this research has been to quantitatively examine the effect of the alkyl substituents on the equilibration. The Taft steric and polar substituent constants are based upon rate constants for a related intermolecular reaction, the hydrolysis of aliphatic carboxylic esters.[7] These rate constants are normally taken to refer to the formation of the tetrahedral intermediate of this hydrolysis, although in fact with esters neither the formation nor the breakdown is entirely rate-limiting, so that the observed rate constant contains several rate constants of the individual stages.[8] The system of this study is particularly attractive for an evaluation of substituent effects since the kinetic information represents a single reaction stage. Moreover, the equilibrium constant is obtained.

Experimental Section

Ortho Esters. 2-Methoxy-2-methyl-1,3-dioxolane was prepared by mixing equivalent amounts of trimethyl orthoacetate and ethylene glycol and adding a small amount of *p*-toluenesulfonic acid catalyst. The methanol produced by the ortho ester interchange was removed by distillation at reduced pressure (water aspirator), and when the reaction was judged complete by NMR, a few drops of triethylamine was added and the ortho ester product obtained by distillation.

The remainder of the ortho esters were prepared starting from the acid chloride. These were commercial available, with the exception of 2-methylbutyryl chloride and 2-ethylbutyryl chloride, which were obtained from the carboxylic acid and thionyl chloride. Freshly distilled acid chloride (0.1 mol) dissolved in 15 mL of dry ether (distilled from sodium) was added to a solution in 35 mL of dry ether of ethylene glycol monomethyl ether (0.1 mol) and pyridine (0.1 mol). After the resultant mixture was refluxed overnight, pyridinium hydrochloride was filtered and the ether washed with 0.1 M HCl and saturated sodium bicarbonate. After the mixture was dried over $MgSO_4$, the ether was removed on a rotary evaporator and the 2-methoxyethyl ester obtained by vacuum distillation. This ester (0.05 mol) and triethyloxonium tetrafluoroborate[9] (0.12 mol) were dissolved in 100 mL of dry methylene chloride (distilled from concentrated H_2SO_4), and the solution refluxed overnight. This procedure forms the 2-alkyl-1,3-dioxolan-2-ylium ion as its tetrafluoroborate salt.[10] This was added directly in the methylene chloride solution to a cooled, stirred solution of sodium methoxide (0.15 mol) in 100 mL of methanol, prepared by adding sodium metal to dry methanol (distilled from MgO). The solvents were removed as much as possible on a rotary evaporator and 100 mL each of water and diethyl ether added; the ether layer was collected and dried over anhydrous K_2CO_3, the ether removed, and the ortho ester obtained by distillation.

2-Methoxy-2-methyl-1,3-dioxolane: bp 118 °C (760 mmHg); ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 3.16 (s, 3 H), 3.78–4.07 (m, 4 H). Anal. Calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 51.05; H, 8.46.

2-Methoxy-2-ethyl-1,3-dioxolane: bp 60 °C (40 mmHg); ^1H NMR ($CDCl_3$) δ 1.07 (t, 3 H, J = 8 Hz), 1.81 (q, 2 H, J = 8 Hz), 3.22 (s, 3 H), 3.86–4.18 (m, 4 H). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.23; H, 9.18.

2-Methoxy-2-isopropyl-1,3-dioxolane: bp 73 °C (40 mmHg); ^1H NMR ($CDCl_3$) δ 0.97 (d, 6 H, J = 7 Hz), 2.10 (septet, 1 H, J = 7 Hz), 3.25 (s, 3 H), 3.90–4.22 (m, 4 H). Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.38; H, 9.79.

2-Methoxy-2-*tert*-butyl-1,3-dioxolane: bp 85 °C (40 mmHg); ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 3.24 (s, 3 H), 3.95–4.28 (m, 4 H). Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.81; H, 10.10.

2-Methoxy-2-propyl-1,3-dioxolane: bp 100 °C (60 mmHg); ^1H NMR ($CDCl_3$) δ 0.76–2.01 (m, 7 H), 3.22 (s, 3 H), 3.90–4.22 (m, 4 H). Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.42; H, 9.81.

2-Methoxy-2-butyl-1,3-dioxolane: bp 80 °C (1.3 mmHg); ^1H NMR ($CDCl_3$) δ 0.70–2.00 (m, 9 H), 3.22 (s, 3 H), 3.84–4.20 (m, 4 H). Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.20; H, 10.17.

