effect of carbocation-stabilizing substituents at the *pro*-acyl carbon atom on the rate of dialkoxycarbonium ion formation (eq 1). The situation is quite the same here: the cyclopropyl group in trimethyl orthocyclopropanecarboxylate raises the rate of this reaction by a factor of 310,[13] which is closely similar to the 290-fold acceleration shown by a cyclopropyl group in the cyclic 1,3-dioxolane series.[2] It seems likely, therefore, that this kind of change in rate-determining step will prove to be a general phenomenon that will appear in the hydrolysis of all ortho esters, cyclic or not, substituted with carbocation-stabilizing groups at the *pro*-acyl carbon atom.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their financial support of this research.

Registry No. 1, 54917-76-9.

Supplementary Material Available: Tables of rate constants (3 pages). Ordering information is given on any current masthead page.

(13) This comparison is based on $k^{1}_{H^+}$ = 263 M^{-1} s^{-1} for trimethyl orthoformate.[14]

(14) Chiang, Y.; Kresge, A. J.; Salomaa, P.; Young, C. I. *J. Am. Chem. Soc.* **1974**, *96*, 4494–4499.

Hydrolysis of Bicyclic Ortho Esters in the 2,6,7-Trioxabicyclo[2.2.1]heptane Series. Confirmation of the Absence of Strain-Relief Rate Acceleration

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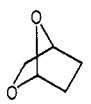
Abstract: The hydrolysis of 2,6,7-trioxabicyclo[2.2.1]heptane and its 1-phenyl derivative in aqueous solution was found to undergo a change in reaction mechanism from rate-determining formation of a dialkoxycarbonium ion intermediate from starting ortho ester at high pH to rate-determining decomposition of the hydrogen ortho ester formed by hydration of this ion at low pH. The initial ring-opening reactions of these bicyclic substrates proved to be not markedly faster than the corresponding reactions of monocyclic and acyclic models, which is consistent with the results obtained in an earlier more limited study. This behavior stands in marked contrast to the appreciable rate accelerations found in the hydrolysis of bicyclic acetals belonging to the same [2.2.1]heptane system; possible reasons for this difference are discussed.

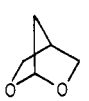
Bicyclic acetals in which the ether oxygen atoms are incorporated into small rings are unusually reactive toward acid-catalyzed hydrolysis.[2] For example, 2,7-dioxabicyclo[2.2.1]heptane (**1**) is



1

$CH_3CH(OCH_3)_2$

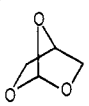
2



3

hydrolyzed in aqueous acetone containing dichloroacetic acid 25 000 times faster than its simple acyclic analogue, dimethyl acetal (**2**), and 2,6-dioxabicyclo[2.2.1]heptane (**3**) is more reactive still: its rate of hydrolysis is 6900 000 times that of dimethyl acetal.[2b] Small bicyclic ring systems of this kind are known to be strained,[3] and these rate accelerations have been attributed to partial relief of this strain upon ring-opening hydrolysis.

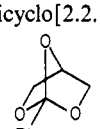
This unusual reactivity, however, appears not to extend to the corresponding ortho esters: 2,6,7-trioxabicyclo[2.2.1]heptane (**4**)



4

$HC(OCH_3)_3$

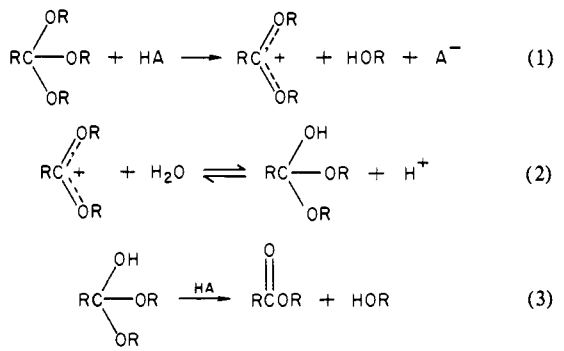
5



6

is actually hydrolyzed more slowly, by some 50%, than its acyclic analogue, trimethyl orthoformate (**5**).[4] This behavior, though unexpected, was rationalized in terms of an early hydrolysis transition state with very little ring opening and consequently little strain relief.

