Kinetics and Mechanism of Amide Acetal Hydrolysis. Carbon–Oxygen vs. Carbon–Nitrogen Bond Cleavage in Acid Solutions

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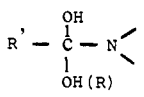
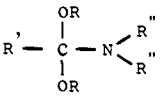
Abstract: Amide acetals $ArC(OMe)_2NMe_2$ competitively cleave the carbon-oxygen bond and carbon-nitrogen bond in acid solutions. The latter is favored for species with electron-donating substituents in Ar, and is also more favored in D_2O solutions. In neutral and basic solutions only C-O cleavage is observed. The relative amount of this cleavage also increases with increasing concentrations of added buffers. Kinetic studies are also reported, and a mechanistic scheme is proposed in which the N-protonated amide acetal is responsible for C-N cleavage, with the neutral substrate accounting for C-O cleavage. This latter process occurs in a noncatalyzed (or water catalyzed) reaction and in a hydronium ion catalyzed reaction and is also catalyzed by the acid component of added buffers. The general question of the acid partitioning in species of this general type is considered, in terms of whether basicity or cation stability is the dominant factor. This depends apparently on the degree to which other groups present can stabilize an adjacent cationic center, and how this affects the position of the transition states. The failure to observe significant C-O cleavage in tetrahedral intermediates related to the amide acetals is attributed to additional stability associated with the O-H group, although other factors such as zwitterion formation or electron-pair orientation may also be involved. It is suggested that acidic partioning of carbinolamines and related species also falls into the general pattern.

Species of the type I are the postulated intermediates of several important acyl transfer, or related, reactions. Numerous examples are now available which suggest that when formed in acidic solutions these species break up with cleavage of the carbon nitrogen bond considerably favored over cleavage of a carbon oxygen bond. This conclusion is reached, for example, in considering the nature of the rate-determining step in ester ammonolysis,[1,2] the nature of the products obtained on imidate ester hydrolysis,[2-7] or the failure to observe significant ^{18}O exchange with amides concurrent with their acid hydrolysis.[7-13] (In the last case, this observation can be used as evidence that I is not involved in the reaction,[7,12,14-16] a claim disputed by recent evidence.[13,17,18]) Predominance of C-O cleavage has been observed in certain systems, but these have all involved molecules with a phenyl or acyl group substituted on oxygen or nitrogen.[19-22]



I



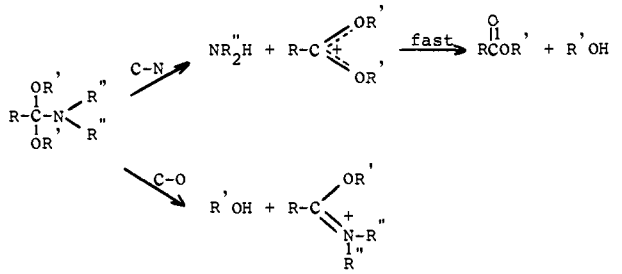
II

The favoring of amine loss is normally attributed to the great basicity of the nitrogen as compared to oxygen. Basicity, however, is not the sole factor which determines the direction of tetrahedral intermediate breakup.[23,24] For example, phenyl acetate, when compared with alkyl esters, displays considerably less carbonyl-^{18}O exchange relative to hydrolysis in acid.[24] The tetrahedral intermediate in this system must lose phenol preferentially over water, and yet this involves the less basic site.

As a further illustration of the complexity of these systems we report here that amide acetals (II),[25] species which can be considered as models for I,[26] competitively cleave in both directions in acid. An analysis of the factors affecting this competition is further reported, including a description of the catalytic requirements of the two modes of cleavage. This leads to a fuller understanding of the interplay of the various factors which influence the partitioning in I and II and indeed in species of this general type where a choice between nitrogen or oxygen loss exists.

Results

Products. The question of concern is which bond does cleave initially in amide acetal hydrolysis. Carbon-nitrogen fission would result in a dialkoxycarbonium ion and an amine; the ion is not stable in aqueous solution,[27] but is instantly hydrolyzed to ester and alcohol. Carbon-oxygen fission would produce an alcohol and imidatonium ion; in nonbasic media, this ion is reasonably stable,[28] particularly when R = aryl. In consequence it is possible to distinguish the primary dissociations in neutral and acidic solutions, either on the basis of the ester:imidatonium ion ratio or on the basis of the amine:imidatonium ion ratio.



Results obtained in 0.1 molar acid solutions are given in Table I, and show that the situation is not as expected,[29] since both types of cleavage are observed. Three general trends can be discerned in the data. In the series $ArC(OMe)_2NMe_2$, C-O cleavage increases with increasing electron withdrawal of the substituent. On addition of increasing amounts of dimethoxyethane (DME), C-O bond cleavage increases. On changing from H_2O to D_2O, C-O cleavage decreases.