2-Methoxy-2-isobutyl-1,3-dioxolane: bp 54 °C (3.3 mmHg); ^1H NMR ($CDCl_3$) δ 0.92 (d, 6 H, J = 7 Hz), 1.42–2.15 (m, 4 H), 3.26 (s, 3 H), 3.88–4.21 (m, 4 H). Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.11; H, 10.04.

2-Methoxy-2-*sec*-butyl-1,3-dioxolane: bp 50 °C (1.5 mmHg); ^1H NMR ($CDCl_3$) δ 0.69–1.98 (m, 9 H), 3.28 (s, 3 H), 3.88–4.19 (m, 4 H). Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.12; H, 10.19.

2-Methoxy-2-neopentyl-1,3-dioxolane: bp 48 °C (1.3 mmHg); ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.74 (s, 2 H), 3.21 (s, 3 H), 3.80–4.12 (m, 4 H). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.92; H, 10.37.

2-Methoxy-2-(1'-ethylpropyl)-1,3-dioxolane: bp 90 °C (15 mmHg); ^1H NMR ($CDCl_3$) δ 0.77–1.89 (m, 11 H), 3.25 (s, 3 H), 3.87–4.22 (m, 4 H). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.14; H, 10.32.

2-Hydroxy-1,1-dideuterioethyl Carboxylates. 2-(Benzyloxy)-1,1-dideuterioethanol was prepared by reduction[11] of ethyl (benzyloxy)acetate[12] with lithium aluminum deuteride (Aldrich). This was esterified by treatment with the appropriate acid chloride in ether containing pyridine, as described in the previous section. The benzyl protecting group was removed by hydrogenolysis in isopropyl alcohol with 10% palladium on activated charcoal.[13] After filtration of the catalyst and solvent removal, the desired esters were obtained by vacuum distillation. For $RCO_2CD_2CH_2OH$: R = CH_3 bp 59 °C (2.2 mmHg); CH_3CH_2, bp 63 °C (1.7 mmHg); $(CH_3)_2CH$, bp 65 °C (1.5 mmHg); $(CH_3)_3C$, bp 52 °C (1.0 mmHg); $CH_3CH_2CH_2$, bp 62 °C (0.8 mmHg); $CH_3CH_2CH_2CH_2$, bp 51 °C (0.1 mmHg); $(CH_3)_2CHCH_2$, bp 44 °C (0.2 mmHg); $CH_3CH_2CHCH_3$, bp 55 °C (0.5 mmHg). The esters with R = $(CH_3)_3CCH_2$ and $(CH_3CH_2)_2CH$ were used directly without distillation. The esters are characterized by a broadened singlet at 3.8 ppm in their ^1H NMR spectrum. Some isomerization to $RCO_2CH_2CD_2OH$ can occur, particularly if the distillation is carried out at higher temperatures. This ester is characterized by a broadened singlet at 4.2 ppm.

Kinetics of Ortho Ester Hydrolysis. Rate measurements were made spectrophotometrically by monitoring the appearance of the carboxylic acid ester in the region 210–220 nm. For the slower runs in phosphate buffer solutions, a Varian 2390 spectrophotometer was employed. The cell compartment was thermostated at 25.0 ± 0.05 °C. Kinetic runs were initiated by injecting 1–2 μL of the neat ortho ester directly into the appropriate solution in the UV cuvette, after the latter had achieved thermal equilibrium. Concentrations of ortho ester were 5–10 mM. The spectrophotometer was interfaced with an Apple IIe microcomputer, where the kinetic analyses were carried out by fitting the absorbance–time data to the exponential equation. The faster kinetic runs in hydrochloric acid solutions were carried out on a Durrum-Gibson stopped-flow spectrophotometer, thermostated at 25.0 ± 0.1 °C. Ortho ester (5–20 mM) was dissolved in 0.002 M NaOH and this solution mixed with the appropriate acid. The photomultiplier output was digitized and the information transferred to a Tektronix 4051 minicomputer, where rate constants were calculated as the slopes of plots of ln ($A_\infty - A$) versus time.

