17-2; **14**, 69611-18-3; **15**, 69611-19-4; **15** sodium salt, 69622-57-7; **16**, 69611-20-7; **17**, 69611-21-8; **17** free acid potassium salt, 69611-29-6; **17** free acid, 69611-28-5; **18**, 69651-43-0; 5-methoxy-8-dimethyl-3,4-dihydronaphthalene, 69611-27-4; 5-methoxy-8-methyl-1-methylene-1,2,3,4-tetrahydronaphthalene, 69611-26-3; 5-acetoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene, 69611-22-9; 6-bromo-5-methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalone, 69611-25-2; ethyl 2[2-(1-methoxy-4,5-dimethyl-5,6,7,8-tetrahydronaphthaleneoxy)]-3-oxobutanoate, 69611-24-1; *p*-cresol, 106-44-5; ethyl 2-chloroacetoacetate, 609-15-4; δ-valerolactone, 108-29-2.

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Amide Acetal Hydrolysis. 2-Aryl-2-(*N*,*N*-dimethylamino)-1,3-dioxolanes. Rapid and Reversible Ring Opening in Neutral and Basic Solutions. Rate-Determining Decomposition of Hydrogen Ortho Esters in Acidic Solutions

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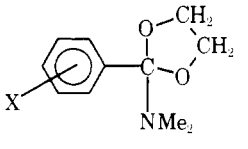
A kinetic and mechanistic investigation of the title amide acetals is reported. At pH >7.5, ring opening to an imidatonium ion (III) is rapid and reversible. Subsequent products are formed at pH >10 by hydroxide attack on III and at pH 7–10 by loss of amine from N-protonated amide acetal. The ion III can be trapped in more acidic solutions (pH <6.5) and its further hydrolysis followed. This proceeds via ring closure reforming amide acetal, which then rapidly decomposes via 1,3-dioxolenium ion. With amide acetal at pH <6.5 hydrolysis proceeds via 1,3-dioxolenium ion, the process leading to this ion now being more rapid than ring opening. At pH >6.0 the formation of the 1,3-dioxolenium ion is the slow step in the overall reaction, but at pH <5.5 there is a changeover, and the rate-limiting step in the overall hydrolysis is the decomposition of the hydrogen ortho ester which results on hydration of the ion.

Recently, we reported[1] a mechanistic investigation of the decomposition in aqueous solutions of the amide acetals Ar-$C(OMe)_2NMe_2$. A scheme was proposed whereby N-protonated amide acetal can lose amine (C–N cleavage), giving rise to a dialkoxycarbonium ion, or the neutral amide acetal can lose alcohol (C–O cleavage), generating an imidatonium ion.

In this paper we report a study of the amide acetals I, molecules which despite their obvious similarity to the substrates of the previous study show a significantly different pattern of behavior.



Ia, X = 4-MeO
b, X = 4-Me
c, X = H
d, X = 4-Cl
e, X = 3-Cl

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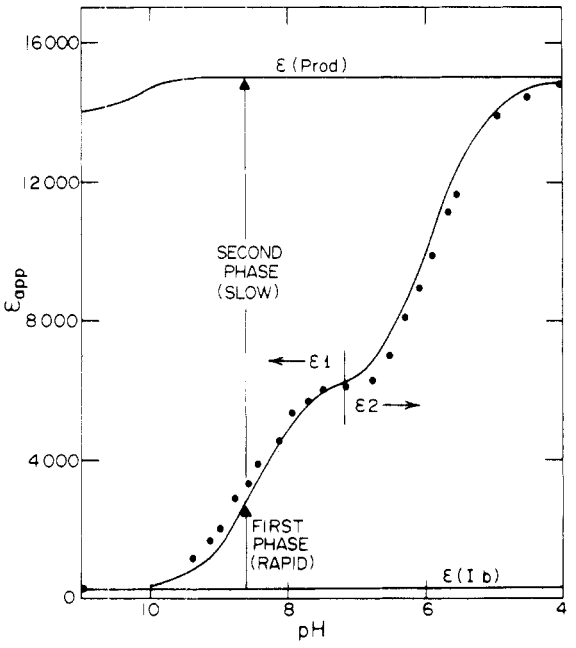


Figure 1. Absorbance change at 240 nm, expressed as an apparent extinction coefficient (absorbance/concentration). The line ϵIb is the extinction coefficient of the amide acetal Ib. The curve ϵ(Prod) represents the absorbance of the ester + amide products. The points are experimental values; the curves are calculated from equations presented in the Discussion using the constants of Table I.