The pH dependence is shown in Figure 1. In acid solution the product ratio remains constant up to a pH of ~3. At this point the amount of C-O cleavage increases, until by pH 7 imidatonium ion is essentially the only product. In carrying out this study, it became apparent that the product ratio is also influenced by the added carboxylic acid buffers employed. The results for acetic acid buffers are summarized in Figure 2, and show the general trend of an increasing amount of imidatonium ion with increasing buffer concentration. Table S1[30] summarizes product data employed in constructing Figures 1 and 2.

In basic solution amide acetals still rapidly hydrolyze but neither ion is stable. The evidence is consistent however with the trend observed in the product-pH profile continuing, that is, complete C-O bond cleavage. For example, $HC(OMe)_2NMe_2$ produces in base essentially 100% $HCONMe_2$,[31] that is, with the C-N bond still intact. The benzamide acetals

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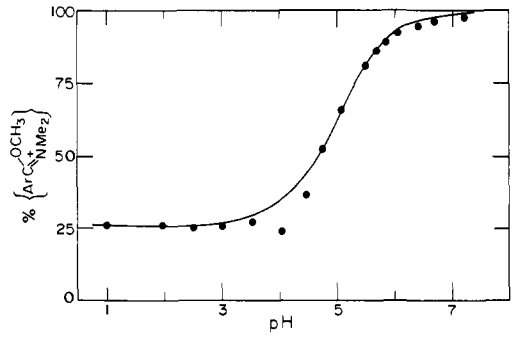


Figure 1. Imidatonium ion product in the hydrolysis of 4-Me-$C_6H_4C(OMe)_2NMe_2$ as a function of pH. Points above pH 2.5 were obtained in buffer solutions, and represent extrapolations to zero buffer concentration. The curve is based on the best fit of eq 2 to the experimental data, with $k_0K_{SH^+}/k_N = 1.2 \times 10^{-5}$, $k_H + K_{SH^+}/k_N = 0.36$.

Table I. Primary Cleavage in $RC(OMe)_2NMe_2$ Hydrolysis in 0.1 N HCl (DCl) Solutions

R	Solvent	% imidatonium ion (C-O cleavage)
H[a]	H_2O	>95[b]
4-$NO_2C_6H_4$	H_2O	94[b]
3-ClC_6H_4	H_2O	80,[b] 84[c]
	D_2O	50,[b] 47[c]
4-ClC_6H_4	H_2O	65[b]
C_6H_5	H_2O	47,[b] 40[c]
4-$MeOC_6H_4$	H_2O	15[b]
4-MeC_6H_4	H_2O	23,[b] 27[c]
	D_2O	9[c]
4-MeC_6H_4	80% H_2O, 20% DME[d]	40[c]
4-MeC_6H_4	60% H_2O, 40% DME	60[c]
4-MeC_6H_4	40% H_2O, 60% DME	80[c]
4-MeC_6H_4	25% H_2O, 75% DME	90[c]

[a] C-O cleavage is also observed with $HC(OEt)_2NMe_2$ and $HC(O\text{-}i\text{-}Pr)_2NMe_2$. [b] By NMR. [c] By UV. [d] Dimethoxyethane.

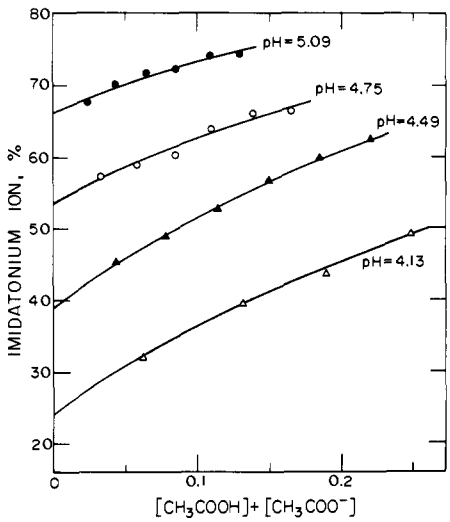


Figure 2. Imidatonium ion product in the hydrolysis of 4-Me-$C_6H_4C(OMe)_2NMe_2$ as a function of buffer concentration. The points are experimental; the curves are based on eq 2.