Kinetics of $RCO_2CD_2CH_2OH$ Isomerization. The labeled ester (0.2–0.5 g) was dissolved in 0.5–1.0 L of aqueous HCl and the solution placed in a constant temperature bath at 25.0 ± 0.05 °C. At appropriate

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Table I. Rate and Equilibrium Constants (25 °C, Ionic Strength 0.1)

2-subst	σ^*	E_s	$10^{-4}k_1^H$, M^{-1} s^{-1}	$10^{-3}k_3^H$, M^{-1} s^{-1}	k_3^0, s^{-1}	$10^5k_{-3}^H$, M^{-1} s^{-1}	$10^{-7}K_3$	$10^9k_{-3}^0$, s^{-1}	$10^6k_{Hyd}^H$, M^{-1} s^{-1}
CH_3	0.00	0.00	1.68 ± 0.04[a]	1.16 ± 0.02	0.57 ± 0.08	4.3 ± 0.4	2.7 ± 0.3	21 ± 4	24 ± 2
CH_2CH_3	−0.100	−0.07	1.80 ± 0.05	1.02 ± 0.05	0.6 ± 0.1	3.9 ± 0.3	2.6 ± 0.2	23 ± 4	22 ± 3
$CH_2CH_2CH_3$	−0.115	−0.36	2.48 ± 0.07	1.35 ± 0.04	0.29 ± 0.08	2.9 ± 0.4	4.7 ± 0.7	6 ± 2	14.4 ± 0.6
$CH_2CH_2CH_2CH_3$	−0.13	−0.39	2.35 ± 0.07	1.36 ± 0.06	0.4 ± 0.1	2.6 ± 0.3	5.2 ± 0.6	8 ± 2	12 ± 1
$CH(CH_3)_2$	−0.19	−0.47	1.88 ± 0.07	0.84 ± 0.02	0.23 ± 0.06	2.6 ± 0.3	3.2 ± 0.4	7 ± 2	10.7 ± 0.5
$CH_2CH(CH_3)_2$	−0.125	−0.93	5.75 ± 0.06	2.6 ± 0.1	1.4 ± 0.5	1.6 ± 0.2	16 ± 2	9 ± 3	4.3 ± 0.6
$CH(CH_3)CH_2CH_3$	−0.210	−1.13	2.68 ± 0.04	1.31 ± 0.01	0.16 ± 0.03	1.3 ± 0.1	10.1 ± 0.8	1.6 ± 0.3	3.7 ± 0.3
$C(CH_3)_3$	−0.300	−1.54	3.38 ± 0.08	0.264 ± 0.003	0.08 ± 0.01	0.86 ± 0.09	3.1 ± 0.3	2.6 ± 0.4	2.6 ± 0.2
$CH_2C(CH_3)_3$	−0.165	−1.74	31.5 ± 0.3	11.6 ± 0.3	0.8 ± 0.1	0.61 ± 0.07	190 ± 22	0.4 ± 0.1	1.3 ± 0.2
$(CH_3CH_2)_2CH$	−0.225	−1.98	4.4 ± 0.1	2.53 ± 0.04	0.23 ± 0.07	0.55 ± 0.05	46 ± 4	0.50 ± 0.15	0.9 ± 0.1

[a] Error given with each number is one standard deviation.

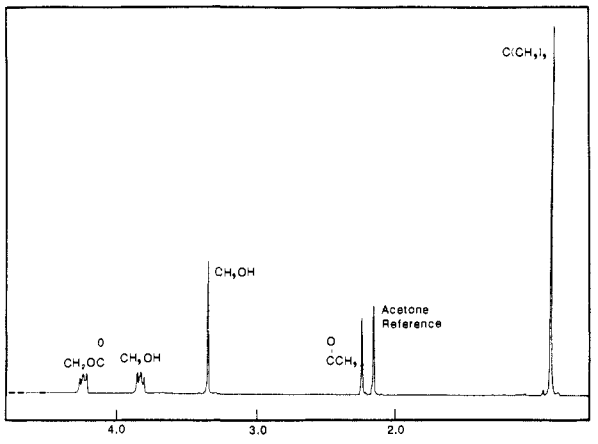

Figure 1. 200-MHz ^1H NMR spectrum of the hydrolysis products of 2-methoxy-2-neopentyl-1,3-dioxolane (1 mg) dissolved in 1 mL of 0.02 M DCl/D_2O.

time intervals 100 mL of the solution was withdrawn and extracted with 200 mL of methylene chloride. The organic layer was dried over $MgSO_4$ and, after filtration, the solvent removed on the rotary evaporator. $CDCl_3$ (1 mL) was added and the NMR spectrum recorded on a Varian T-60 spectrometer. The relative intensity of the signals at 3.8 and 4.25 ppm was determined by multiple (5–10 times) integration.

Kinetics of $RCO_2CD_2CH_2OH$ Hydrolysis. These studies were carried out with the solutions involved in the isomerization experiments. At appropriate times, a small portion of this solution was placed in a UV cuvette and the optical density at 215 nm recorded. Hydrolysis of aliphatic carboxylates exhibits a decrease in absorbance at this wavelength.[14] Since relatively dilute acids were involved and the hydrolysis was slow, the Guggenheim method was employed to calculate the rate constants.

