Nature of the Slow Step in the Hydrolysis of Cyclic and Bicyclic Ortho Esters Containing 1,3-Dioxane Rings

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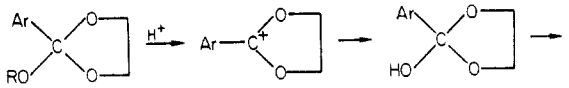
A kinetic investigation is reported of the hydrolysis of a series of ortho esters containing 1,3-dioxane rings. Included are monocyclic 2-aryl-2-methoxy-1,3-dioxanes and bicyclic 1-aryl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octanes. Both types of compounds exhibit a change in the slow step in product formation with changing pH. At high pH the 1,3-dioxan-2-ylium ion forming step is rate determining, while at low pH the slow step involves the decomposition of the hydrogen ortho ester intermediate of the hydrolysis, and both this intermediate and the 1,3-dioxan-2-ylium ion intermediate accumulate in significant amounts during hydrolysis. A similar change in the slow step has previously been observed in the hydrolysis of 2-aryl-2-alkoxy-1,3-dioxolanes. Quantitative comparison of the dioxane and dioxolanes shows that the conversion of an ortho ester (or hydrogen ortho ester) to a cyclic dialkoxycarbonium ion (three sp^3 centers to sp^2 centers) is more favorable for a six-atom ring than for a five-atom ring. This result is opposite that observed for reactions which convert one sp^3 center to an sp^2 center. The initial ring-opening stage in the hydrolysis of the bicyclo ortho esters is shown to be *not* reversible. This is done by generating the 1,3-dioxan-2-ylium ion intermediate from a different source, a 5-(hydroxymethyl)-2-(dimethylamino)-1,3-dioxane, and finding that under the conditions of kinetic control only the dihydroxy ester product is formed. Alternate synthetic routes involving acyclic amide acetals for the preparation of the cyclic and bicyclic ortho esters are described, a major advantage of these reactions being the use of very mild acidic conditions. Also described is the use of nitrosonium tetrafluoroborate as a hydride-transfer agent with a cyclic acetal to form a 1,3-dioxan-2-ylium ion.

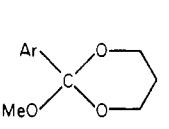
Recent investigations in our laboratories have demonstrated that there is a change in the slow step in the overall hydrolysis of 2-alkoxy-2-aryl-1,3-dioxolanes[1-3] such that under certain conditions all three reaction stages in the overall hydrolysis can be directly observed (eq 1). These



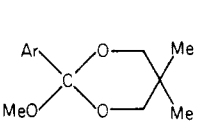
ArCOOR' (1)

studies verify the three-stage mechanism commonly accepted[4] for the hydrolysis of acetals and ortho esters and have, moreover, provided direct kinetic and thermodynamic data pertaining to each stage.

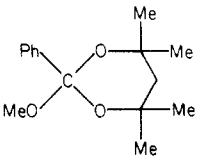
Our experiments demonstrated[2] that the structural requirements necessary for the ortho ester to exhibit the change in the slow step are the presence of both the 2-aryl group and the ring. 1,3-Dioxolane ortho esters with a hydrogen atom or a methyl group at the 2-position have the first stage as rate limiting at all acidities, and this is also true for trimethyl orthobenzoate, which lacks the ring. We felt it of interest to determine if the change in the slow step is a feature of the 1,3-dioxolane ring or can occur with other ring systems. The present study is concerned with a series of ortho esters which contain a 1,3-dioxane ring (1-7).



1, Ar = C_6H_5
2, Ar = 4-$CH_3OC_6H_4$



3, Ar = C_6H_5
4, Ar = 4-$CH_3OC_6H_4$



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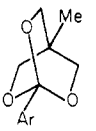

6, Ar = C_6H_5
7, Ar = 4-$CH_3OC_6H_4$

Experimental Section

2-Phenyl-2-methoxy-1,3-dioxane (1) and 2-Phenyl-2-methoxy-5,5-dimethyl-1,3-dioxane (3). Trimethyl orthobenzoate was mixed with an equimolar amount of the appropriate diol in the presence of a trace of *p*-toluenesulfonic acid. The mixture was evacuated to 0.1 mmHg and stirred at room temperature for several hours as methanol was removed. The product was then distilled by increasing the temperature.

Compound **1** was formed in 70% yield and had the following: bp 80 °C (0.3 mmHg); NMR ($CDCl_3$) δ 7.2-7.6 (m, 5 H), 4.6-3.8 (m, 4 H), 3.09 (s, 3 H), 1.5-2.5 (m, 2 H).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.03; H, 7.27. Found: C, 68.4; H, 7.41.

Compound **3** was formed in 85% yield and had the following: bp 85 °C (0.15 mmHg); NMR ($CDCl_3$) δ 7.2-7.6 (m, 5 H), 3.96 (d, 2 H, J = 10 Hz), 3.37 (d, 2 H, J = 10 Hz), 3.06 (s, 3 H), 1.17 (s, 3 H), 0.85 (s, 3 H).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.6; H, 8.40.