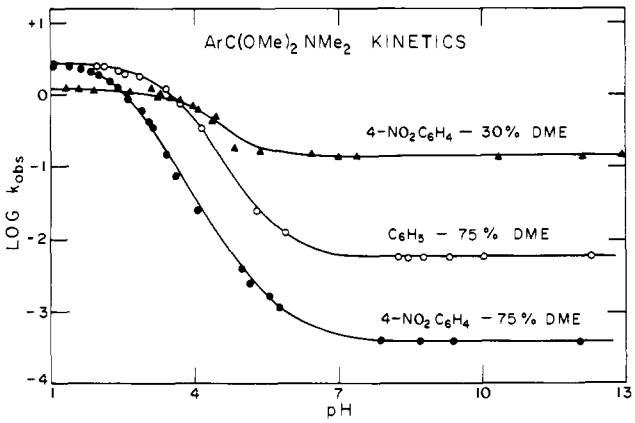


Figure 3. Observed rate constants for hydrolysis of $ArC(OMe)_2NMe_2$ in dimethoxyethane-water. The points are experimental and in the intermediate pH region are based on extrapolation of rate constants obtained in buffer solution to zero buffer concentration. The curves are based on fitting the experimental data to eq 1 and use the values of the constants in Table II.

produce esters with only small traces of amide. This, however, is also the result of hydrolyzing imidatonium ion[28,32] under the same conditions.

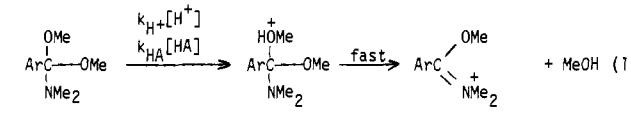
Kinetics. The amide acetals prove, in general, to be extremely labile, with a half-life of <1 s in water at all values of pH. Kinetics can be followed however in mixed aqueous solutions, for example, DME-H_2O. The inert cosolvent slows down the reaction so that rates can be obtained in neutral and basic solutions. This then permits the use of stopped-flow experiments for acidic solutions. Stopped-flow experiments in water itself are not possible even though the rates may be in the appropriate range, since no pure aqueous solution exists in which the amide acetals are stable.

Three rate-pH profiles are presented in Figure 3; the data are available in Tables S2-S4.[30] The "pH" refers to that measured on a pH meter, applying a correction factor for the mixed solvent system. The rates are observed first-order rate constants obtained spectrophotometrically. Conditions were used such that k_{obsd} refers to disappearance of amide acetal. The general features of these profiles are pH independent regions in acid and base, with a change-over at intermediate pH.

The kinetic studies also reveal that the hydrolysis is subject to catalysis by added buffer. In the case of buffers of neutral or basic pH, the acidic component of the buffer apparently is the catalytically active form. As the plateau region is approached, the situation becomes complex. This plateau region, however, is due to protonation of the substrate and, taking this into account, the data are consistent with either general acid catalysis on the neutral substrate or base catalysis on the protonated substrate.

Discussion

Scheme I can be proposed to account for the mechanistic details of the primary cleavage steps in the hydrolysis of the simple amide acetals studied here. The N-protonated substrate is responsible for C-N dissociation, while the neutral substrate gives rise to C-O dissociation. The latter process can occur in a noncatalyzed (or water catalyzed) reaction, and in a hydronium ion catalyzed reaction, and is also subject to catalysis by added weak acids. In Scheme I the latter two are written with proton transfer concerted with bond cleavage. Also consistent with the data[33] is the stepwise pathway involving the O-protonated amide acetal, with proton transfer being rate determining (eq 1). Although insufficient experimental evi-



dence exists to distinguish the two possibilities in the present case, we favor the concerted pathway, principally because this

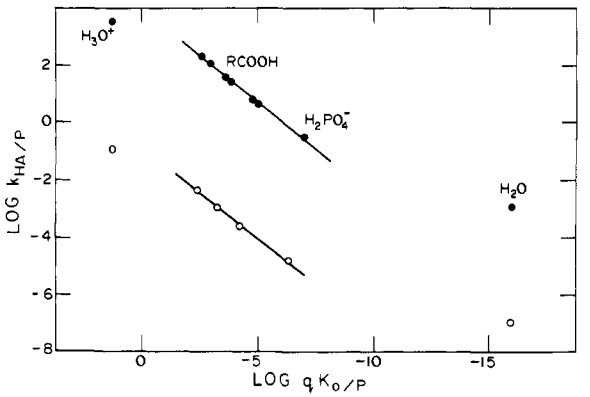
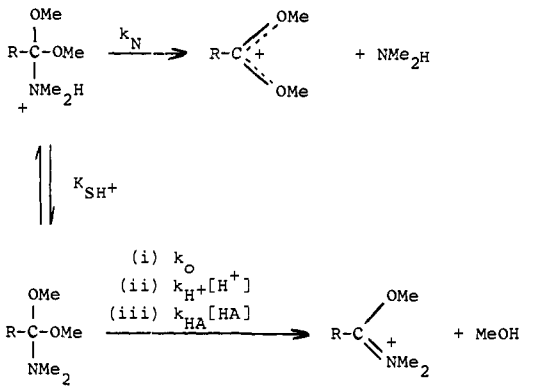