Results and Discussion

Products of Ortho Ester Hydrolysis. The hydrolysis of 2-aryl-2-methoxy-1,3-dioxolanes has been established to proceed with exocyclic C–O bond cleavage in stage 1, as shown in eq 1–3.[15] That the same mechanism applies with the 2-alkyl systems was shown by product analysis, three representative substrates, R = methyl, *tert*-butyl, and neopentyl (neoPe), being chosen for evaluation. The experiment involved hydrolysis in dilute DCl/D_2O, with a 200-MHz ^1H NMR spectra being immediately recorded. Figure 1 shows the spectrum obtained with the neopentyl compound; the other two systems behaved in the same manner, with the exception of the expected differences in the alkyl portion of the spectra. These spectra clearly show the formation of methanol and the 2-hydroxyethyl alkanoate, with less than 3% of the alternative products ethylene glycol and the methyl alkanoate. Arguments have been made that this situation is only consistent with an initial exocyclic cleavage, since an initial endocyclic cleavage should result in at least some of the latter products.[15]

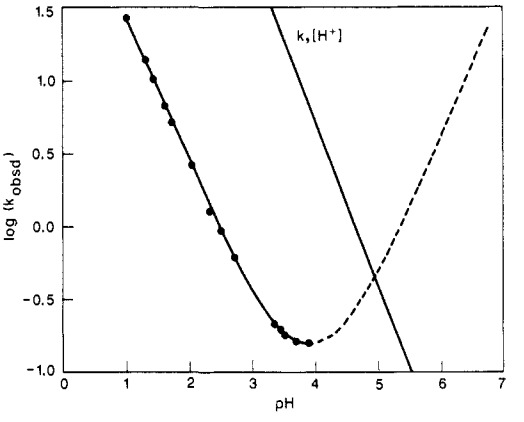

Figure 2. Rate constant–pH profiles for stage 1 and stage 3 in the hydrolysis of 2-methoxy-2-*tert*-butyl-1,3-dioxolane. The curve represents stage 3, with the points experimental numbers from HCl solutions (pH 1–3) or dilute formate buffers (pH 3–4), and the profile drawn as $2.64 \times 10^2[H^+] + 0.08 + 5 \times 10^8[OH^-]$.[18] The line $k_1[H^+]$ represents stage 1 and is based upon the H^+ catalytic coefficient 3.4×10^4 M^{-1} s^{-1} determined at pH 6–7.

Kinetics of Ortho Ester Hydrolysis. The best experimental indicator of a change in rate-limiting step in an ortho ester hydrolysis is a rate constant for H^+ catalysis measured at low pH that is smaller than that measured at high pH.[2,3] Accordingly, rate constants for the hydrolysis of the 10 2-alkyl-substituted ortho esters were obtained in HCl solutions with pH 1–3 and in phosphate buffers with pH 6–7. The raw data are available as supplementary material.

The first-order rate constants in phosphate buffers displayed a dependency upon buffer concentration. This is expected since this type of ortho ester usually exhibits general-acid catalysis in the dialkoxycarbocation-forming stage.[2b,3g,15,16] Analysis of this catalysis is normally carried out according to eq 5, although Kresge

$$k_{obsd} = k^0 + k^H[H^+] + k^{Buff}[H_2PO_4^-] \quad (5)$$

and co-workers have also found a small contribution from H_3PO_4, despite its very low concentration at pH 6–7.[3g] Our studies were not carried out in sufficient detail to investigate this latter point. The important constant for further discussion is that associated with H^+ catalysis, k^H, and these values based upon extrapolation to zero buffer concentration are listed in Table I under the heading k_1^H. This symbolism is employed since we argue that the kinetics at this pH refer to the first stage in the hydrolysis. Within experimental error there was no contribution from the k^0 rate constant, which would represent a pH-independent first stage.