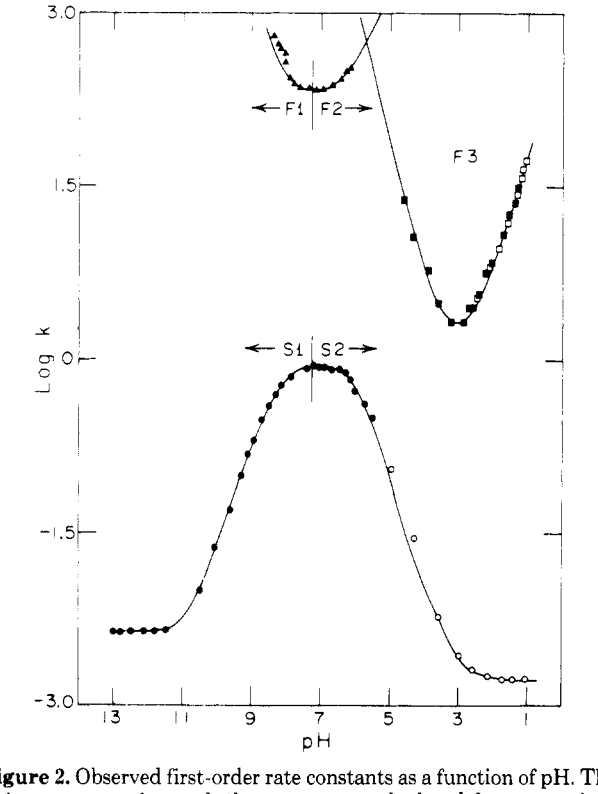


Figure 2. Observed first-order rate constants as a function of pH. The points are experimental; the curves are calculated from equations presented in the Discussion using the constants of Table I. See text for explanation of symbols.

Results

The results, and subsequent analysis, will be presented in terms of the 4-methyl compound (Ib), which was investigated in the most detail. The qualitative behavior of the other four amide acetals is identical, although there are obviously quantitative differences.

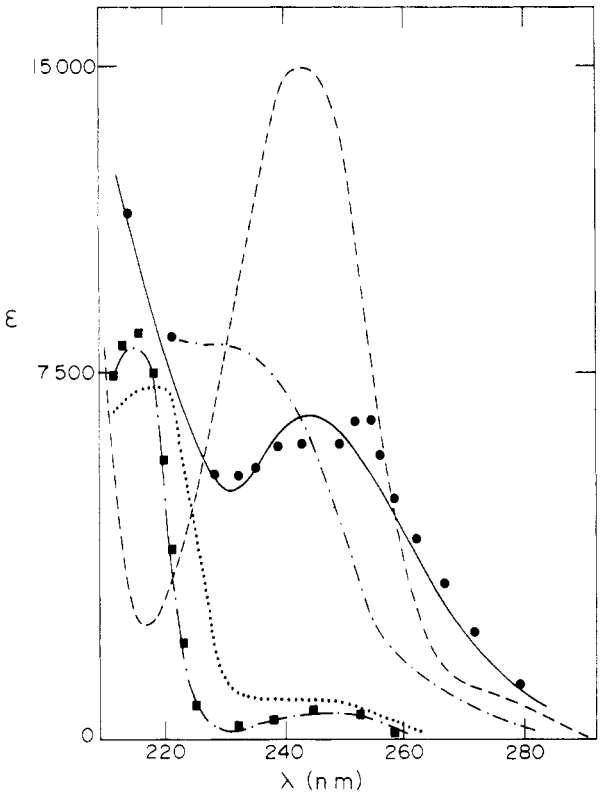
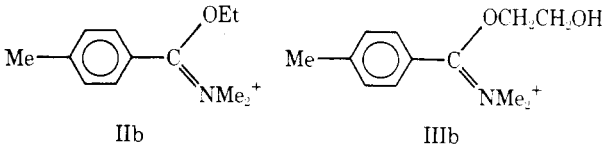


Figure 3. Ultraviolet spectra: (·····) 2-(4′-methylphenyl)-2-(*N*,*N*-dimethylamino)-1,3-dioxolane; (-·-) 2-(4′-methylphenyl)-2-methoxy-1,3-dioxolane; (- -) *O*-ethyl-*N*,*N*,4-trimethylbenzimidatonium fluoroborate; (·····) *N*,*N*,4-trimethylbenzamide; (- · -) β-hydroxyethyl 4-methylbenzoate; (■) spectrum observed immediately after addition (2 ms) of amide acetal to 0.001 N HCl; (●) spectrum observed after completion of initial rapid phase (40 ms) on addition of amide acetal to phosphate buffer (pH 7.2).

Products. At pH <9.5, β-hydroxyethyl 4-methylbenzoate is the only product. In more basic solutions this is accompanied by a small amount of amide (*N*,*N*,4-trimethylbenzamide). The ratio of ester/amide in 0.005 N NaOH is 90:10.

Kinetics; pH >6.5. In this pH region, two consecutive first-order spectral changes are observed, with the actual change occurring in each kinetic phase varying as a function of pH. The UV change as a function of pH at 240 nm is depicted in Figure 1. The first kinetic phase is very rapid (rate constants ▲ in Figure 2), with a spectral change corresponding to conversion of the starting amide acetal to some intermediate. The second phase is much slower (Figure 2, ●), with a spectral change corresponding to conversion of the intermediate to the ultimate products.