Figure 4. Brønsted plot for C-O cleavage of amide acetals. The closed circles represent data obtained kinetically in 30:70 DME-H_2O with *N,N*-dimethyl-4-nitrobenzamide dimethyl acetal. The open circles represent data obtained using product ratios in pure water with *N,N*-dimethyl-4-methylbenzamide dimethyl acetal, and plot $k_{HA}K_{SH^+}/k_N$ (see text). The H_2O point represents the k_0 rate divided by 55.5. Least-squares lines through the carboxylic acid points have slopes of 0.64 (●) and 0.61 (○).

Scheme I



has been established to be the operable route in closely related systems.[34-38]

Making the assumption that the equilibrium involving the N-protonation is rapid, eq 2 can be derived for the observed

$$k_{obs} = \frac{k_0K_{SH^+} + (k_N + k_{H^+}K_{SH^+})[H^+]}{K_{SH^+} + [H^+]} + \frac{k_{HA}K_{SH^+}[HA]}{K_{SH^+} + [H^+]} \quad (2)$$

rate constant for amide acetal disappearance. The first term of this equation accurately predicts the form of the rate-pH profiles in Figure 3. The pH-independent region in base corresponds to the k_0 pathway with $k_{obsd} = k_0$. As the pH is decreased, the term in $(k_N + k_{H^+}K_{SH^+})[H^+]$ becomes important and a rate which is approximately first order in $[H^+]$ is observed.[39] This corresponds to pathways involving H^+-catalyzed C-O cleavage and C-N cleavage of the protonated substrate. These are kinetically indistinguishable but can be separated by product analysis. For the systems of Figure 3, the particular combination of solvent and substituent produce a situation where C-O bond cleavage predominates throughout and therefore $k_{H^+}K_{SH^+} > k_N$, but this is not always true (Table I). The plateau region in acid arises when the substrate becomes fully protonated. This plateau will occur regardless of the nature of the reaction in acid. In the case of C-O bond cleavage in strong acid, the reaction is kinetically $[H^+]$ independent since the substrate must be deprotonated first.

The rate data of Figure 3 have been fitted to the first term of eq 2 and furnish values of k_0, K_{SH^+}, and k_{H^+} which are given in Table II. These constants behave much as expected, for example, in their substituent and solvent dependency. This

Table II. Specific Rate Constants and Dissociation Constants for $ArC(OMe)_2NMe_2$ in Dimethoxyethane-Water

Ar	Solvent	k_0, s^{-1}	k_{H^+}, M^{-1} s^{-1}	pK_{SH^+}
4-$NO_2C_6H_4$	30% DME	0.13	1.2×10^4	4.0
4-$NO_2C_6H_4$	75% DME	0.00038	5.0×10^2	2.3
C_6H_5	75% DME	0.0057	5.2×10^3	3.3
ρ	75% DME	−1.5	−1.3	+1.3

table makes amide acetals out to be quite weak as nitrogen bases. This is somewhat misleading however, being due to the substituent and solvent requirements necessary to obtain the kinetic data. Interestingly, extrapolation of these data to water suggests that a pK_{SH^+} of 5-6 applies for nitrogen protonation of species such as $PhC(OR)_2NR_2'$. This is very much in the range estimated by Guthrie[26] on the basis of structural considerations.

It can be commented here that in its C-O cleavage reaction the amide acetals display similar catalytic behavior to that shown by certain ketals and ortho esters where highly stabilized oxycarbonium ions are produced.[33,40] These are also characterized by a general acid catalyzed hydrolysis and also often have a significant neutral hydrolysis rate. In such a comparison, the amide acetals must be considered to produce a considerably more stabilized cationic species, so stable in fact that the neutral hydrolysis has a half-life of <1 s in pure water.

Buffer Catalysis. The second term of eq 2 corresponds to the buffer catalysis. This is observed as general acid catalysis at high pH where the substrate is substantially unprotonated, but changes to apparent general base catalysis at low pH when the substrate becomes fully protonated. The buffer data are also consistent with general base catalysis on the protonated substrate, but we feel this is unlikely in view of the analogy of the amide acetals to acetals, etc.

Sufficient data have been obtained for one system to construct a Brønsted plot (Figure 4). The catalytic coefficients, k_{HA}, were obtained by correcting for protonation using the pK_{SH^+} value of 4.0 (Table II) obtained by fitting the pH-rate profile.[41] The acid dissociation constants are those pertaining to the mixed solvent system, with the exception of H_2O and H_3O^+ where the values are those estimated in water. Figure 4 also depicts a Brønsted plot in pure water based on product ratio (see later). The reliability of these plots is attested by their close similarity, in spite of the different methods used in obtaining them.