In HCl solutions the observed rate constants follow eq 6. Values of k^0 and k^H were determined by a weighted least-squares

$$k_{obsd} = k^0 + k^H[HCl] \quad (6)$$

analysis[17] and are listed in Table I under the headings k_3^0 and

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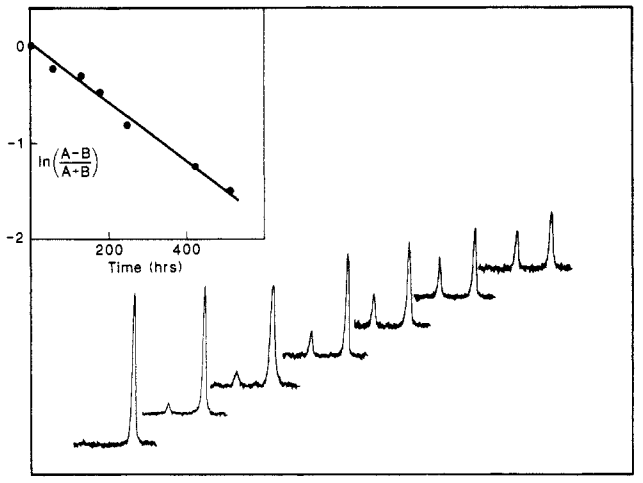


Figure 3. 60-MHz ^{1}H NMR spectra in the 4.3–3.7 ppm range obtained with 2-hydroxy-1,1-dideuterioethyl trimethylacetate when dissolved in 0.1 M HCl. The peak to the right in each spectrum is at 3.8 ppm and the peak to the left at 4.25 ppm. Spectra were recorded in $CDCl_3$ after extraction from the aqueous solution at times from left to right of 0, 50, 120, 172, 240, 410, and 540 h. The inset shows the peak intensity plotted according to eq 8.

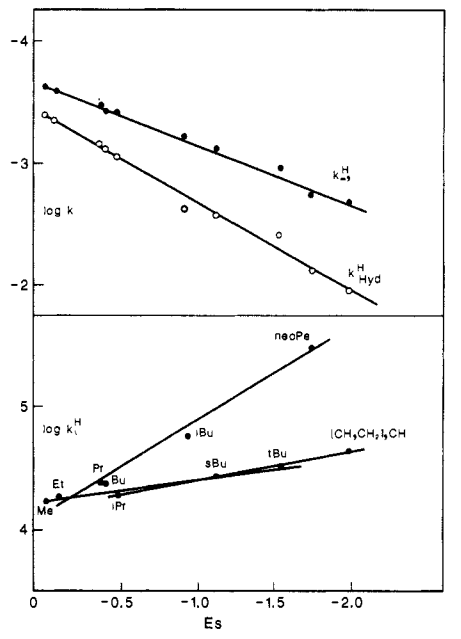


Figure 4. Correlations with E_s substituent constant.

k_3^H, respectively. The subscript "3" is now used since these kinetics represent the third stage. That a change in rate-limiting step has occurred between pH 6–7 and pH 1–3 is clearly indicated in each case by k_3^H being smaller than k_1^H. A further indicator is the presence of the k_3^0 term, which represents a pH-independent hydrogen ortho ester breakdown. The numerical values of k_3^0 do carry a large uncertainty, but in each case the number is significant. With the *tert*-butyl system, experiments were conducted in the pH 3–4 region with dilute (1–5 mM) formate buffers. At this pH the k_3^H process is of lesser importance, and the rate–pH profile, shown in Figure 2, clearly indicates the presence of the pH-independent term.

Figure 2 also illustrates in graphical terms the change in rate-limiting step between low pH and high pH. With k_3^H less than k_1^H stage 3 is slower than stage 1 at low pH, and thus the former is rate-limiting in product formation. The availability to stage 3 of the additional pathways, however, results in it becoming faster at higher pH. The actual crossover is seen in the figure by the intersection of the two profiles. This occurs somewhere near pH 5, dependent upon the actual value for k_3^{OH}, the rate constant for OH^- catalysis of stage 3.[18]

Tetrahedral Intermediate Formation. This was studied by preparing ethylene glycol monoesters specifically 1,1-dideuteriated. These rearrange to their 2,2-dideuteriated isomers with the 2-hydroxy-1,3-dioxolane as an intermediate (eq 7). The rearrangement was followed by ^{1}H NMR spectroscopy, as illustrated by Figure 3. The original ester has its CH_2 resonance at 3.80 ppm, with that for the isomer at 4.25 ppm. If the assumptions are made that the tetrahedral intermediate is present in stationary-state amounts and that isotope effects are negligible, so that $k_{cyc} = k_{cyc}'$, $k_{op} = k_{op}'$, and there is a 50:50 mixture at equilibrium, then eq 8 is obtained, where A and B are the relative NMR integrations at 3.80 and 4.25 ppm, respectively. This equation predicts a linear plot of ln $[(A - B)/(A + B)]$ versus time, and this is the case, as illustrated in the inset to Figure 3. The slopes of such plots provide k_{cyc} as first-order rate constants. These isomerizations proved to be slow, and with one exception, kinetic runs were carried out only in 0.1 M HCl. The acetate was studied at three concentrations in 0.02–0.10 M HCl, and k_{cyc} was found to be proportional to H^+ concentration, indicative of H^+ catalysis.