It is possible, however, that the situation may have been complicated by a change in the rate-determining step. Recent studies of ortho ester hydrolysis have shown that changes from a mechanism in which the first step of this reaction, eq 1, is rate determining to one in which the third step, eq 3, is slower can be effected by making structural changes that accelerate the rate of the first step.[5] Introduction of strain, as in a bicyclic system, is just such a structural change, and the rate constant measured for the bicyclic substrate, 2,6,7-trioxabicyclo[2.2.1]heptane, might



(1)

(2)

(3)

(1) (a) University of Toronto. (b) University of Arizona.

(2) (a) Hall, H. K., Jr.; Carr, L. J.; Kellman, R.; De Blauwe, F. *J. Am. Chem. Soc.* **1974**, *96*, 7265–7269. (b) Hall, H. K., Jr.; De Blauwe, F. *Ibid.* **1975**, *97*, 655–656. Hall, H. K., Jr.; De Blauwe, F.; Carr, L. J.; Rao, V. S. *J. Polym. Sci., Polym.* **1976**, *56*, 101–115.

(3) See, for example: Greenberg, A.; Liebman, J. F. "Strained Organic Molecules"; Academic Press: New York, 1978; pp 70–77.

(4) Hall, H. K.; De Blauwe, F.; Pyriadi, T. *J. Am. Chem. Soc.* **1975**, *97*, 3854.

(5) (a) Ahmad, M.; Bergstrom, R. G.; Cashen, M. J.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *J. Am. Chem. Soc.* **1977**, *99*, 4827–4829. (b) Ahmad, M.; Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *Ibid.* **1979**, *101*, 2669–2677. (c) McClelland, R. A.; Ahmad, M.; Bohonek, J.; Gedge, S. *Can. J. Chem.* **1979**, *57*, 1531–1540. (d) McClelland, R. A.; Gedge, S.; Bohonek, J. *J. Org. Chem.* **1981**, *46*, 896–891. (e) Burt, R. A.; Chiang, Y.; Kresge, A. J.; McKinney, M. A. *J. Am. Chem. Soc.* **1982**, *104*, preceding paper in this issue.

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therefore have been that for the slower reaction of step 3 instead of the rate constant for the intended faster reaction of step 1.

In order to investigate this matter, we undertook to examine the kinetics of hydrolysis of **4** in more detail. We also make a parallel study of the hydrolysis of the phenyl-substituted analogue, 1-phenyl-2,6,7-trioxabicyclo[2.2.1]heptane (**6**), for which we found it possible to obtain additional information not readily available with the purely aliphatic substrate **4**.

Experimental Section

Materials. The synthesis of 2,6,7-trioxabicyclo[2.2.1]heptane by transetherification from triethyl orthoformate and glycerol has already been described.[6] 1-Phenyl-2,6,7-trioxabicyclo[2.2.1]heptane was made in the same way, but a higher temperature, 200 °C, was needed to drive the product out of the reaction mixture as it formed. Three recrystallizations from ethyl ether at −78 °C gave fine white needles. This substance was characterized by the exact mass of the parent ion in its mass spectrum, m/e 178.0608 (calcd for $C_{10}H_{10}O_3$, 178.0630) and its NMR spectra ($CDCl_3$) [^1H: δ 4.0 (m, 4 H, CH_2), 5.0 (m, 1 H, CH), 7.2–7.8 (2 m, 5 H, C_6H_5); ^{13}C: δ 70.0 (CH_2), 75.8 (CH), 119.8 (C), 126.8, 128.1, 130.1, and 130.8 (aromatic C)]. All other materials were purchased commercially as best available reagent grades. Solutions were prepared by using deionized water purified further by distillation in an all-glass apparatus.