2-(4-Methoxyphenyl)-2-methoxy-1,3-dioxane (2) and 2-(4-Methoxyphenyl)-2-methoxy-5,5-dimethyl-1,3-dioxane (4). *N,N*-Dimethyl-4-methoxybenzamide dimethyl acetal[5] was mixed with an equimolar amount of 1,3-propanediol or 2,2-dimethyl-1,3-propanediol and evacuated to 0.1 mmHg at room temperature to remove methanol. This procedure forms a 2-(*N,N*-dimethylamino)-1,3-dioxane by alcohol interchange.[6] The reaction can be conveniently monitored by using NMR spectroscopy by following the disappearance of the signal of the methoxy protons of the starting amide acetal. After the alcohol exchange was complete, dry diethyl ether was added, followed by a solution containing dry acetic acid and dry methanol, in quantities corresponding to a 100-150% excess of the original amide acetal. This solution was stirred for 3-5 min and then shaken with excess

(1) Ahmad, M.; Bergstrom, R. J.; Cashen, M. J.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *J. Am. Chem. Soc.* **1977**, *99*, 4827.
(2) Ahmad, M.; Bergstrom, R. J.; Cashen, M. J.; Chiang, Y.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *J. Am. Chem. Soc.* **1979**, *101*, 2669.
(3) McClelland, R. A.; Ahmad, M.; Bohonek, J.; Gedge, S. *Can. J. Chem.* **1979**, *57*, 1531.
(4) Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264; Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581.
(5) McClelland, R. A. *J. Am. Chem. Soc.* **1978**, *100*, 1844.
(6) McClelland, R. A.; Ahmad, M. *J. Org. Chem.* **1979**, *44*, 1855.

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0.1 M NaOH. The ether layer was dried (K_2CO_3), followed by distillation to yield the desired ortho ester.

Compound **2** was formed in 65% yield (based on starting amide acetal): bp 110 °C (0.2 mmHg); NMR ($CDCl_3$) δ 7.53 (d, 2 H, J = 9 Hz), 6.90 (d, 2 H, J = 9 Hz), 4.6–3.9 (m, 4 H), 3.85 (s, 3 H), 3.09 (s, 3 H), 1.5–2.5 (m, 2 H).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.19. Found: C, 64.04; H, 7.27.

Compound **4** was formed in 70% yield: bp 95 °C (0.05 mmHg); NMR ($CDCl_3$) δ 7.51 (d, 2 H, J = 9 Hz), 6.88 (d, 2 H, J = 9 Hz), 3.94 (d, 2 H, J = 10 Hz), 3.81 (s, 3 H), 3.38 (d, 2 H, J = 10 Hz), 3.09 (s, 3 H), 1.17 (s, 3 H), 0.87 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.5; H, 7.63.

2-Phenyl-2-methoxy-4,4,6,6-tetramethyl-1,3-dioxane (5). 2,4-Dimethyl-2,4-pentanediol, prepared from 4-methyl-4-hydroxy-2-pentanone and methylmagnesium bromide,[7] was condensed with benzaldehyde to give 2-phenyl-4,4,6,6-tetramethyl-1,3-dioxane. This acetal was added to a twofold excess of nitrosonium tetrafluoroborate in liquid sulfur dioxide at −70 °C.[8] The solution was stirred and allowed to come to room temperature over a period of 2 h. Dry ether was added, resulting in the formation of a pale brown solid with an NMR spectrum ($CDCl_3$ solution) corresponding to that expected for 2-phenyl-4,4,6,6-tetramethyl-1,3-dioxan-2-ylium (**8**) fluoroborate: δ 7.5–8.2 (m, 5 H), 2.12 (s, 2 H), δ 1.85 (s, 12 H). This salt was not further purified but was dissolved in anhydrous methylene chloride and added to a stirred solution of sodium methoxide in methanol at 0 °C. A standard workup[2] yielded **5**: 25% yield based on acetal; bp 120 °C (0.5 mmHg); NMR ($CDCl_3$) δ 7.2–7.6 (m, 5 H), 3.01 (s, 3 H), 2.33 (s, 1 H), 2.13 (s, 1 H), 1.77 (s, 6 H), δ 1.63 (s, 6 H).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.55; H, 8.63.

1-Phenyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (6). Trimethyl orthobenzoate was mixed with an equimolar amount of 1,1,1-tris(hydroxymethyl)ethane in the presence of a trace of p-toluenesulfonic acid, and the mixture evacuated to 0.1 mmHg and stirred. The temperature was slowly increased to 100 °C as the contents of the flask turned to a viscous syrup, which then turned crystalline on cooling. The bicyclic ortho ester was purified by sublimation at 120 °C (0.05 mmHg): NMR ($CDCl_3$) δ 7.2–7.7 (m, 5 H), 4.03 (s, 6 H), 0.82 (s, 3 H).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.7; H, 7.22.

5-Methyl-5-(hydroxymethyl)-2-phenyl-2-(dimethylamino)-1,3-dioxane (9). N,N-Dimethylbenzamide dimethyl acetal[5] and an equimolar amount of tris(hydroxymethyl)ethane were evacuated to 0.1 mmHg as methanol was removed, as monitored by NMR spectroscopy by the disappearance in the signal at δ 3.21 due to the O-methyl of the starting amide acetal. The remaining product was used immediately in further experiments. Attempts to purify the sample by distillation or even allowing the sample to stand overnight result in conversion to substantial quantities of bicyclic ortho ester **6**. The NMR spectrum ($CDCl_3$) shows the presence of the expected cis and trans isomers of the 1,3-dioxane, in a ratio of about 60:40, with two signals (singlets) due to the N-methyl protons at δ 2.06 (major) and δ 2.15 (minor) and two signals (singlets) due to the 5-methyl protons at δ 0.69 (minor) and 0.81 (major). The phenyl protons appear as a multiplet at δ 7.3–7.5. The remainder of the signals are in the region δ 3.0–4.0 but are difficult to assign because of substantial overlap.