Full spectra related to this system are given in Figure 3. Figures 1 and 2 reveal a tendency for plateau regions at pH 7–7.5. There is reason to believe (Discussion) that this corresponds to a situation where the intermediate spectrum corresponds to one species, with only a few percent of other material. This spectrum, constructed at pH 7.2 (Figure 3, ●), bears a strong resemblance to that of the imidatonium ion IIb. We propose that the intermediate spectrum at pH 7–7.5 is that of the ring-opened imidatonium ion IIIb.



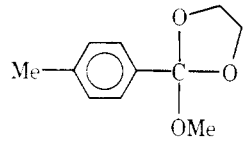
IIb IIIb

Outside of this pH region the intermediate spectra are adequately described as a mixture of that of IIIb plus some other

species, at pH >7.5, this other species being the amide acetal, and at pH <7.0, the ester product.

pH <6.0; Trapped Imidatonium Ion. At pH <7.0 the initial kinetic phase therefore corresponds to conversion of the amide acetal to a mixture of imidatonium ion IIIb and ester product, and the subsequent phase corresponds to conversion of the ion to the same ester. Figure 1 shows that as the pH is decreased the initial phase results in a greater amount of ester and a correspondingly smaller amount of imidatonium ion, and by about a pH of 4 little or none of the ion is even formed. This obviously places a limit on the pH region where the conversion of ion to ester can be followed on direct addition of amide acetal. It is possible, however, to form the ion at pH 7.5 and immediately trap it into more acidic solutions. Rate constants obtained in this way are represented in Figure 2 by the symbols ○.

pH <5.0; Amide Acetal Precursor. As indicated in the last section, there is only one apparent kinetic phase in this pH region resulting in ester product. Rate constants for this change are depicted in Figure 2 by the symbols ■. The ortho ester IVb hydrolyzes to produce the same ester product, and



IVb

in the region pH <3 the first-order rate constants obtained for its hydrolysis,[2,3] following the appearance of this product (Figure 2, □), are identical with those obtained with the amide acetal. With the amide acetal at very low pH, a transient UV signal corresponding to the 2-(4′-methylphenyl)-1,3-dioxolenium ion can also be detected during hydrolysis. The characteristics of this detection will not be discussed in this paper; a similar observation is made with the ortho ester IVb under the same conditions and this aspect is considered in detail in a separate paper.[2,3]

Close examination also reveals that the spectral change which is being observed in this pH region is not simply that of amide acetal → ester. The initial spectrum, obtained immediately after mixing in the stopped-flow spectrophotometer, is in fact slightly different from that of the amide acetal (Figure 3, ■). This spectrum has a close resemblance to that of the ortho ester IVb. Our proposal will be that this spectrum corresponds to a hydrogen ortho ester intermediate, and that what follows kinetically is the conversion of this species to ester. There obviously must be steps connected with the conversion of amide acetal to the hydrogen ortho ester intermediate, but the implication is that these occur within the dead time (2 ms) of the stopped-flow apparatus and are not observed (except in those solutions where the signal of the 1,3-dioxolenium ion is detected).

Imidatonium Ion Hydrolysis. The hydrolysis of the imidatonium ion IIb has also been studied for comparison purposes. The results are fully consistent with those obtained for other imidatonium ions.[4] In acid solutions, ethyl 4-methylbenzoate is formed with no detectable *N,N*,4-trimethylbenzamide. In base solutions (0.005 N NaOH), the ester/amide ratio is 95:5. First-order rate constants for the hydrolysis follow:

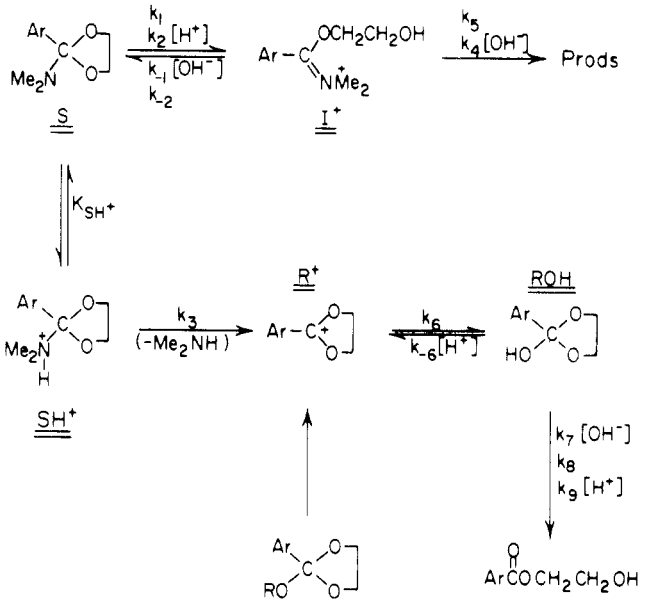
$$k_{obsd} = k_4[OH^-] + k_5 \quad (1)$$

with $k_4 = 1.5 \times 10^3\ M^{-1}\ s^{-1}$ and $k_5 = 4.4 \times 10^{-5}\ s^{-1}$.