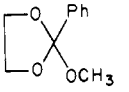
Kinetics. Rates of hydrolysis were measured spectroscopically by monitoring the increase in UV absorption due to carboxylic acid ester product, at 230 nm (absorption maximum) for 1-phenyl-2,6,7-trioxabicyclo[2.2.1]heptane and at 210–220 nm (shoulder) for 2,6,7-trioxabicyclo[2.2.1]heptane; a few rates were also measured by following the decrease in phenyldialkoxycarbonium ion absorbance at 268 nm. Slower runs were performed in the thermostatted (25.0 ± 0.05 °C) cell compartment of a Cary Model 118C spectrometer, and observed first-order rate constants were evaluated as visually determined slopes of plots of ln ($A_\infty - A$) vs. time; final absorbances, A_∞, were measured after 10 half-lives. Faster runs were performed using a Durrum–Gibson stopped-flow apparatus. The output of this machine was fed directly through an analog-to-digital converter into a transient recorder; the data were then transferred to a Tektronix Model 4051 minicomputer that calculated first-order rate constants by linear least-squares analysis and also provided visual displays.

Results

Rates of hydrolysis of 2,6,7-trioxabicyclo[2.2.1]heptane and its 1-phenyl derivative were measured in aqueous HCl or $HClO_4$ solutions of pH 1–2 and also in buffer solutions of considerably higher pH. For the parent compound at low pH, the rate of appearance of carboxylic acid ester product passed through a short induction period at all of the acid concentrations investigated (0.01–0.06 M HCl). Data obtained after this induction period, however, conformed well to the first-order rate law, and observed rate constants were therefore evaluated by discarding the initial deviant portions. Observed first-order rate constants obtained in this way were accurately proportional to HCl concentration (Table S1);[7] linear least-squares analysis gave the second-order catalytic coefficient, $k_{H^+} = (1.59 \pm 0.02) \times 10^2$ M^{-1} s^{-1}.

Rates of appearance of carboxylic acid ester product from 1-phenyl-2,6,7-trioxabicyclo[2.2.1]heptane at low pH, on the other hand, showed no induction period and obeyed the first-order rate law throughout their entire course. The range of acid concentration investigated here was somewhat greater than for the parent substrate (Table S1),[7] and although good proporitonality between observed first-order rate constants and acid concentration was found at the higher acidities, significant deviations were observed at the two lowest concentrations used (+20% at 0.002 M HCl and +5% at 0.005 M HCl). Such deviations may reasonably be attributed to base catalysis of hydrogen ortho ester decomposition (eq 3), inasmuch as the hydroxide ion promoted reaction is very fast and becomes evident even at rather low pH.[5b,c] These low concentration points were therefore not included in the linear least-squares evaluation of a hydronium ion catalytic coefficient, which gave $k_{H^+} = (1.07 \pm 0.01) \times 10^2$ M^{-1} s^{-1}.

A rate constant for hydroxide ion catalysis of hydrogen ortho ester decomposition can in fact be calculated from these low acidity deviations. Hydroxide ion concentrations required for this purpose were calculated from the autoprotolysis constant of water and activity coefficients for H^+ and HO^- recommended by Bates.[8] Least-squares analysis of the data gave $k_{HO^-} = (3.1 \pm 0.4) \times 10^{10}$ M^{-1} s^{-1}, which is similar to the hydroxide ion rate constant estimated previously for the hydrogen ortho ester derived from the monocyclic substrate, 2-phenyl-2-methoxy-1,3-dioxolane (**7**).[5b]



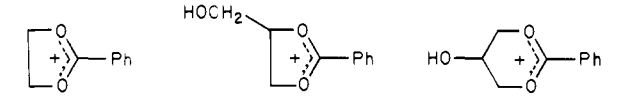
7

Rate constants for the hydrolysis of 1-phenyl-2,6,7-trioxabicyclo[2.2.1]heptane were also measured at higher acid concentrations in $HClO_4$ solutions of a greater ionic strength. Under these conditions, dialkoxycarbonium ion intermediates may sometimes be detected in the hydrolysis of ortho esters,[5] and such was in fact the case here: a new UV absorption band with λ_{max} 268 nm, which is typical of aryl-substituted dialkoxycarbonium ions, could be seen to rise rapidly and decay somewhat more slowly. Rates of reaction could be measured by monitoring the decay of this new absorbance as well as by following the rate of increase of benzoate ester at 230 nm; both processes followed first-order kinetics and gave identical rate constants at any given acidity (Table S1).[7]