In general these plots are much as expected for a reaction of the type involved here.[37] An α value of 0.6 is obtained from the carboxylic acid points, and the point for the neutral reaction shows a large positive deviation from this line. Considering the stability of the cation product, it is interesting that this α value still lies in the range associated with general acid catalyzed acetal hydrolysis (0.5-0.75).[33,37]

Products. The ratio of C-O to C-N bond cleavage can be related to the constants of Scheme I by eq 3. The first term

$$\frac{C\text{-}O}{C\text{-}N} = \frac{k_0 + k_{H^+}[H^+]}{\frac{k_N}{K_{SH^+}}[H^+]} + \frac{k_{HA}[HA]}{\frac{k_N}{K_{SH^+}}[H^+]} \quad (3)$$

corresponds to the observed product variation with changing pH (Figure 1). In basic and neutral solution, predominant C-O cleavage is observed, via the k_0 pathway. As the acidity is increased the terms in $[H^+]$ become important, and C-N cleavage can be observed. This reaches a limit at high $[H^+]$ corresponding to the ratio given in eq 4. Fitting the product

$$\left(\frac{C\text{-}O}{C\text{-}N}\right)_{H^+} = \frac{k_{H^+}K_{SH^+}}{k_N} \quad (4)$$

data as a function of pH to eq 3 gives values of the terms $k_0K_{SH^+}/k_N$ and $k_{H^+}K_{SH^+}/k_N$ (Figure 1).

The effect of added buffers of increasing the relative amount of C–O cleavage is seen in the second term of eq 2 and is attributable to the general acid catalysis of this reaction. The buffer data, when plotted in the form C–O/C–N vs. [HA]/[H^+] gives values of $k_{HA}K_{SH^+}/k_N$ as the slope.[42] For the same substrate K_{SH^+} and k_N are constant, so that plotting the various terms provided by the pH and buffer analyses produces a Brønsted plot for the C–O cleavage reaction, as shown in Figure 4.

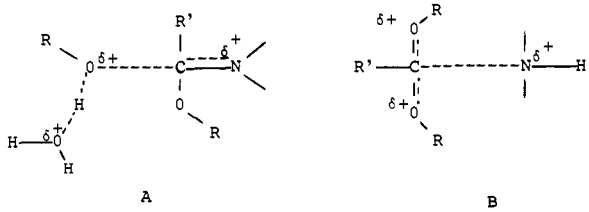
Equation 4 demonstrates that the effect of substituent on the product ratio in acid (Table I) is a net substituent effect on three processes. A plot of log (C–O/C–N) vs. σ is linear (correlation coefficient = 0.995) with a slope of +1.8, this ρ value being determined by the ρ values on k_{H^+}, K_{SH^+} and k_N. The data of Table II, albeit in a different solvent, suggest that the values for k_{H^+} and K_{SH^+} are very similar, and in a direction such that the product of $k_{H^+}K_{SH^+}$ is virtually insensitive to substituent change. Accordingly, much of the overall ρ can be attributed to the term in $1/k_N$. Thus, the ρ value for the dissociation of the protonated amide acetal is of the order −1.8, a not unreasonable value.[33]

The solvent isotope effect is also consistent with the overall scheme and eq 4. For this purpose one can regard this effect as being determined by the ratios of rate constants for two acid catalyzed reactions, one of which is general acid catalyzed (the k_{H^+} term) and one of which is specific acid catalyzed (the k_N/K_{SH^+} term). The latter will certainly show a pronounced inverse isotope effect.[43] The former will probably show a normal effect,[43] although the actual degree does not seem to be predictable.[33] In consequence the specific acid catalyzed reaction is more favored in D_2O.

Finally, the effect of organic cosolvent can be at least partially understood, in terms of the pronounced solvent dependency of K_{SH^+} (Table II). As dimethoxyethane is added, the amide acetal nitrogen becomes substantially less basic, K_{SH^+} is greater, and C–N bond cleavage is favored. The effects of solvent on k_{H^+} and k_N cannot be ignored, of course, but their solvent dependency should be in the same direction and the effects will tend to cancel.

C–O vs. C–N Bond Cleavage. The most intriguing observation of this study is that amide acetals partition in both directions in acid. In considering the factors that influence this partitioning, a case can be made for either direction. The nitrogen is the more basic heteroatom, by a considerable amount, and this will favor C–N cleavage. The oxygen, though less basic, becomes a better leaving group once it is protonated[23] (or partially protonated), and, more importantly, its departure leaves behind a much more stable cation. The question seems to boil down to one of whether basicity or carbonium ion stability is the dominant factor.