Discussion

We will define reaction stages and associated rate constants and equilibrium constants as those in Scheme I. The processes

Scheme I



described by the constants k_1, k_2, k_3, and K_{SH^+} are identical with those of the acyclic amide acetals.[1] With the cyclic compounds, the alcohol leaving group remains part of the same molecule when C–O cleavage occurs, raising the possibility of reversibility of this stage because of its intramolecular nature. The k_4 and k_5 processes refer to the further hydrolysis of the imidatonium ion.[4] The k_6 through k_9 processes refer to the hydration of the 1,3-dioxolenium ion and the decomposition of the hydrogen ortho ester product of this hydration. These reaction stages are common to the amide acetal and a 1,3-dioxolane ortho ester and are discussed in detail elsewhere[2,3] in the context of the ortho ester hydrolysis. Our purpose here is to show that these pathways can also be observed with the amide acetals.

pH >7. In these solutions we propose that amide acetal and imidatonium ion interconvert via the k_1,k_{-1} pathway, with this interconversion being rapid compared to further reaction stages resulting in ester and amide product (k_3, k_4, k_5). We additionally require that N-protonated amide acetal not be present in significant amounts. This is probably true; the pK_{SH^+} values for ammonium ions of this type have been estimated to be of the order of 5–6.[1] In terms of this proposal, the initial kinetic phase corresponds to the rapid equilibration of the amide acetal and imidatonium ion, and the absorbance change which occurs here corresponds to the conversion of the former to the equilibrium mixture. The absorbance on completion of the equilibration ($\epsilon 1$, Figure 1) takes the form of a titration curve,

$$\epsilon 1 = \frac{K_{I^+}}{[H^+] + K_{I^+}}\epsilon_S + \frac{[H^+]}{[H^+] + K_{I^+}}\epsilon_{I^+} \quad (2)$$

where K_{I^+} is defined in the form of an acidity constant as $[S][H^+]/[I^+]$ and is given by

$$K_{I^+} = \frac{k_{-1}K_w}{k_1} = \frac{k_{-2}}{k_2} \quad (3)$$

The first-order rate constants for this phase (F1 of Figure 2) refer to equilibration of S and I^+ and are given by

$$k_{obsd}(F1) = k_1 + k_{-1}[OH^-] \quad (4)$$

The rate constants for the second phase refer to product formation, from an equilibrium mixture of S and I^+, and are given by eq 5, making the assumption that both this equilibrium and the simple protonic equilibrium are rapid on the time scale of product formation.

Table I. Rate and Equilibrium Constants in the Hydrolysis of 2-Aryl-2-(*N*,*N*-dimethylamino)-1,3-dioxolanes[a]

aryl	registry no.	10^2k_1, s^{-1}	10^5k_2, $M^{-1}\,s^{-1}$	10^8k_{-1}, $M^{-1}\,s^{-1}$	$10^{-3}k_{-2}$, s^{-1}	pK_{I^+}	$10^8k_3/K_{SH^+}$, $M^{-1}\,s^{-1}$	10^3k_4, $M^{-1}\,s^{-1}$
4-methoxyphenyl	69440-29-5	2.4	4.0	0.76	1.3	8.5	10.5	1.2
4-methylphenyl	69440-30-8	1.9	3.9	0.82	1.7	8.3	2.1	1.8
phenyl	59700-73-1	1.4	3.1	1.19	2.7	8.1	0.35	3.1
4-chlorophenyl	69440-31-9	0.92	1.4	4.4	6.9	7.3	0.059	9.6
3-chlorophenyl	69440-32-0	0.60	1.0	5.7	9.6	7.0	0.011	13
ρ value		−0.9	−1.0	1.5	1.4	−2.4	−4.3	1.6

[a] At 25 °C, μ = 0.1.

$$k_{obsd}(S1) = \frac{((k_3K_{I^+}/K_{SH^+}) + k_5)[H^+] + k_4K_w}{[H^+] + K_{I^+}} \quad (5)$$

The tendency for plateau regions in Figures 1 and 2 at pH 7–7.5 implies that in this region imidatonium ion is the predominant species in equilibrium with amide acetal ($[H^+] > K_{I^+}$). The proposal that the k_1 pathway, and not k_2, is the important route for establishing this equilibrium, and further that this equilibration is rapid compared with the reaction which forms ester product via k_3, requires that

$$k_1 > (k_2 + (k_3/K_{SH^+}))[H^+] \quad (6)$$

This behavior is very similar to that of the acyclic amide acetals, whose results are also interpreted in terms of the dominance of the k_1 pathway in solutions as acidic as pH 7.[1]

pH 5.5–7.0; Fast Phase. However, at some acidity the relationship of eq 6 will start breaking down, and the pathways involving the $[H^+]$ term will become competitive (and eventually dominate).