$$\ln [(A - B)/(A + B)] = -k_{cyc}t \quad (8)$$

The H^+-catalyzed cyclization is the microscopic reverse of the H^+-catalyzed third stage of the ortho ester hydrolysis, the process symbolized by the rate constant k_3^H. We define, therefore, k_{-3}^H as the second-order rate constant for the cyclization and have calculated these (Table I) as $10k_{cyc}$, with the k_{cyc} measured in 0.1 M HCl. With forward and reverse rate constants available, the equilibrium constants K_3 ([ethylene glycol monoester]/[2-hydroxy-1,3-dioxolane]) can then be calculated as k_3^H/k_{-3}^H. One further constant can also be calculated, namely the rate constant k_{-3}^0 (as k_3^0/K_3), which corresponds to pH-independent cyclization.

During the course of the isomerization experiments, we became aware that the esters were undergoing hydrolyses. (The dideuteriated isomers cannot be completely equilibrated before hydrolysis is complete.) Rate constants for hydrolysis were also measured in 0.10 M HCl. These are listed in Table I as second-order rate constants k_{Hyd}^H obtained by multiplying by 10.

Alkyl Group Effects. The general form of the Taft equation is given with the first term of the right-hand side accounting for steric effects, and the second term, polar effects. The latter are known to be important for at least some of the reactions under investigation here. For example, rate constants k_1^H for the first stage in the hydrolysis of 2-aryl-2-methoxy-1,3-dioxolanes follow the Hammett σ constant with $\rho = -1.6$,[19] with rate constants k_3^H for the third stage, ring opening of 2-aryl-2-hydroxy-1,3-dioxolanes, giving $\rho = -1.1$.[2b] There is now some feeling, however, that for simple alkyl groups σ^* values are essentially constant, the variation found in the original Taft derivation being due to a residual steric

$$\log (k/k_0) = \delta E_s + \rho^*\sigma^* \quad (9)$$

(17) In plots of k_{obsd} versus $[H^+]$, the points at lower acidity are important since they define the pH-independent k^0. Simple linear regression treats all data points as if they have the same absolute error in k_{obsd}, whereas it is closer to the truth that they have the same relative errors. The former has the effect of weighting larger k_{obsd} to a greater extent and, in this way, introducing large errors in k^0. Our procedure was to rewrite the equation as log k_{obsd} = log $(k^0 + k^H$ + [HCl]), a procedure that gives each point an equal weighting, and to perform a least-squares fit to this equation with a curve-fitting routine: Cox, R. A., CURFIT, Department of Chemistry, University of Toronto.

(18) The curve drawn for stage 3 in Figure 2 is based on an value of k_3^{OH} of 5×10^8 M^{-1} s^{-1}, which is an upper limit based upon the experimental data. A higher value would have manifested itself as an upward curvature in the experimental points near pH 4. The hydrogen ortho ester 2-hydroxy-2-phenyl-1,3-dioxolane has $k_3^{OH} = 6 \times 10^9$ M^{-1} s^{-1}, indicative of rate-limiting deprotonation.[4f]

(19) Chiang, Y.; Kresge, A. J.; Young, C. I. *Finn. Chem. Lett.* **1978**, 13–18.

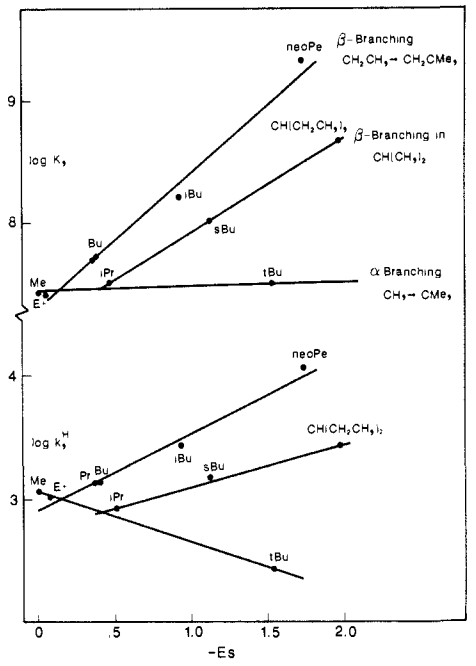


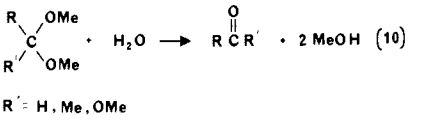
Figure 5. Correlations with E_s substituent constant.