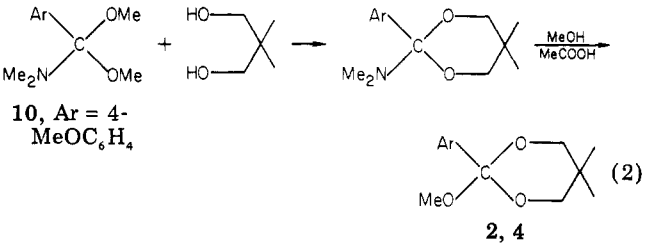
1-(4-Methoxyphenyl)-2,6,7-trioxabicyclo[2.2.2]octane (7). N,N-Dimethyl-4-methoxybenzamide dimethyl acetal[5] was treated with an equimolar amount of tris(hydroxymethyl)ethane as described in the synthesis of **9** above. After complete exchange, as monitored by using NMR spectroscopy, the remaining viscous liquid was dissolved in dry ether and a 150% excess of acetic acid added. After 1 min the solution was washed with excess 0.1 M NaOH. The ether layer was dried (K_2CO_3), and the ether removed. The ortho ester was obtained by sublimation at 110 °C (0.10 mmHg): NMR ($CDCl_3$) δ 7.46 (d, 2 H, J = 9 Hz), 6.79 (d, 2 H, J = 9 Hz), 4.02 (s, 6 H), δ 3.75 (s, 3 H), 0.83 (s, 3 H). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.5; H, 6.76.

Kinetics. Kinetic studies on the ortho esters were carried out as previously described[2] by following the appearance of ester product at λ_{max} = 232 nm (for phenyl ortho esters) or λ_{max} = 254 nm (for methoxyphenyl ortho esters). In certain cases (see below) the 1,3-dioxan-2-ylium ion intermediates could be detected (λ_{max} = 265 nm, phenyl; λ_{max} = 300 nm, methoxyphenyl), and their rates of disappearance were also monitored.

Hydrolysis of Amide Acetal 9. This hydrolysis was established to produce dihydroxy ester at pH 7 in two ways. (a) Amide acetal **9** (0.1 g) was added to a pH 7 phosphate buffer (100 mL), and after 10 s the solution was extracted with ether. The ether was removed on a rotary evaporator. The NMR spectrum of the remaining viscous substance showed peaks due only to the dihydroxy ester and no peaks due to ortho ester **6**. (b) Amide acetal **9** was added to the pH 7 phosphate buffer to give a solution of concentration 10^{-4} M **9**. The UV spectrum was immediately recorded. This spectrum was identical with that of dihydroxy ester (λ_{max} = 232 nm). There is, moreover, no further increase in absorbance at 232 nm. Such an increase would be observed if significant quantities of ortho ester **5** had been produced from the amide acetal. This ortho ester is not indefinitely stable and hydrolyzes to dihydroxy ester with a half-life of 40 min at pH 7.

Results and Discussion

Synthesis. Ortho esters **1**, **3**, and **6** were prepared by acid-catalyzed alcohol interchange by the reaction of trimethyl orthobenzoate with the appropriate diol or triol in the presence of a trace of p-toluenesulfonic acid. Although the same procedure starting with trimethyl 4-methoxyorthobenzoate can probably be used for the synthesis of the ortho esters with the 4-methoxyphenyl substituent, we approached their preparation differently, taking advantage of the availability in our laboratories of the amide acetal **10**.[5] Mixing this amide acetal with the appropriate diol results in alcohol interchange to produce a cyclic amide acetal, the equilibrium being displaced to the side of this latter material by removing methanol by evacuation. These cyclic amide acetals were then treated with acetic acid and methanol, giving excellent yields of the ortho esters **2** and **4** (eq 2). This reaction presumably proceeds



10, Ar = 4-$MeOC_6H_4$

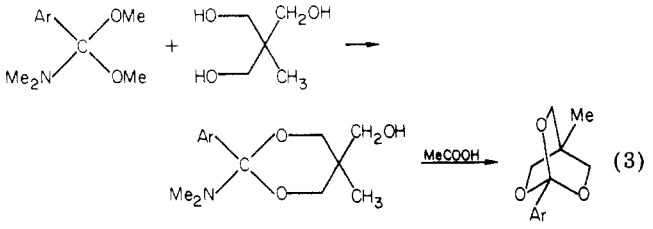
2, 4 (2)

with the acetic acid protonating the dimethylamino group and the neutral amine then departing and being replaced by methanol. The major advantage of this method over the direct ortho ester interchange is its use of considerably milder acid conditions. *No* acid catalyst is required for the actual alcohol interchange. In fact, acid should be avoided in this step since its presence could result in removal of the dimethylamino group.[5] The acetic acid used in the replacement of the amine group is a considerably weaker acid than the strong acids required with the ortho esters. Moreover, the time of exposure to the acetic acid is very short. The substitution is complete virtually within the mixing time, and the acid can almost be immediately neutralized. The amide acetal approach seems to be general, at least for the preparation of cyclic ortho esters. We have now successfully used it for the synthesis of 1,3-dioxolane ortho esters containing various substituents on the 4- and 5-carbons, as well as with different alkoxy groups.[9] Attempts to use this method to produce acyclic