That conditions can be such that either can prevail can be seen on considering the transition states (A and B) for the two



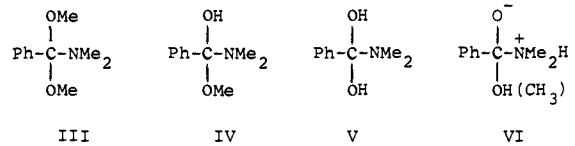
A

B

processes. In C–O cleavage, positive charge is being transferred from H_3O^+ to nitrogen (mainly), while, in C–N cleavage, the charge is being transferred from the nitrogen (of the protonated substrate) to oxygen. If the transition states were to resemble the cations, C–O cleavage would be favored, since this would place the majority of the charge on nitrogen. Conversely, if the transition states were to resemble the starting material, C–N charge would be favored.

In considering the amide acetals, it must be concluded that, for those substrates which show predominant C–O cleavage (e.g., R′ = H, 4-$NO_2C_6H_4$), the transition states more closely resemble the ions than those of substrates with predominant C–N cleavage (e.g., R′ = 4-$MeOC_6H_4$). Why this should be so can be seen by considering that the progression from the former to the latter results in more stable cations. In particular, their energy is lower relative to that of the amide acetal, and the transition state shifts toward the starting material. Interestingly, a similar conclusion regarding the effect of aromatic substituent on transition state development has been previously reached for acetal hydrolysis, based on variations in secondary deuterium isotope effects.[44]

Tetrahedral Intermediates. One observation to be accounted for is the difference between the amide acetals and the tetrahedral intermediates which they model, a difference strikingly revealed on comparing III–V. While compound III shows very



III IV V VI

close to a 1:1 partitioning between the two modes of cleavage, this number must be greater than 100:1 in favor of C–N for IV[7] and V,[7,13] the tetrahedral intermediates formed on acid hydrolysis of the *O,N,N*-trimethylbenzimidatonium ion and benzamide, respectively. Three explanations can be advanced to account for this.

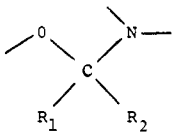
(i) Compounds IV and V have available the zwitterionic structure VI, and this will almost certainly rapidly break down with C–N cleavage. However, while such species are extremely important,[20,37] we feel that they are probably not responsible for the difference under discussion, at least in reasonably acidic solutions (e.g., pH 0–1). Basically, one can argue that, if zwitterions are involved, in stronger acids (e.g., 50% H_2SO_4) where their importance should be diminished, an increase in C–O cleavage should be observed, perhaps to the degree found with the corresponding amide acetal.[45] This is not the case.[7,46,47] In addition, the ammonolysis of esters in strongly acidic solutions apparently proceeds via amine attack on protonated ester;[48] the reverse is loss of amine from N-protonated IV, and not from VI.

(ii) Compounds IV and V are formed as intermediates in a hydrolysis reaction. Following the reasoning of Deslongchamps and co-workers,[32,49] the initially formed intermediate is incapable of expelling the OH or OR group which was already attached to the acyl carbon, since the nitrogen lone pair is not antiperiplanar to it. This long pair must in fact be antiperiplanar to the oxygen derived from the water molecule. This brings up the possibility that C–O cleavage does occur in IV and V, but only with this latter oxygen, and in consequence is never observed. This is an attractive possibility, but again it can probably be ruled out, at least for acid solutions. Basically the kinetic studies carried out here on the amide acetals would suggest that the lifetime of the tetrahedral intermediates should be great enough to allow conformational equilibration (see, for example, the acid rates in Figure 3). Additionally, kinetic studies on imidate hydrolysis suggest that the water attack is rate determining.[4,5] This would not be the case if the above proposal were valid.

(iii) The third explanation returns to cation stability and its relation to transition state development and involves the fact that the cations derived from IV and V have an additional stabilizing feature not present in III, in that they can hydrogen bond to solvent (>O^+—H . . .OH_2).[50] This stabilization is not small[50] and is probably of sufficient magnitude to account for

the differences. In other words, the additional solvation of the cations from IV and V shifts the transition state closer to the tetrahedral compounds than in the corresponding III, and C–N cleavage totally dominates.

Carbinolamines. In concluding, it can be commented that the behavior of species of the general formula VII appears to



VII

follow the pattern outlined here. Numerous examples of these are known, including carbinolamines,[51-59] carbinolamine ethers,[36] oxazalidines,[60] and *N*-glucosylamines,[61] and the conclusion is that these cleave preferentially C–O in acid. This implies a transition state which is more advanced toward the ion intermediates than that of the amide acetals, and this is exactly what is expected. The combinations of $R_1 + R_2$ employed in these various studies do not stabilize an adjacent cationic center to the same extent as the combination of RO + R′ in the amide acetals.