effect coupled with an error component.[20] For this reason, and also because ρ values do not appear to be enormously large in magnitude, we will assume in the analysis of the data of Table I that polar contributions are constant for each reaction, so that the variations in rate or equilibrium constant represent a steric effect. The original Taft E_s values will also be employed. There are now a number of modified scales.[20c,21] Use of these does not affect the general conclusions. The Taft scale, $E_s(R) = \log [k_{Hyd}^H(RCOOR')/k_{Hyd}^H(CH_3COOR')]$ is based upon an H^+-catalyzed tetrahedral intermediate formation and is thus the most appropriate for the reaction in question here.

Figures 4 and 5 show the correlations of the various rate constants and the equilibrium constant K_3 with E_s. (No attempt was made to analyze k_3^0 and k_{-3}^0 where the precision is limited.) The H^+-catalyzed ring closure (k_{-3}^H) and, not surprisingly, the H^+-catalyzed ester hydrolysis are satisfactorily correlated, although the slopes δ are less than unity, 0.45 and 0.71, respectively. The other three constants, however, give poor fits. (It can be noted that the situation is not dramatically improved by including the polar term.) We will focus on k_3^H and K_3, since these represent processes actually involving the tetrahedral intermediate. The rate constant k_3^H shows the interesting behavior of *decreasing* in the series Me, Et, *i*-Pr, *t*-Bu, where there is methyl substitution on the carbon α to the reaction center, but *increasing* in the series Et, Pr, *i*-Bu, neoPe, where methyl substitution is on the β carbon. Each series is approximately linear in E_s with slopes δ of −0.4 (α branching) and 0.6 (β branching). The situation arises here where *t*-Bu is 4.4 times slower than Me, while neoPe is 10 times faster, so that despite similar E_s values neoPe ($E_s = -1.74$) is 44 times faster than *t*-Bu ($E_s = -1.54$). The equilibrium constant K_3 also exhibits two different and approximately linear relationships, increasing significantly with increased β branching (δ −1.1) but, within experimental error, remaining constant with increased α branching ($\delta = 0.0$). In other words, tetrahedral intermediate formation in the thermodynamic sense is just as easy with the pivalate (*t*-Bu) derivative as with the acetate (Me). Kinetically, this effect arises through an almost exact cancellation of the substituent effects on the rate constants in the two directions, which both decrease in the order Me, Et, *i*-Pr, *t*-Bu. It can also be noted that both k_3^H and K_3 have a second β-branching line, *i*-Pr, *s*-Bu, $CH(CH_2CH_3)_2$, roughly paralleling the Et → neoPe line.

The separation into two families, one for α branching and one for β branching, has been noted previously with several systems.[22] However, it seems particularly surprising in the present case, since the process under consideration so closely resembles the defining reaction for E_s. In accounting for the poor overall correlation, one important consideration to note is that E_s reflects free energy differences between an alkanoic acid ester and its transition state for H^+-catalyzed hydrolysis, while K_3, for example, measures free energy differences between an ester and the tetrahedral intermediate. The assumption is usually made that the transition state resembles the unstable intermediate, but in fact, in the present comparison the two must be different since the former is positively charged while the latter is neutral. Even if the bonding in the transition state were to resemble that of the intermediate, the solvation would be different. The large negative E_s values for bulky substituents such as *tert*-butyl and neopentyl are usually attributed to steric congestion in the tetrahedral form. The variations observed in K_3 are consistent with such an explanation for neopentyl and other β-branched substituents. However the implication is that there is very little increase in steric crowding with α branching. This leads to the suggestion that E_s values may carry a large component associated with steric hindrance to solvation of the positive charge in the transition state, and it is this factor that results in pivalate esters undergoing hydrolyses more slowly than acetates. We can note that there is a good correlation with E_s for the rate constant in the tetrahedral intermediate-forming direction, so that in this regard the acyl transfer of this study is not unusual. The low δ may simply mean that there is less steric crowding for the intramolecular OH addition as compared with H_2O addition.