(7) Pihlaja, K.; Ketola, M. *Acta Chem. Scand.* **1969**, *23*, 715.
(8) Olah, G. A.; Salem, G.; Staral, J. S.; Ho, T.-L. *J. Org. Chem.* **1978**, *43*, 173.

ortho esters, however, have not been as successful. For example, the direct reaction of **10** with methanol and acetic acid results in the formation of substantial amounts of *N,N*-dimethyl-4-methoxybenzamide, in addition to the desired ortho ester. This amide product can be accounted for by an acetic acid catalyzed loss of methanol from the amide acetal, producing an imidatonium ion which is demethylated by acetate.[10] With the cyclic amide acetals formation of amide is not a problem. It can be noted that with these compounds the reaction resulting in loss of alcohol is much more readily reversible, since the reverse reaction is intramolecular.

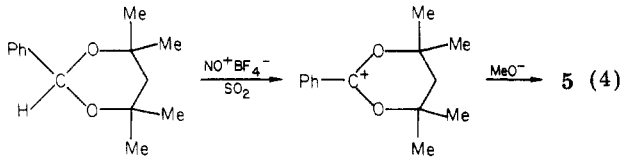
For the preparation of the bicyclic ortho ester **7**, the amide acetal **10** was treated with the appropriate triol, again producing a cyclic amide acetal by alcohol interchange. Addition of acetic acid to this compound results in the immediate formation of bicyclic ortho ester in high yield (eq 3). This synthesis is, of course, closely related



(3)

to that described above, with the difference being that here no external source of alcohol is required. The route via the amide acetal again has the advantage of using much milder acid conditions. It also has the advantage of forming the first ring in a reaction with which there is usually little problem (at least with 1,3-dioxolane and 1,3-dioxane rings). The bicyclic system is then assembled in a second, separate step, and, if required, high dilution conditions can be used to minimize intermolecular reactions and oligomer formation.

The ortho ester **5** was prepared from the 1,3-dioxan-2-ylium ion **8** by treatment with sodium methoxide in methanol (eq 4). The ion was formed by removal of



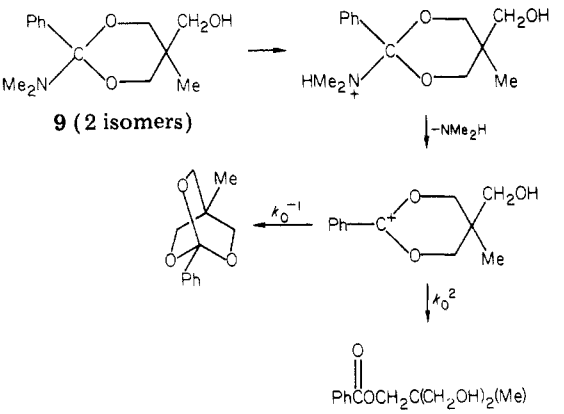
(4)

11 8

hydride ion from acetal **11**. We found that with this acetal hydride transfer to the triphenylcarbenium ion failed,[11] whether the ion was added as its tetrafluoroborate salt or its perchlorate salt and in both acetonitrile and liquid SO_2 solvents. We were successful in obtaining good yields of **8** using nitrosonium tetrafluoroborate in liquid sulfur dioxide. This reagent has recently been reported to be an excellent hydride acceptor for the formation of carbonium ions from substituted alkanes.[8] This appears to be the first example of its use as a hydride acceptor in a reaction with an acetal.

Reversibility of the First Stage in the Hydrolysis of Bicyclic Ortho Esters 6 and 7. Although in principle

Scheme I



the first stage in an ortho ester hydrolysis is reversible, for acyclic systems this can be reasonably ignored. The probability of an external alcohol molecule competing with a solvent water molecule is simply too small. With the bicyclic ortho esters **6** and **7**, however, the first stage must involve ring opening. The reverse reaction therefore is intramolecular and is a practical consideration.[12] The question of its importance cannot be answered unambiguously by simple consideration of the kinetics of hydrolysis.[12] It has been suggested that the first stage is not substantially reversible for bicyclic ortho esters of the general type of **6** and **7**.[13] This was argued on the basis of a comparison of rate constants of the bicyclic ortho esters and model acyclic systems.

Our approach has been to generate the oxocarbonium ion, the product of the first stage, from a different precursor. The amide acetal **9** serves extremely well in this respect. In solutions with pH <10, this amide acetal, like other cyclic amide acetals, loses amine very readily[6] (Scheme I). This reaction at pH 7 has a half-life for loss of amine and formation of product of less than 1 s. The half-life of the bicyclo ortho ester **6** at pH 7 is 40 min. Thus, the 1,3-dioxan-2-ylium ion is generated from the amide acetal under conditions in which the bicyclic ortho ester is stable to hydrolysis, and if this ion were to react more readily with the intramolecular OH group than with a solvent water molecule, the ortho ester would be observed as the product. In fact, the only product is dihydroxy ester, the limit on the amount of ortho ester which would have been detected being about 5%. We conclude that the first stage of the ortho ester hydrolysis is therefore essentially irreversible at pH 7; the oxocarbonium ion, once formed, proceeds on to product.