Experimental Section

Materials. Dimethoxyethane was distilled from lithium aluminum hydride before use. Reagents used in the preparation of buffer solutions were not further purified.

N,N,O-trimethylimidatonium ions were prepared as their borofluorate salts by treatment of the appropriate *N,N*-dimethylamide with trimethyloxonium borofluorate[62] in methylene chloride following a standard procedure.[2] These salts were obtained initially as viscous oils, which, in a few cases, slowly crystallized. The oil or solid was shaken with several portions of dry ether, residual traces of ether being removed by evacuation in a desiccator. The purity of the salts was checked by NMR.

N,N-Dimethylformamide dialkyl acetals were commercially available (Aldrich). *N,N*-Dimethylbenzamide dimethyl acetal and substituted derivatives were prepared by slowly adding a solution of the imidatonium borofluorate in methylene chloride to a cooled solution in methanol of sodium methoxide, the latter being in excess. The solvents were removed on a rotary evaporator, and the product distilled away from the remaining salts under reduced pressure, followed by redistillation. Boiling points, NMR data, and analytical data are given in Table S5.[30]

Products from Formamide Acetals. The substrate (0.3 mL) was added from a syringe to a rapidly stirring aqueous solution (5 mL), and the NMR spectra were immediately recorded in the region of δ 3.8–2.5. In aqueous acidic solutions, the initial spectrum showed peaks corresponding to imidatonium ion (characteristic *N*-Me hydrogens at δ 3.1 and 3.3) and alcohol. Only a trace (<10%) of dimethylammonium ion was initially present. Moreover, this slowly appeared, accompanied by disappearance of imidatonium ion. Extrapolation to zero mixing time suggests that imidatonium ion is the only initial product. In more acidic solutions where imidatonium ion hydrolysis is retarded (e.g., 30% H_2SO_4), *no* dimethylammonium ion can be observed in the initial NMR spectrum.

In basic solutions, only peaks corresponding to *N,N*-dimethylformamide and alcohol are present.

Products from Benzamide Acetals. NMR Analysis. The substrate was added to the aqueous solution as above; this results in separation of a small amount of oil or solid corresponding to the insoluble ester product. In the case of aqueous acids, the latter was separated, the aqueous solution transferred to an NMR tube, and the spectrum recorded as above. The ratio of C–O/C–N cleavage was determined as the ratio of the *N*-Me peaks of the imidatonium ion and the peaks due to the dimethylammonium ion. Control experiments demonstrate that the imidatonium ion is soluble and does not undergo hydrolysis in the time required for the measurements.

In the case of basic solutions the mixture was extracted with ether, the ether removed, and the NMR of the product recorded. This showed predominantly peaks due to the methyl benzoate ester, with only small traces of the dimethylbenzamide.

UV Analysis. A solution (10 μL) of the amide acetal dissolved in dimethoxyethane was added to the rapidly stirring aqueous solution (10.00 mL), so that the final concentration of amide acetal was 10^{-4} M. The resultant solution was transferred to a UV cell (10-mm path length), and the absorbance at a selected wavelength immediately recorded on a Cary 14 spectrophotometer. The wavelength chosen corresponded to that for which there is the largest difference in extinction coefficient between ester and imidatonium ion. For example, for *N,N*,4-trimethylbenzamide dimethyl acetal, at λ 240 nm, ϵ(ester) was 14 600 and ϵ(imidatonium ion) was 6500. The ratio of C–O/C–N cleavage (imidatonium ion/ester) was calculated according to the formula

$$\frac{\text{imidatonium ion}}{\text{ester}} = \frac{\epsilon(\text{ester}) - \epsilon(\text{obsd})}{\epsilon(\text{obsd}) - \epsilon(\text{imidatonium ion})}$$

where ϵ(ester) and ϵ(imidatonium ion) are extinction coefficients obtained with authentic samples of these species, and ϵ(obsd) is the absorbance/concentration of amide acetal.

Taking the precaution of recording the UV absorbance as quickly as possible after mixing (i.e., <5 min), the imidatonium ion is stable (except in base). The half-life, for example, of the *N,N,O*-trimethylbenzimidatonium ion in 0.01 N HCl is 4.0 h. A comparison of results obtained using both UV and NMR methods is shown in Table I, and shows good agreement. The UV measurements are capable of greater internal consistency (for the same DME solution of the same amide acetal) but require precise knowledge of extinction coefficients and concentration. The data which are presented in Figures 1 and 2 and Table S1 were obtained using this method.