In these more acidic solutions the amide acetal can undergo two initial reactions, C–O cleavage via the k_1 or k_2 pathway or C–N cleavage via the k_3 pathway. The rate constants now take the form

$$k_{obsd}(F2) = \frac{k_1 + ((k_3/K_{SH^+}) + k_2)[H^+]}{1 + ([H^+]/K_{SH^+})} \quad (7)$$

This equation accounts for the increase in the rate constants seen in the section F2 of Figure 2, with the provision that the amide acetal is not substantially N-protonated ($[H^+] < K_{SH^+}$). It is predicted that these rate constants should level off when protonation does occur. This leveling off cannot be observed, however, because of a change in rate-determining step (see later). The implication is that the value of pK_{SH^+} must be less than 6.

The fast process observed at pH <7 therefore corresponds to conversion of amide acetal to a mixture of imidatonium ion and ester. The following equation can be derived for the apparent extinction coefficient after completion of this phase ($\epsilon 2$ of Figure 1).

$$\epsilon 2 = \frac{(k_1 + k_2[H^+])\epsilon_{I^+} + (k_3/K_{SH^+})[H^+]\epsilon_{ester}}{k_1 + (k_2 + (k_3/K_{SH^+}))[H^+]} \quad (8)$$

At pH 7 the k_1 process (noncatalyzed C–O cleavage) dominates so that $\epsilon 2 \approx \epsilon_{I^+}$. At lower pH there is a transition as the terms in hydronium ion become important, and in the limit a new plateau is reached where

$$\epsilon 2\ (acid) = \frac{k_2\epsilon_{I^+} + (k_3/K_{SH^+})\epsilon_{ester}}{(k_2 + (k_3/K_{SH^+}))} \quad (9)$$

The fact that $\epsilon 2$ levels off at the value of ϵ_{ester} implies that $k_3/K_{SH^+} > k_2$, that is, that the amide acetal undergoes predominant C–N cleavage in acid solutions.

pH <7.0; Slow Phase. The slow kinetic phase at pH 7.0–5.5, as well as the kinetic behavior at lower pH of the trapped imidatonium ion, refer to decomposition of this ion. This can occur by direct reaction with a water molecule (k_5) or by ring closure to amide acetal and decomposition of that species via the dioxolenium ion (C–N cleavage). Assuming that the equilibration of S and SH^+ is rapid and making the steady-state assumption in these species produces

$$k_{obsd}(S2) = k_5 + \frac{(k_{-2}k_2/k_1K_{SH^+})[H^+] + (k_{-1}K_w/k_1)(k_3/K_{SH^+})}{\left(\frac{k_2 + k_3/K_{SH^+}}{k_1}\right)[H^+] + 1} \quad (10)$$

Kinetic Analysis. Table I lists values of the various constants of Scheme I which best fit the experimental data. The consistency of our analysis[5] can be seen in Figures 1 and 2 by comparing the curves, which are calculated from the constants of Table I and the various equations presented, with the points which are experimental measurements.

In terms of our analysis and the derived rate constants the mechanistic behavior of the cyclic amide acetals can be explained in the following simple terms. In strongly basic solutions hydrolysis proceeds at a rate which is independent of pH, with a mechanism corresponding to rate-determining attack of hydroxide ion on the small amount of imidatonium ion present in equilibrium with the amide acetal. Products are those expected for the hydrolysis of an imidatonium ion in basic solution. For example, the 90:10 ratio of ester/amide obtained starting with the cyclic amide acetal is very similar to the 95:5 ratio obtained with the imidatonium ion IIb.

As the pH is decreased the hydrolysis becomes approximately first order in hydronium ion (see curve S1). This corresponds to hydrolysis via dioxolenium ion, with the amide acetal being the predominant species in equilibrium with both imidatonium ion and with its N-protonated form. Curve S1 then breaks to a plateau region. This can be accounted for in terms of a shift in the position of the equilibrium between amide acetal and imidatonium ion, with ester product still being formed through the dioxolenium ion and its amide acetal precursor. The two sections in acid (curve S2) correspond to hydrolysis of the ring-opened imidatonium ion, this hydrolysis occurring via ring closure re-forming amide acetal, followed by loss of amine. The rate-determining step in the overall reaction here is the conversion of imidatonium ion to amide acetal; the latter, once formed, proceeds to 1,3-dioxolenium ion rather than reverting back to imidatonium ion. The two sections differ simply in the mode of catalysis of the ring closure reaction (hydroxide ion catalysis and no catalysis (or water catalysis)). The plateau at intermediate pH can also[6] be viewed as an extension of these two regions, being the result of a change in rate-determining step. Amide acetal reverts to imidatonium ion faster than its conversion to dioxolenium ion.