General Kinetic Observations. First-order rate constants for the hydrolysis of each ortho ester have been obtained over the pH range 1–8 and are listed in Table S1 of the supplementary material. These rates are based in most cases on the formation of product, a hydroxy ester from the monocyclic ortho esters or a dihydroxy ester from the bicyclic ortho esters. In addition, all of the ortho esters generate in the more concentrated acids a transient UV signal corresponding to the intermediate 1,3-dioxan-2-ylium ion, and rate constants for the disappearance of this ion have also been measured.

The kinetic behavior exhibited by the seven ortho esters is qualitatively similar. More importantly, these 1,3-dioxanes exhibit the same pattern of behavior observed with

(9) McClelland, R. A.; Harris, J., to be submitted for publication.
(10) De Wolfe, R. H. "Carboxylic Ortho Acid Derivatives"; Academic Press: New York, 1970; pp 420–506.
(11) (a) On the other hand, the reaction of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane with triphenylcarbonium tetrafluoroborate produces excellent yields of 4,4,5,5-tetramethyl-1,3-dioxolan-2-ylium tetrafluoroborate.[11b] (b) Meerwein, H.; Hederich, V.; Morschel, H.; Wunderlich, K. *Justus Liebigs Ann. Chem.* **1960**, *635*, 1.
(12) Willi, A. V. "Comprehensive Chemical C. Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1977; Vol. 8, pp 49–52.
(13) Bouab, O.; Lematy, G.; Moreau, C. *J. Chem. Soc., Chem. Commun.* **1978**, 678.

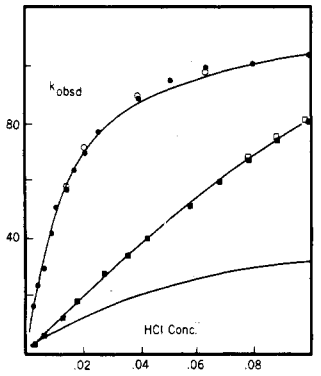


Figure 1. First-order rate constants (s^{-1}, 25 °C, ionic strength 0.1) in the hydrolysis of 2-(4-methoxyphenyl)-2-methoxy-1,3-dioxane (●, ○), 1-(4-methoxypheny)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (■, □), and 2-(4-methoxyphenyl)-2-methoxy-1,3-dioxolane (bottom curve). Closed symbols refer to rate constants obtained by following the appearance of product. Open symbols refer to rate constants obtained by following the disappearance of the 1,3-dioxan-2-ylium ion intermediate.

the 2-aryl-1,3-dioxolanes.[1-3] The important features of this behavior are summarized below.

(a) At high pH (generally phosphate buffers of pH 5–7) first-order rate constants for product formation follow eq 5, showing catalysis by the hydronium ion and the acid component of the buffer.

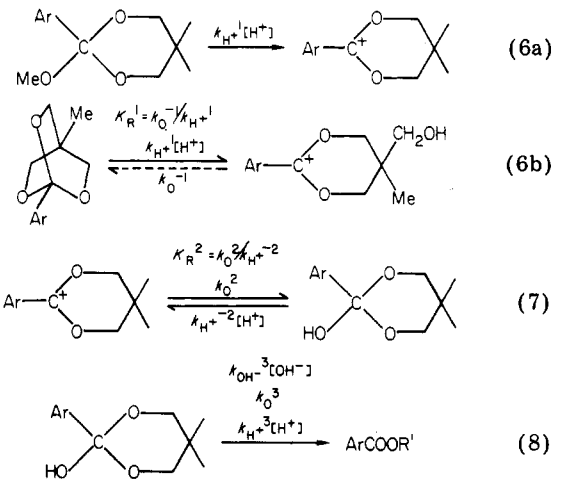
$$k_{obsd} = k_{H^+}{}^1[H^+] + k_{HA}{}^1[HA] \quad (5)$$

(b) At low pH (generally HCl solutions of pH 1–3) the kinetics of product formation are still accurately first order, but the rate constants are significantly smaller than values of $k_{H^+}{}^1[H^+]$ calculated on the basis of the values of $k_{H^+}{}^1$ obtained at high pH. In more dilute HCl solutions the rate constants are linear in H^+ concentration but also show a significant contribution from a pH-independent pathway. In more concentrated HCl solutions, the observed rate constants begin to level off (Figure 1), this leveling off being most serious with the ortho esters which have a 4-methoxyphenyl substituent. Associated with this leveling off, the transient signal of the 1,3-dioxan-2-ylium ion is observed to a significant extent. The rate of disappearance of this signal is equal to the rate of appearance of product.

(c) At some intermediate pH, product formation does not follow accurate first-order kinetics. The absorbance vs. time curves can, however, be fit by the equations describing two consecutive first-order reactions.[2,14]

Mechanism. These observations show that there is a change in the slow step of the hydrolysis of the 1,3-dioxanes 1–7 of the same type as that observed with the 2-aryl-2-alkoxy-1,3-dioxolanes.[1-3] We define rate and equilibrium constants for the specific stages as in eq 6–8. It can be noted that with both the monocyclic and bicyclic ortho esters the second and third stages are similar. The first stage with the bicyclic ortho ester necessarily involves a ring opening. The irreversibility of this stage at pH 7 implies that $k_0{}^{-1} \ll k_0{}^2$ and also means that this system can be analyzed in the same way as the monocyclic 1,3-dioxanes (see later). We write the first stage with the monocyclic system with loss of the exocyclic alkoxy group. Although the experiments necessary to demonstrate this unambiguously were not carried out, this seems reasonable from the analogy with the 2-aryl-1,3-dioxolanes.[2]