These first-order rate constants showed a falling off from strict proportionality to acid concentration at higher acidities. Such behavior has also been observed before and has been attributed to the effect of acid in shifting the equilibrium between dialkoxycarbonium ion and hydrogen ortho ester (eq 2).[5] As before, the data were fitted to an expression, eq 4, which takes this effect

$$k_{obsd} = \frac{k_0 + k_{H^+}[H^+]}{1 + [H^+]/K_R} \qquad (4)$$

into account and allows for an uncatalyzed (k_0) as well as a hydronium ion catalyzed (k_{H^+}) route for the conversion of hydrogen ortho ester to carboxylic acid ester (eq 3). This analysis gave $k_0 = 0.19$ s^{-1} and $k_{H^+} = 178$ M^{-1} s^{-1}, plus $K_R = 2.68$, $pK_R = -0.43$, as the acidity constant of the diakoxycarbonium ion intermediate, i.e., the equilibrium constant of eq 2. This acidity constant is similar to that determined before for the parent substance, 2-phenyl-1,3-dioxolenium ion (**8**): $pK_R = 0.1$; the small



8 9 10

difference is in the direction expected for the acid-strengthening inductive effect of the hydroxy substituent in either of the two isomeric ions that may be formed in the present system: 2-phenyl-4-hydroxymethyl-1,3-dioxolenium ion (**9**) or 2-phenyl-5-hydroxy-1,3-dioxenium ion (**10**). The hydronium ion catalytic coefficient determined by this analysis, $k_{H^+} = 178$ M^{-1} s^{-1}, is consistent with that measured at the lower 0.10 M ionic strength, $k_{H^+} = 107$ M^{-1} s^{-1}, and the difference between the two, i.e., the ionic strength effect, is similar to that observed before in the hydrolysis of analogous monocyclic ortho esters.[5b] Both of the present values of k_{H^+} are also consistent with the corresponding rate constants measured during the hydrolysis of the monocyclic analogues, 2-phenyl-2-methoxy-1,3-dioxolane (**7**): $k_{H^+} = 610$ M^{-1} s^{-1} ($\mu = 1.0$ M) and $k_{H^+} = 300$ M^{-1} s^{-1} ($\mu = 0.10$ M).[5b]

Rates of hydrolysis were also determined in buffer solutions, in formic and acetic acid and biphosphate ion buffers in the case of 2,6,7-trioxabicyclo[2.2.1]heptane and in biphosphate and tris(hydroxymethyl)methylammonium ion (Tris·H^+) buffers for 1-phenyl-2,6,7-trioxabicyclo[2.2.1]heptane. The data (Table S2)[7]

(6) Yokoyama, Y.; Padias, A. B.; De Blauwe, F.; Hall, H. K., Jr. *Macromolecules* **1980**, *13*, 252–261.

(7) Tables S1 and S2 are available as Supplementary Material; see paragraph at the end of this paper.

(8) Bates, R. G. "Determination of pH"; Wiley: New York, 1973; p 49.

showed weak general-acid catalysis by the carboxylic acids and somewhat stronger general-acid catalysis by the biphosphate ion, but catalysis by Tris·H^+ could not be detected. This is the expected pattern;[5e] it can be understood in terms of electrostatic interactions between the charges on these acids and the positive charge being generated on the substrate in the rate-determining transition state.[9]