Most studies of alkyl group effects have focused on rate constants where one of the states, the transition state, is ill-defined. Wiberg and co-workers have recently reported thermochemical studies for the carbonyl additions of eq 10.[23-25] The enthalpy



R' = H, Me, OMe

changes are poorly correlated with E_s, with better correlations seen in free energy changes, although the ortho ester could not be studied in the latter regard. A further study worth noting is that of DeTar and Tenpas, who via force field calculations determined differences in steric energies of $RC(OH)_3$ and RCOOH.[26] With a wide variety of alkyl groups, including those in the α- and β-branched series, a good correlation with E_s was observed. This raises the possibility that it is the intramolecular nature of the present system which is responsible for the poor E_s correlation. We are currently working on experiments designed to generate acyclic alkyl hydrogen ortho esters, but this is not easily done. Finally, we can note recent experiments involving the direct measurement of rate constants of water addition to alkyldiethoxycarbocations $RC^+(OEt)_2$.[27] This study showed that the *t*-Bu cation reacts more quickly than Me. This result is also very

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surprising since the reaction is a close model of water addition to a protonated ester $RC^+(OH)OEt$, the tetrahedral intermediate-forming step in H^+-catalyzed ester hydrolysis. As in the present study, an explanation can be advanced invoking steric effects on solvation.[27]

Acknowledgment. The continued financial support of the Natural Sciences and Engineering Research Council of Canada is acknowledged.

Supplementary Material Available: Table of first-order rate constants for product formation in 2-methoxy-2-alkyl-1,3-dioxolanes (4 pages). Ordering information is given on any current masthead page.

Reactivity Control by Microencapsulation in Simple Ammonium Ion Vesicles

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Received October 13, 1987

Abstract: The quantitative oxidation of Ellman's anion (**2**) to Ellman's reagent (**3**) by *o*-iodosobenzoate (**4**) can be kinetically controlled by microencapsulation in vesicles of dioctadecyldimethylammonium chloride (DODAC (**1b**)). Reactions at pH 8 between **2** and excess **4** occur rapidly on the surface of DODAC vesicles ($k \sim 0.16$–$0.24\ s^{-1}$). When either **2** or **4** is encapsulated within the DODAC vesicles, rapid reaction with the other *exovesicular* reagent does not occur; instead, a slow ($k \sim (2$–$7) \times 10^{-3}\ s^{-1}$) permeation-limited oxidation is observed, in which **4** is probably the key permeant. Individually encapsulated **2** and **4** react with each other only to the extent of ~5–10% over 20 h, a rate retardation >18 000 relative to the unmodulated exovesicular reaction. Similarly, the cleavage of Ellman's reagent (**3**) to Ellman's anion (**2**) by dithionite can be controlled by DODAC vesicles. The rapid, exovesicular cleavage ($k \sim 33$–$35\ s^{-1}$) disappears when endovesicular **3** is challenged by exovesicular dithionite and is replaced by the slow ($k \sim (5$–$7) \times 10^{-4}\ s^{-1}$) hydrolysis of **3**. In contrast to the observed facile vesicular DODAC control of these anion–anion reactions, the cleavage of neutral *p*-nitrophenyl diphenyl phosphate by **4** is not strongly affected by encapsulation of either substrate or **4**.

A decade has elapsed since Kunitake[1] and Fendler[2] introduced dialkyldimethylammonium ion surfactant vesicles as simple membrane models. It was quickly demonstrated that the rates of (e.g.) esterolysis[3] or electron-transfer[4] reactions occurring between reagents *separated* by these surfactant bilayers could be modulated by them.[5] Additionally, intravesicular bimolecular reactions between nucleophiles and reactive esters or phosphates were strongly accelerated due to reactant concentration on the membrane.[3,5]

Control of reagent and substrate permeation across bilayers is crucial to the rational use of synthetic vesicles as "microreactors".[1c,2,6,7] Additionally, liposomes or vesicles have long been used as drug delivery vehicles; the vesicle both protects the encapsulated drug from the external environment and controls its release via permeation.[2d] One widely studied method of enhancing control over permeation is by polymerizing the surfactant monomers that comprise the vesicle to impart greater structure and impermeability to the bilayers.[8] Variations of this approach include polymer-encased liposomes[9] and surfactant-coated polymer capsules.[10]

In our laboratory, we have focused on the applicability of *nonpolymerized*, simple dialkyldimethylammonium ion vesicles **1** (16_2 or 18_2) as agents of reactivity control. In a previous

$$R_2\overset{+}{N}Me_2,X^-$$

1a, R = *n*-$C_{16}H_{33}$ (16_2); **1b**, R = *n*-$C_{18}H_{37}$ (18_2)

X = Cl or Br

communication, we reported that the oxidation of 16_2-vesicle-entrapped Ellman's anion (**2**) to Ellman's reagent (**3**) by exo-

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