The change in the slow step can be explained[2] by a greater magnitude of $k_{H^+}{}^1$ as compared to $k_{H^+}{}^3$. This



necessarily gives rise to a situation where there is a change in the relative magnitudes of the specific rates of the first stage ($k_{H^+}{}^1[H^+]$) and third stage ($k_{H^+}{}^3[H^+] + k_0{}^3 + k_{OH^-}{}^3[OH^-]$) as the acidity is varied. At high pH the term in hydroxide ion dominates in the latter expression, and the third stage is the faster of the two. The rate of product formation is then equal to the rate of the first stage, so that the kinetic parameters obtained at high pH reflect the first stage only and provide values of $k_{H^+}{}^1$. At low pH the hydronium ion term dominates in the rate expression for the third stage, and with a situation where $k_{H^+}{}^1 > k_{H^+}{}^3$, the third stage is slower. Under these conditions, the second stage, for reasons discussed previously,[2] becomes a fast preequilibrium preceeding the slow third stage. Addition of ortho ester to these acidic solutions results in the rapid formation of an equilibrium mixture of oxocarbonium ion and hydrogen ortho ester. This is followed by the slower conversion of this equilbrating mixture to product, and what is observed kinetically is this latter process. Observed rate constants for product formation, which are necessarily equal to the rate constants for the disappearance of oxocarbonium ion present after equilibration,[15] are given by eq 9. These rate constants are equal to $k_0{}^3 + k_{H^+}{}^3[H^+]$

$$k_{obsd} = \frac{k_{H^+}{}^3[H^+] + k_0{}^3}{1 + [H^+]/K_R{}^2} \quad (9)$$

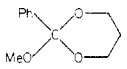
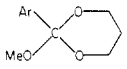
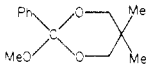
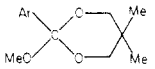
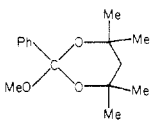
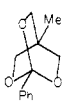
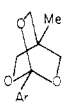
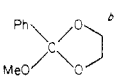
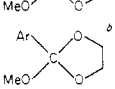
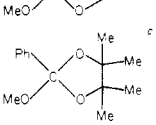
when $[H^+] \ll K_R{}^2$, that is, when the equilibrium of stage two lies to the hydrogen ortho ester side. When $[H^+] \approx K_R{}^2$, or, in other words, a significant amount of the ion is present in this equilibrium, the rate constants begin to level off.

The detailed arguments showing how the basic observations lead to these conclusions have been presented previously.[2] For our purposes here we need only refer to the following major points of the analysis. (a) The fact that observed rate constants in acid solutions are significantly smaller than the values expected from measurements in neutral solutions points to a "break" in behavior and a change in the slow step. (b) The accumulation of significant amounts of the intermediate ion in the acid solution and the observation that the rates of disappearance of this ion and the rates of appearance of product are identical show that the latter rate is not equal to the rate of formation of ion. (c) There is a change-over region where product formation is not a first process, corresponding to acidities where the rates of the first and third

(14) Frost, A. A.; Pearson, R. G. In "Kinetics and Mechanism", 2nd ed.; Wiley: New York, 1961; p 167.

(15) There is also a disappearance of oxocarbonium ion associated with the setting up of the equilibrium between the ion and the ortho ester,[2] but in none of the ortho esters of this study could this be observed.

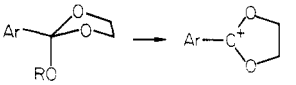
Table I. Rate and Equilibrium Constants in the Hydrolysis of Ortho Esters (25 °C, Ionic Strength = 0.1, Maintained with NaCl)

ortho ester[a]	$k_{H^+}{}^1$, M^{-1} s^{-1}	$pK_R{}^2$	$k_{H^+}{}^3$, M^{-1} s^{-1}	$k_{H_2O}{}^3$, s^{-1}
	3.0×10^4	0.3[d]	3.0×10^3	1.0
	1.2×10^5	1.8	7.6×10^3	1.0
	1.7×10^4	−0.4[e]	1.1×10^3	1.3
	6.6×10^4	1.1	2.8×10^3	1.1
	1.1×10^6	3.7	3.4×10^3	0.16
	2.9×10^3		4.5×10^2	0.7
	7.1×10^3	0.5	1.1×10^3	0.7
	5.4×10^3	−0.6[e]	3.0×10^2	1.5
	1.9×10^4	1.1	7.5×10^2	1.4
	3.1×10^4	1.4	1.3 × 10	0.074

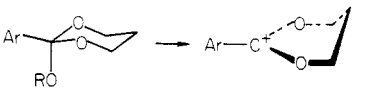
[a] Ar ≡ 4-methoxyphenyl. [b] Reference 2. [c] Reference 3. [d] $pK_R{}^2 = 1.0$, at ionic strength = 1 ($NaClO_4$). [e] Based on $pK_R{}^2$ values obtained at an ionic strength of 1.0 and using the relationship[2] $pK_R{}^2$ ($\mu = 0.1$) = $pK_R{}^2$ ($\mu = 1$) − 0.7.

stages are crossing and are nearly identical.