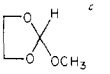
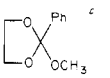
These data were extrapolated to zero buffer concentration by performing linear least-squares analysis on sets of observed first-order rate constants measured at constant buffer ratios. The buffer-independent rates so obtained, which represent uncatalyzed and hydronium ion catalyzed reactions, $k_0 + k_{H^+}[H^+]$, were then used to calculate hydronium ion catalytic coefficients. Hydronium ion concentrations required for this purpose were estimated by using literature pK_a's: 3.75 for HCO_2H,[10] 4.76 for CH_3CO_2H,[11] 7.20 for H_2PO_4,[12] and 8.07 for Tris·H^+[13] and activity coefficients for HCO_2^-, $CH_3CO_2^-$, $H_2PO_4^-$, HPO_4^{--}, and H_3O^+ recommended by Bates[8] plus a value for Tris·H^+ calculated by the Debye–Hückel equation with an ion-size parameter of 6 Å.[14] Linear least-squares analysis of the relationship between these buffer-independent rates and hydronium ion concentrations produced the following results: for 2,6,7-trioxabicyclo[2.2.1]heptane, $k_{H^+} = (3.38 \pm 0.03) \times 10^2$ M^{-1} s^{-1} and $k_0 = (0.52 \pm 1.46) \times 10^{-4}$ s^{-1}, and for 1-phenyl-2,6,7-trioxabicyclo[2.2.1]heptane, $k_{H^+} = (4.12 \pm 0.03) \times 10^3$ M^{-1} s^{-1} and $k_0 = (5.26 \pm 1.57) \times 10^{-5}$ s^{-1}.

Discussion

Reaction Mechanism. Our measurements show that the specific rate of hydrolysis of 1-phenyl-2,6,7-trioxabicyclo[2.2.1]heptane catalyzed by the hydronium ion in buffer solutions at high pH, $k_{H^+} = 4120$ M^{-1} s^{-1}, is decidedly greater than that in dilute HCl solutions of low pH, $k_{H^+} = 107$ M^{-1} s^{-1}. This indicates that the same quantity is not being measured under the two sets of reaction conditions and that a change in rate-determining step has taken place between low and high pH. Detection of a phenyl-substituted dialkoxycarbonium ion intermediate at low pH coupled with the mode of decay of this ion, i.e., adherence to eq 4, shows that the slow step under these conditions is decomposition of a hydrogen ortho ester intermediate, eq 3, and that the preceding reaction of dialkoxycarbonium ion with water, eq 2, is a rapid equilibrium. Base catalysis of hydrogen ortho ester decomposition, however, is very efficient, e.g., $k_{HO^-} = 3 \times 10^{10}$ M^{-1} s^{-1}, and at higher pH this step speeds up and the first reaction of the three-step reaction sequence, generation of the dialkoxycarbonium ion, which is not catalyzed by bases, becomes rate determining. This mechanistic argument is similar to that which we have advanced before, in greater detail but on the basis of similar evidence, in support of a change in rate-determining step in the hydrolysis of certain other ortho esters.[5]

The evidence we have obtained for the hydrolysis of the other substrate, the unsubstituted bicyclic ortho ester 2,6,7-trioxabicyclo[2.2.1]heptane, also points to a change in rate-determining step. The hydronium ion catalytic coefficient measured in buffer solutions here, $k_{H^+} = 338$ M^{-1} s^{-1}, is again greater than that determined at low pH, $k_{H^+} = 159$ M^{-1} s^{-1}. Completely aliphatic dialkoxycarbonium ions have no ultraviolet absorption above 200 nm,[15] and we consequently were unable to detect the carbocationic intermediate in this case as we could for the 1-phenyl derivative, but the induction period that the unsubstituted ortho ester showed during the hydrolysis in HCl solutions clearly indicates a two-phase process. This induction period stems from the circumstance that the hydronium ion catalytic coefficient measured for this substrate at high pH is only twice as great as that measured at low pH; i.e., when H_3O^+ is the only catalytic species present, generation of the dialkoxycarbonium ion intermediate is only twice as fast as hydrogen ortho ester decomposition. With this origin, this induction period should persist over the entire range of HCl concentrations investigated, as it did, and it should also bear a constant relationship to the half-life of the subsequent first-order process, as it also did.[16]

Table I. Rate Constants for the Hydrolysis of Some Ortho Esters in Aqueous Solution at 25 °C

substrate	$k^1_{H^+}$, M^{-1} s^{-1} [a]	$k^3_{H^+}$, M^{-1} s^{-1} [b]
	338	159
	4120	107
 [c]	175	>900
 [c]	5400	300
$HC(OCH_3)_3$ [d]	263	
$PhC(OCH_3)_3$ [d]	70	

[a] Rate constant for dialkoxycarbonium ion formation, eq 1. [b] Rate constant for hydrogen ortho ester decomposition, eq 3. [c] Reference 5b. [d] Reference 16.