Rate and equilibrium constants derived for the other amide acetals, which exhibit qualitatively the same mechanistic features, are also presented in Table I. Plots of log k or log K vs. the σ substituent constant are reasonably linear, and the ρ values are also presented in this table. Although these will not be specifically discussed it can be noted that each value

is reasonable for the type of reaction to which it refers, corroborating the mechanistic interpretation.

One major difference between the cyclic and acyclic amide acetals which deserves comment is the ratio of acid-catalyzed C–O cleavage to C–N cleavage, reactions which are kinetically equivalent[1] and which determine the pathway for primary decomposition of the amide acetal in acid media. This ratio is given by[1]

$$\left(\frac{\text{C–O}}{\text{C–N}}\right)_{H^+} = \frac{k_2}{k_3/K_{SH^+}} \tag{11}$$

and for the cyclic 4-methylphenyl compound has the value 1.9×10^{-3}, indicative of the preference of this compound for C–N cleavage in acid. For the acyclic analogue the competition is much closer; the ratio of eq 11 has a value of 0.3.[1] This difference is probably a further manifestation of the phenyl group effect.[7] It is now well established that 2-aryl-1,3-dioxolenium ions are more stable than related aryldimethoxycarbonium ions, since resonance with the aromatic ring is sterically inhibited in the latter.[7-9] Thus the C–N cleavage pathway which forms these ions (k_3) is expected to be faster with the cyclic system. As a comparison 2-aryl-2-methoxy-1,3-dioxolanes undergo acid-catalyzed loss of the methoxy group at a rate approximately 100 times greater than acyclic analogues.[3,7,9] A similar difference in k_3[10] is all that is required to account for the results with the amide acetals.

A further feature which deserves comment is a comparison of intramolecular and intermolecular reactions in the decomposition of the ring-opened imidatonium ion. This involves comparing k_{-1} vs. k_4, or k_{-2} vs. k_5, and in both cases the intramolecular reaction is favored. For the noncatalyzed processes the difference is not overwhelming, the intramolecular reaction being favored by a factor of about 50.[11] However, for the hydroxide ion catalyzed reactions the intramolecular process is substantially more favored by a factor of 4×10^4. Similar results are obtained on comparing noncatalyzed and hydroxide ion catalyzed ring closure reactions in the hydrolysis of tropone ethylene ketal, where a complete kinetic analysis is also possible.[12] An explanation in terms of differing transition state structures is detailed in that study.[12]

pH <5.0; Hydrogen Ortho Ester Decomposition. As has now been outlined, the cyclic amide acetals undergo predominant C–N cleavage in acid-producing β-hydroxyethyl ester. What we propose is that in this overall reaction there is a change in rate-determining step. At pH >6 the C–N cleavage step itself is the slow step, but at pH <5 this reaction becomes very rapid, and the decomposition of the hydrogen ortho ester becomes rate limiting. What is observed kinetically for the appearance of product is the kinetics of the hydrogen ortho ester decomposition. Rate constants take the form

$$k_{obsd}(F3) = k_7[OH^-] + k_8 + k_9[H^+] \tag{12}$$

with terms corresponding to hydroxide ion catalysis, no catalysis or water catalysis,[13] and hydronium ion catalysis.

Evidence for this interpretation is straightforward.[14] The rate behavior of the amide acetal in solutions with pH <3 is identical with that of a corresponding ortho ester. This can only occur if what is being followed is a common step of each, and, for reasons outlined elsewhere,[2,3] this common step must be the breakdown of the hydrogen ortho ester. The above explanation also requires that hydrogen ortho ester accumulate, and this is observed. There is an intermediate with a UV spectrum which is slightly different from that of the amide acetal, and which is more similar to that of an ortho ester. (There should be little difference in the UV spectrum of an ortho ester and a hydrogen ortho ester, since only a change of OR to OH is involved).

The hydrogen ortho ester aspect will not be discussed in detail here, since it is the subject of a separate paper. Two features of the amide acetals can be noted. One is that this system provides an extremely rapid entry into the later stages of the ortho ester hydrolysis over a considerable pH region. The dioxolenium ion is formed from amide acetal with a first-order rate constant given by

$$k_{obsd} = \frac{k_3[H^+]}{K_{SH^+} + [H^+]} \tag{13}$$

and in acid solutions where the amide acetal is fully protonated this reaches a maximum value of k_3. A precise value cannot be placed on this rate constant, but it must be large. The H^+-dependent limb of curve F2 which represents k_{obsd} of eq 13 shows no sign of attaining a maximum value and already rate constants are of the order of 300–500 s^{-1}. In more acidic solutions dioxolenium ion must be formed from amide acetal with a rate constant in excess of this. A lower limit of 10^3 s^{-1} can be placed on this process.