Values of $k_{H^+}{}^1$, $K_R{}^2$, $k_0{}^3$, and $k_{H^+}{}^3$ obtained with the ortho esters of this study are presented in Table I, along with the values of the same constants obtained with analogous 1,3-dioxolanes. In general, the constants obtained with the two ring systems are similar, and it is difficult to explain all of the small differences without detailed knowledge of the structure and geometry of the various molecules, ions, and transition states. One general observation related to ring-size effects can, however, be made. A comparison of $k_{H^+}{}^1$ values shows that the conversion of ortho ester to oxocarbonium ion is more favorable with the six-atom ring than with the five-atom ring. This is also true for the conversion of hydrogen ortho ester to oxocarbonium ion, as revealed by the $pK_R{}^2$ values. This latter observation, being based on equilibrium constants, also shows that the ring effect is determined by the relative stabilities of the hydrogen ortho ester or ortho ester and the oxocarbonium ion. The effect of ring size at first glance seems unusual since it is generally expected that reactions which convert an sp^3 center to an sp^2 center will be more favored for the five-atom ring[16] (eq 10 and 11). However, the reactions being considered here involve a conversion of three sp^3 centers to sp^2 centers, while in the previous comparisons[16] only one center is so changed. It was argued previously



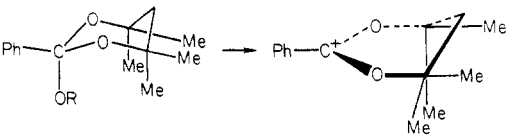
(10)



(11)

that for rings which contain only sp^3 hybridized atoms, incorporation into a five-atom ring results in more strain and steric compression than the incorporation into a six-atom ring. On the other hand, cyclic molecules which contain one sp^2 center were argued to show a reverse effect, with the five-atom ring being relatively more stable. Thus, a reaction which converts one center from sp^3 hybridization to sp^2 hybridization is considerably more favored in the five-atom ring. In our system, it is probably fair to say that for the rings with only sp^3-hybridized atoms, the ortho ester and the hydrogen ortho ester, similar effects are in operation; the five atom ring is relatively less stable. Now, however, the process of converting three centers of sp^2 hybridization must result in an increase in the relative energy difference. In other words, the energy difference between a 1,3-dioxolan-2-ylium ion and a 1,3-dioxan-2-ylium ion is greater than the energy difference between a 1,3-dioxolane and a 1,3-dioxane, with the five-atom system being of higher energy in each case. Although it is difficult to quantitatively explain the increased energy difference, it can be seen why the five-atom oxocarbonium is less stable. The 1,3-dioxolan-2-ylium ion is probably planar or very nearly planar, resulting in eclipsing of the atoms or groups on the sp^3 carbon atoms and resulting also in ring strain, as the three sp^2 centers are forced to adopt ring bond angles considerably less than 120° in order to be accommodated in the ring. The 1,3-dioxan-2-ylium ion can, however, assume a nonplanar conformation, while maintaining planarity in the dialkoxycarbonium ion portion. This reduces the eclipsing interactions at the sp^3 carbon atoms and also permits more normal bond angles in the ring.

One system which deserves specific comment involves the ortho ester with the 4,4,6,6-tetramethyldioxane ring. For this compound very large $k_{H^+}{}^1$ and $pK_R{}^2$ values are found, indicating a strong tendency for the ortho ester and hydrogen ortho ester to be converted to the 1,3-dioxan-2-ylium ion. In this system there are present severe 1,3-diaxial interactions in the neutral species (if these even exist in chair forms). These interactions can be significantly lessened in the more planar ion (eq 12).



(12)

It is, of course, interesting that the bicyclic ortho esters exhibit the same change in slow step. We should like to point out that this behavior will be seen regardless of the extent of the reversibility of the first stage. Treatment of the bicyclic system with the inclusion of the reverse of the first stage results in eq 13 and 14. Equation 13 refers to

$$k_{obsd} = \frac{k_{H^+}{}^1 k_0{}^2}{k_0{}^2 + k_0{}^{-1}}[H^+] \quad (13)$$

high pH and is based on a stationary-state assumption in the 1,3-dioxan-2-ylium ion. At high pH the rate of product formation should be equal to the rate of formation of hydrogen ortho ester, because of the efficient hydroxide ion catalysis of the conversion of this species to product.

(16) Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221.

$$k_{obsd} = \frac{k_{H^+}{}^3\left(\frac{K_R{}^2}{K_R{}^2 + K_R{}^1}\right)[H^+] + k_0{}^3\left(\frac{K_R{}^2}{K_R{}^2 + K_R{}^1}\right)}{1 + \frac{[H^+]}{K_R{}^2\left(\frac{K_R{}^2}{K_R{}^2 + K_R{}^1}\right)}} \quad (14)$$

Equation 14 refers to low pH and is based on the assumption that the third stage is the slow stage in product formation, and both the first stage and the second stage are reversible equilibria preceding it. These two equations reduce to the equations previously discussed, $k_{obsd} = k_{H^+}{}^1[H^+]$ and eq 4, when $k_0{}^2 \gg k_0{}^{-1}$.[17] In their present form, however, eq 5 and 6 also satisfy the observed kinetic data, the only requirement for their derivation being that $k_{H^+}{}^1 > k_{H^+}{}^3$ (and $k_{H^+}{}^{-2} > k_{H^+}{}^3$).