These mechanistic assignments allow us to identify the hydronium ion catalytic coefficients measured at high pH as the specific rate constant for step 1, eq 1, of the three-step reaction sequence, $k^1_{H^+}$, and the catalytic coefficient measured at low pH as the rate constant for step 3, eq 3, $k^3_{H^+}$. We can then understand the relatively small size of the difference between high- and low-pH catalytic coefficients for the unsubstituted substrate as compared with the 1-phenyl derivative, i.e., a factor of 2 vs. a factor of 40.

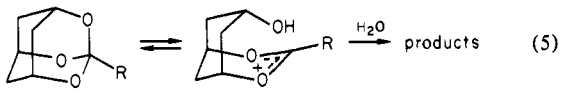
As Table I shows, phenyl substitution at the *pro*-acyl carbon atom in this system has little effect on the rate of step 3, but it accelerates step 1 markedly. This is a consequence of the ability of phenyl to stabilize an adjacent positive charge, such as that produced in step 1, plus the fact that step 3 has open to it a concerted mechanism which avoids positive charge generation. It is this differential effect of substituents on steps 1 and 3 that gives rise to a change in rate-determining step during the hydrolysis of some ortho esters.

Reactivity. This mechanistic analysis has shown that both of the bicyclic ortho esters examined here undergo a change in rate-determining step during their hydrolysis reactions. Nevertheless, this does not alter the conclusion reached from the limited original study of one of these substrates,[4] for the present data also show no markedly unusual reactivity attributable to relief of bicyclic ring strain. This may be seen by examining the $k^1_{H^+}$ values of Table I, which are the rate constants for the reaction step where ring opening converts the bicyclic system into a monocyclic one. For example, the unsubstituted bicyclic ortho ester reacts only twice as fast as its monocyclic counterpart, 338/175 = 1.93, and a similar comparison for the phenyl derivatives shows that here the bicyclic substrate is actually less reactive than its monocyclic analogue, 4120/5400 = 0.76. The same conclusion is reached by comparing the unsubstituted bicyclic ortho ester with an acyclic model such as trimethyl orhtoformate: the rate constants here are again quite similar, 338/263 = 1.29. To be sure, the bicyclic phenyl derivative is some 60 times more reactive than its acyclic counterpart, trimethyl orthobenzoate, 4120/70 = 59, but hy-

(9) Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1973**, *95*, 803–806. Chwang, W. K.; Eliason, R.; Kresge, A. J. *Ibid.* **1977**, *99*, 805–808.
(10) Harned, H. S.; Embree, N. D. *J. Am. Chem. Soc.* **1934**, *56*, 1042–1044.
(11) Harned, H. S.; Ehlers, R. W. *J. Am. Chem. Soc.* **1933**, *55*, 652–656.
(12) Grybowski, A. K. *J. Phys. Chem.* **1958**, *62*, 555–559.
(13) Data, S. P.; Grybowski, A. K.; Weston, B. A. *J. Chem. Soc.* **1963**, 792–796.
(14) Roy, R. N.; Robinson, R. A.; Bates, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 8231–8235.
(15) Ramsey, B. G.; Taft, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 3058–3063.
(16) Hydroxide ion catalysis of hydrogen ortho ester decomposition would upset this relationship, but even with a rate constant as great as $k_{HO^-} = 5 \times 10^{10}$ M^{-1} s^{-1} such catalysis could contribute only 4% to the observed rate at the lowest acidity employed, 0.01 M HCl, and correspondingly less at the higher acid concentrations.