"pH" in Aqueous Dimethoxyethane. Kinetic runs were carried out in aqueous solutions containing either 75% dimethoxyethane or 30% dimethoxyethane, where the number refers to volume percent. The ionic strength of all solutions was maintained constant at 0.1 with sodium chloride. Because of the possibility of specific salt effects in these less polar solvents, a number of salts were used in one set of experiments, but there was little difference.

The pH referred to in Figure 3, and used in calculating the pK_{SH^+} and k_{H^+} values in Table II, is the pH as determined on a pH meter, using essentially the approach previously described by Archie and Westheimer.[63] To do this, the pH meter was calibrated with aqueous buffers, and then the pH of a solution in the mixed solvent of 0.01 M HCl and 0.09 M NaCl was measured. The deviation of this reading from 2.00 was then used as a correction factor on the pH readings of other solutions in the same solvent mixture. The deviations are in fact very small, the standard HCl solution in 30% DME giving an apparent pH of 1.85, the solution in 75% DME, 1.70. In the latter case, a slight difference is seen from the correction factor used by Archie and Westheimer.[63] This is probably due to a difference in ionic strengths.

In constructing the Brønsted plot of Figure 4 for 30% DME, the pK_a values for the carboxylic acids and biphosphate were calculated in that solvent at an ionic strength of 0.1, using the corrected pH reading, obtained as described above, in conjunction with the known buffer ratio. In each case several buffer ratios were employed, and each yields the same value of pK_a (±0.05). For the six carboxylic acids the pK_a values obtained in this way are all 0.5 (±0.1) long units more positive than the value in H_2O; the pK_a value for $H_2PO_4^-$ is 7.4.

Kinetics. Kinetics were followed using UV spectroscopy. The substrate *N,N*-dimethyl-4-nitrobenzamide dimethyl acetal, displays a peak with λ_{max} 265 nm, with a broad intense shoulder on the high wavelength side. All possible products also have λ_{max} in the vicinity of 265 nm, but lack the shoulder. Kinetics were therefore carried out by following the decrease in the absorbance on this shoulder (λ 335–350 nm, substrate concentration 5×10^{-4} mol/L^{-1}). (Interestingly in acidic solutions where the kinetics suggest that the substrate is partially protonated, the intensity of this shoulder is considerably decreased.)

For *N,N*-dimethylbenzamide dimethyl acetal, the increase in absorbance at λ 273 nm was followed, substrate concentration 10^{-3} mol/L^{-1}. This wavelength corresponds to an isobestic point for conversion of *N,N,O*-trimethylbenzimidatonium ion to methyl benzoate.

Four experimental approaches were employed. (a) For substrates in 75:25 DME–H_2O solutions where the half-life is >2–3 s, 3 μL of a DME solution of the substrate was injected directly into a thermostated UV cell, and the absorbance change followed on a Unicam sp 1800 spectrophotometer. (b) For the 4-nitro substrate in 75:25 DME–H_2O solutions where the half-life was <2 s, substrate was

dissolved in the neutral solvent and mixed in a Durrum-Gibson stopped-flow spectrophotometer with an acidic solution in the same solvent. (c) For the benzamide acetal in this solvent where the rates are large, substrate was dissolved in a neutral solution of 95:5 DME-H_2O and mixed in the Durrum-Gibson with solutions of 55:45 DME-H_2O. (d) For the 4-nitro substrate in 30:70 DME-H_2O, a similar technique was used with substrate in 55:45 DME-H_2O being mixed with 5:95 DME-H_2O. In approach d the rate of hydrolysis even in the neutral 55:45 DME-H_2O solvent is sufficiently fast that these solutions must be prepared immediately before use. This was done by thermostating the solvent in an external water bath, adding substrate, transferring the solution to the syringe, and immediately recording the stopped-flow trace.

Rate constants were evaluated as slopes of plots of ln $(A_t - A_\infty)$ or ln $(A_\infty - A_t)$ vs. time. Excellent linear plots were obtained in all cases.

In the case of approaches c and d some concern might be expressed over the use of the nonequivalent solutions. Archie and Westheimer[63] have previously employed similar solutions in stopped-flow kinetic studies on reactive phosphoranes. In our experiments controls without substrate reveal that there is negligible deflection of the oscilloscope trace on mixing; that is, the baseline remains flat under the conditions of the actual kinetic runs. Further assurance on the reliability of the kinetics is supplied by the excellent first-order plots obtained.

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Supplementary Material Available: Product data employed in constructing Figures 1 and 2 (Table S1), rate-pH profiles (Tables S2-S4), and boiling points and NMR and analytical data (Table S5) (16 pages). Ordering information is given on any current masthead page.

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