The second feature concerns the pH region, where the change in rate-determining step occurs. With the ortho esters this change occurs at pH 2–3.5, and since these solutions are fairly acidic, only the hydronium ion catalyzed pathway (k_9) and noncatalyzed pathway (k_8) are important in the decomposition of the hydrogen ortho ester.[2,3] When the pH is increased such that the hydroxide ion catalyzed step (k_7) takes over, hydrogen ortho ester decomposition is no longer rate determining and thus starting with ortho ester, no value of k_7 can be assigned. With the amide acetals, however, the change in rate-determining step occurs at higher pH, where curves F2 and F3 cross in Figure 2. The hydroxide ion catalyzed decomposition is very efficient, so much so that it becomes important at pH 3.5–4. Thus, starting with amide acetal, there is no problem in observing this pathway and in obtaining a value of k_7.

Experimental Section

Materials. Reagents used in the preparation of buffer solutions were best commercial grade and were not further purified. *O*-Ethyl-*N*,*N*-dimethylimidatonium fluoroborate salts were prepared by treatment of the appropriate *N*,*N*-dimethylamide with triethyloxonium fluoroborate.[15] 2-Aryl-2-methoxy-1,3-dioxolanes were prepared as described elsewhere.[8,9] The β-hydroxyethyl benzoate esters were prepared by hydrolyzing the above ortho esters in acidic 50:50 acetonitrile/water followed by a standard workup.

2-Aryl-2-(*N*,*N*-dimethylamino)-1,3-dioxolanes were prepared as follows: ethylene glycol (0.01 mol), dried by distillation at atmospheric pressure discarding the first 50% of distillate, and *N*,*N*-dimethylbenzamide dimethyl acetal[1] (0.01 mol) were placed in a small distillation apparatus (reagents are not totally miscible). The mixture was stirred under vacuum (1–4 mmHg) at room temperature for 1–4 h until evolution of methanol ceased and the solution was homogeneous. The desired product was then distilled by increasing the temperature. The cyclic amide acetals have a similar NMR spectrum to their acyclic analogues when comparing the aromatic region and the position of the NMe_2 peak, the latter characteristically at δ 2.1–2.3. The cyclic amide acetals are differentiated from their acyclic analogues by the absence of the methoxy peak at δ 3.0–3.1 and the appearance of an AA′BB′ symmetrical multiplet at δ 3.5–4.1. Boiling points are as follows: 4-$MeOC_6H_4$, 105 °C (0.5 nmHg); 4-MeC_6H_4, 95 °C (0.3 mmHg); C_6H_5, 70 °C (0.3 mmHg); 4-ClC_6H_4, 120 °C (1.0 mmHg); 3-ClC_6H_4, 100 °C (0.2 mmHg). All five amide acetals gave satisfactory elemental analysis.

Kinetics. Kinetics were followed using UV spectroscopy, generally at a wavelength corresponding to λ_{max} of the β-hydroxyethyl product. Reactions in basic media (half-life >2–3 s) were followed on a Unicam sp 1800 spectrophotometer by addition of 3 μL of a dimethoxyethane solution of amide acetal directly into a thermostatted UV cell. Faster reactions were followed on a Durrum-Gibson stopped-flow spectrophotometer. Since the amide acetals are not indefinitely stable even in aqueous base, the following experimental approach was employed. The acidic or neutral aqueous buffer was loaded in one syringe of the apparatus, where it was allowed to thermally equilibrate. Amide acetal, as a solution in dimethoxyethane, was added to a solution of 0.002

M NaOH which had been thermostatted in an external water bath. This solution was immediately transferred to the second syringe of the stopped flow apparatus and the reaction trace was recorded. Imidatonium ions III were trapped into acid solutions by placing a small amount of amide acetal in a syringe needle and rapidly passing through this 2 mL of dilute phosphate buffer (pH 7.2) such that the resultant solution was immediately injected into an acidic buffer.

Rate constants were evaluated as slopes of plots of $\ln (A_\infty - A_t)$ vs. time. Excellent linearity was observed in all cases. All solutions in which rate constants were obtained were at ionic strength 0.1. For studies requiring buffered media, rate constants were obtained at three or four different total buffer concentrations maintaining the same buffer ratio and extrapolated to zero buffer concentration.

Product Analysis. The ratio of ester to amide was analyzed by dissolving substrate (0.1 g) in aqueous solution (100 mL), and after a time corresponding to ten half-lives of hydrolysis, the solution was extracted with ether. The ether was removed, and the products were analyzed by NMR spectroscopy.

The intermediate absorbances of Figures 1 and 2 were obtained using stopped-flow spectroscopy as previously described. These have been corrected for the partial hydrolysis of the amide acetal which occurs in the sodium hydroxide solution prior to mixing.

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Registry No.—Ethylene glycol, 107-21-1; *N,N*-dimethylbenzamide dimethyl acetal, 35452-04-1; *N,N*-dimethyl-*p*-methoxybenzamide dimethyl acetal, 66475-66-9; *N,N*-dimethyl-*p*-methylbenzamide dimethyl acetal, 66475-67-0; *N,N*-dimethyl-*p*-chlorobenzamide dimethyl acetal, 66475-65-8; *N,N*-dimethyl-*m*-chlorobenzamide dimethyl acetal, 66475-64-7.