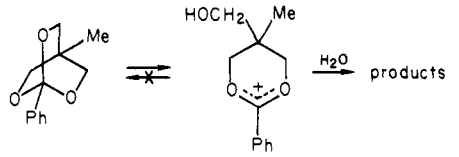
drolysis of the latter substance is subject to a special steric effect that does not operate in the case of cyclic substrates,[17] and this comparison is therefore not a valid indication of unusual bicyclic reactivity. The fact remains, therefore, that even though both of the bicyclic ortho esters examined here undergo a change in rate-determining step during their hydrolysis reactions, neither shows any unusual reactivity.[18]

It is possible that this lack of unusual reactivity is only an apparent effect and that an unusually fast ring opening is in fact occurring but is masked by a very efficient ring reclosure. Such reversibility would reduce the observed value of $k^1_{H^+}$. In the hydrolysis of simple acyclic ortho esters in aqueous solution this step is not reversible because liberated alcohol molecules are much less abundant than solvent water, and they consequently essentially never recapture a dialkoxycarbonium ion intermediate.[19] In cyclic systems, however, where the alcohol product remains bound to the dialkoxycarbonium ion, recapture may be facilitated. Reversibility has in fact been demonstrated in the hydrolysis of several trioxaadamantanes, eq 5, and observed rate constants here are many orders of magnitude below those of acyclic models.[20]



(5)

These adamantyl systems, however, seem to form a special case. Attack of water on the dialkoxycarbonium ion from the same side as the alcohol departs from is blocked by the alcohol moiety, which cannot get away without forcing the ring to which it is attached into an unfavorable boat conformation. Attack by water from the other side is also hindered by the same alcohol group, this time through the unfavorable interaction between it and the group R which such attack would enforce. There is no evidence for reversibility of this step in the hydrolysis of other less rigid cyclic ortho esters, and in one system not too different from the presently studied substrates, eq 6, it has definitely been shown to be absent.[5d]



(6)

If, moreover, ring strain is producing a marked acceleration of ring opening in our system, then that strain would have to be regenerated upon ring closure, and this makes reversibility all the more unlikely. It seems improbable, therefore, that reversibility of the initial ring-opening reaction is responsible for the lack of unusual reactivity in our case.

An early transition state with little carbon–oxygen bond breaking and consequently little ring opening appears to be a more likely cause of the contrasting behavior of these ortho esters and analogous bicyclic acetals (e.g., **1** and **3**), where unusual reactivity attributable to relief of ring strain is readily apparent.[2] Some evidence for this comes from a comparison of substituent effects at the *pro*-acyl carbon atom on acetal and ortho ester hydrolysis. The magnitude of ρ in a Hammett-equation correlation of rates of substituted benzaldehyde diethyl acetals in aqueous solution is −3.3,[21] whereas a similar correlation of rates of hydrolysis of a series of trimethyl orthobenzoates gives $\rho = -1.2$[22] and for a series of 2-phenyl-2-methoxy-1,3-dioxolanes gives $\rho = -1.6$.[23] This shows that less positive charge is generated at the *pro*-acyl carbon atom in the transition state for ortho ester hydrolysis than in that for acetal hydrolysis, and carbon–oxygen bond breaking is consequently less advanced in the ortho ester reaction than in the acetal process.

However, the fact that ortho ester hydrolysis in the presently studied bicyclic system is accelerated, albeit weakly, by phenyl substitution at the *pro*-acyl carbon atom (4120/338 = 12.2) indicates that some carbon–oxygen bond breaking has taken place by the time this transition state is reached. Since this gives no unusual bicyclo reactivity, it seems likely that the 2,6,7-trioxabicyclo[2.2.1]heptane system is not as severely strained as the 2,6- or 2,7-dioxabicyclo[2.2.1]heptane ring systems, **1** and **3**. It is interesting in this connection that 7-oxabicyclo[2.2.1]heptane, (**11**)

11


12

is said to be less strained than the parent hydrocarbon, norbornane, (**12**), by 3–6 kcal mol^{-1}.[24] Since the strain energy of norbornane itself is only 17 kcal mol^{-1},[25] introduction of three oxygens into this molecule might, provided the strain relief is cumulative, result in a relatively strain-free system.

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Supplementary Material Available: Tables S1 and S2 of rate constants (6 pages). Ordering information is given on any current masthead page.

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(18) The small difference between $k^1_{H^+}$ and $k^3_{H^+}$ found here for 2,6,7-trioxabicyclo[2.2.1]heptane makes it likely that the rate measured originally for this substrate (in an aqueous–acetone solvent) was in fact that of step 1.

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