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Registry No. 1, 76109-82-5; 2, 76109-83-6; 3, 72320-30-0; 4, 76109-84-7; 5, 76109-85-8; 6, 70637-00-2; 7, 76109-86-9; 8 tetrafluoroborate, 76109-88-1; *cis*-9, 76109-89-2; *trans*-9, 76109-90-5; 10, 66475-66-9; 11, 62977-15-5; trimethyl orthobenzoate, 707-07-3; 1,3-propanediol, 504-63-2; 2,2-dimethyl-1,3-propanediol, 126-30-7; 2,4-dimethyl-2,4-pentanediol, 24892-49-7; benzaldehyde, 100-52-7; 1,1,1-tris(hydroxymethyl)ethane, 77-85-0; *N,N*-dimethylbenzamide dimethyl acetal, 35452-04-1.

Supplementary Material Available: Table S1 of rate constants (4 pages). Ordering information is given on any current masthead page.

(17) For reduction of eq 14 to eq 9 the condition actually is $K_R{}^2 \gg K_R{}^1$ or $k_0{}^2/k^{-2}{}_{H^+} \gg k_0{}^{-1}/k^1{}_{H^+}$. Unless there is something highly unusual in $k_{H^+}{}^{-2}$ or $k_{H^+}{}^1$, this condition is met whenever $k_0{}^2 \gg k_0{}^{-1}$.

Analysis of the Acidities of 3- and 4-Substituted Pyridinium and Anilinium Ions[1]

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An analysis has been carried out of the gas- and aqueous-phase acidities of meta- and para-substituted pyridinium and anilinium ions by using substituent parameter treatments and ab initio molecular orbital theory calculations at the STO-3G level of approximation. The following conclusions are indicated. (1) Field/inductive effects (F) of strongly electron-attracting dipolar substituents are the major factor in the strongly enhanced acidities. Thus, for example, resonance stabilization of *p*-nitroaniline is only a relatively minor contributor to the greatly increased gas-phase acidity of *p*-nitroanilinium compared to anilinium ion. (2) Resonance effects of +R substituents in general are small or negligible for pyridinium ion acidities in aqueous solution and are small and perhaps reversed in the gas phase. (3) Strong π-donor (–R) substituents do contribute large acid-weakening resonance effects particularly to pyridinium ion acidities. (4) In the gas phase, there is a leveling in the π-donor effects of the strongest –R substituents, e.g., $N(CH_3)_2$. (5) The ratio of R effects at the meta relative to the corresponding para position (i.e., $\alpha = R^m/R^p$) are substantially greater in the gas phase than in aqueous solution. (6) F effects correlate well with the σ_I substituent parameters. (7) Hydrogen bond acceptor substituents, e.g., $N(CH_3)_2$ or CH_3CO, are found to have more positive σ_I values in aqueous solution than in the gas phase. (8) The acidities of para-substituted anilinium ions are found to be unsuitable for the definition of inherent σ_p^- or σ_R^- parameters. (9) Polarizability effects of meta and para substituents containing electronegative atoms and no large alkyl or aryl groups are found to be small or negligible in the gas-phase acidities.

There is currently substantial interest and controversy in the interpretation of the effects of 3- and 4-substituents on the acidities of pyridinium ions.[5] We report in this paper an analysis based upon theoretical and experimental data for the effects of 3- and 4-substituents on the acidities of both pyridinium ions and another common NH^+ system, anilinium ions. Ab initio molecular orbital theory calculations at the STO-3G level of approximation and gas-phase ion cyclotron resonance spectroscopic data are utilized. Through critical analysis of suitable comparisons of theoretical results with experimental results in both the gas phase and in aqueous solution, new evidence and insights are provided.

Both the anilinium ion and pyridinium acidities in aqueous solution have been previously considered in terms of the Hammett equation.[6] For select 3-substituents, the $\sigma_m\rho$ relationship is found to hold with relatively high precision. However, for 4-substituents the two series have come to be regarded as of opposite types in their resonance effects. Para-substituted anilinium ion acidities were used

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(2) La Trobe University.

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(4) (a) Australian National University. (b) University of California.

(5) (a) J. M. Essery and K. Schofield, *J. Chem. Soc.*, 2225 (1963); (b) A. Fischer, W. J. Galloway, and J. Vaughan, *ibid.*, 3591, 3596 (1964); (c) G. B. Ellam and C. D. Johnson, *J. Org. Chem.*, **36**, 2284 (1971); (d) R. T. C. Brownlee and R. D. Topson, *Tetrahedron Lett.*, 5187 (1972); (e) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973); (f) C. A. Grob and R. W. Taft, *J. Am. Chem. Soc.*, **96**, 1236 (1974); (g) C. D. Johnson, I. Roberts, and P. G. Taylor, *J. Chem. Soc., Chem. Commun.*, 897 (1977); (h) E. M. Arnett, B. Chawla, L. Bell, M. Taagepera, W. J. Hehre, and R. W. Taft, *J. Am. Chem. Soc.*, **99**, 5729 (1977); (i) M. Charton, *J. Org. Chem.*, **44**, 2097 (1979); (j) D. H. Aue and M. T. Bowers in "Gas-phase Ion Chemistry", M. T. Bowers, Ed., Academic Press, New York, 1979; (k) W. R. Davidson, J. Sunner, and P. Kebarle, *J. Am. Chem. Soc.*, **101**, 1675 (1979); (l) M. Sawada, M. Ichigara, Y. Yukawa, T. Nakachi, and Y. Tsuno, *Bull. Chem. Soc. Jpn.*, **53**, 2055 (1980).

(6) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

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