References and Notes

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(5) It can be noted that the value of k_4 obtained in the analysis is a very reasonable one, being similar to the value which is actually measured for the analogous imidatonium ion IIb. A value of k_5 is not given in Table I since in our analysis this is not statistically distinguishable from zero. This is also reasonable. Using IIb as a model k_5 should be of the order of $4\text{–}5 \times 10^{-5}$ s^{-1}. In eq 5 k_5 appears in the term $(k_3K_I{}^+/K_{SH^+}) + k_5$. The first part of this term has the value 1.1 s^{-1} and overwhelms any contribution from k_5. In eq 10 k_5 appears by itself added to the remainder of the equation. The minimum value of k_{obsd} in the pH region to which eq 10 applies is 2.7×10^{-3} s^{-1}, a number of the order of 50 times greater than the "predicted" value of k_5. This means that, although the k_5 process may contribute ~2% to this minimum rate, with the errors involved in the raw experimental data an accurate value cannot be obtained.
(6) This is a case where the equilibrium assumption and the steady-state assumption are equivalent.
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(10) Unfortunately, a direct comparison of k_3 (or k_3/K_{SH^+}) for cyclic vs. acyclic amide acetals is not possible at present, since the acyclic systems were of necessity studied in mixed solvents.[1]
(11) This assumes that the value of k_5 for the ring-opened imidatonium ion is the same as the value for an *O*-ethyl imidatonium ion (see ref 5).
(12) R. A. McClelland, M. Ahmad, and G. Mandrapilias, *J. Am. Chem. Soc.*, **101**, 970 (1979).
(13) Although this may not be apparent from Figure 2 the term in k_8 is statistically valid.
(14) There might be a question as to whether the base-catalyzed limb of F3 actually refers to hydrogen ortho ester decomposition, since the evidence associated with the similarity of rate constants for amide acetal and ortho ester is lacking here. We suggest firstly that there is no other interpretation for this process consistent with any simple mechanisms that can be pictured for this system. Secondly, and more importantly, in a separate paper[3] a set of experiments is described starting directly with a 1,3-dioxolenium ion in which all three kinetic processes for decomposition of the hydrogen ortho ester are observed. Although these data refer to 50% acetonitrile (of necessity) their feature is that the hydroxide ion catalysis (k_7) is extremely efficient, and the actual value of k_7 is of the same order of magnitude as that obtained with the amide acetal in water alone.
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Sequential Protonation and Dealkylation Modes of Monocyclic Phosphite Esters

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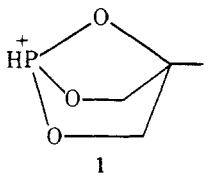
Protonated forms of monocyclic phosphites of the type $MeOP\overline{(OC_nO)}$ in $HFSO_3$ at −50 °C exhibit $^1J_{PH}$ couplings which decrease in the order five membered > six membered > seven membered for the same degree of methyl substitution on the ring. Within a ring of given size, this coupling also decreases with increased methyl substitution. In highly methyl-substituted esters, a ring-opening dealkylation by solvolysis readily takes place near −50 °C, resulting in the formation of $MeO(H)P^+(OH)OC_nOSO_2F$ ions. In dilute acid at room temperature, dealkylation occurs on the MeOP group. NMR data from the only other reported attempt to protonate a monocyclic phosphite ester (ref 3) are inconsistent with the present study and probably represent a dealkylated acyclic product.

Because phosphite esters are easily solvolyzed in acidic media, systematic studies of these compounds in protonated form have until recently[1] been restricted to acyclic systems[2,3] such as $P(OR)_3$ and $P(OAr)_3$, which are strain-free and hence relatively unreactive. Prior to our report of the P–H coupling constants of **1–4**[1] (Table I), there has appeared only a single disclosure of a $^1J_{PH}$ value for a cyclic phosphite ester, namely, **5**.[3]

In this paper we describe our low temperature ^{31}P NMR investigations of **5–11** dissolved in $HFSO_3$. Evidence is presented which indicates the following: (1) the $^1J_{PH}$ and δ ^{31}P data reported for **5** are incorrect, (2) $^1J_{PH}$ values are a function of ring substitution as well as ring size, (3) the appearance of a new protonated species with time or with a moderate in-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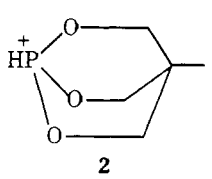
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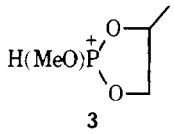
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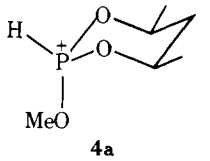
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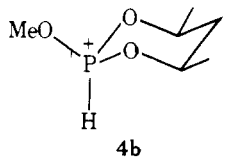
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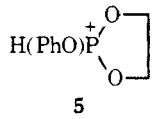
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