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Kinetics and Mechanism of the Hydrolysis of Anilide Acetals

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Abstract: A kinetic study of the hydrolysis of anilide acetals $\mathrm{ArC(OMe)_2NMeAr'}$ is reported. At high pH (>10) a pH independent C–O cleavage reaction is observed producing methanol and benzimidatonium ion; the latter is further hydrolyzed to amide and ester products. Substituent and solvent effects support a simple ionization mechanism with a transition state near the ion. At pH <10, the anilide acetals hydrolyze to benzoate ester, aniline, and methanol in a reaction involving initial nitrogen protonation and C–N cleavage to a dialkoxy carbocation and aniline. At pH 7–10 this reaction shows specific H^+ catalysis attributable to a pre-equilibrium protonation followed by rate-determining cleavage. Estimation of the pK_a of the protonated anilide acetal (–1) provides an estimate of its rate of C–N cleavage ($\approx 10^8\ s^{-1}$) which is near the diffusion limit. At pH <7 there is a change in the rate-determining step in product formation in this C–N cleavage reaction, and what is observed kinetically is the decomposition of the hemiorthoester $\mathrm{ArC(OMe)_2OH}$, the product of hydration of the dialkoxy carbocation. The principal piece of evidence for the changeover is the observation that the rate constants in acid solution are independent of the aniline moiety of the anilide acetal.

We have recently studied the hydrolysis of a series of benzamide acetals, $\mathrm{ArC(OMe)_2NMe_2}$.[1] These species model the tetrahedral intermediate of an amide hydrolysis or ester aminolysis, and also provide an interesting comparison with simple acetals and ortho esters.[2] One of the questions emerging from this previous study concerns the effect of a reduction in nitrogen basicity. Consequently we have now prepared a series of benzanilide acetals $\mathrm{ArC(OMe)_2NMeAr'}$ and report the results of this study.[3]

Experimental Section

Materials. Anilide acetals with no substituent in the aniline ring were prepared in the following way. The appropriate *N*-methylbenzanilide (0.10 mol) and methyl trifluoromethanesulfonate (0.11 mol) were dissolved in dry methylene chloride (25 mL) and the solution left overnight. Dry ether (50–100 mL) was added, resulting in separation of the *O,N*-dimethyl-*N*-phenylbenzimidatonium trifluoromethanesulfonate as a solid or a viscous oil. This salt was separated by filtration or decantation, washed with ether, redissolved in methylene chloride, and added dropwise to a stirred, cooled (0 °C) solution of sodium (0.2 mol) dissolved in dry methanol (50 mL). The solvents were removed on a rotary evaporator and hexane was added to dissolve the product. Undissolved salts were removed by filtration, the hexane removed, and the anilide acetal purified by distillation.

Anilide acetals substituted in the aniline ring were prepared by starting from the benzanilide, O-methylating first, followed by N-methylating. Reaction of the benzanilide with methyl trifluoromethanesulfonate, as described previously, produced an *O*-methyl-*N*-arylbenzimidatonium salt. This was added to a separatory funnel containing aqueous sodium carbonate and ether. After vigorous shaking the ether layer was dried ($\mathrm{MgSO_4}$), the ether removed, and the product distilled. This material, an *O*-methyl *N*-arylbenzimidate ester, was N-methylated with methyl trifluoromethanesulfonate as described above (except that shorter reaction times are required). This produces the *N,O*-dimethyl-*N*-arylbenzimidatonium salt, which was then treated as described previously to yield the anilide acetal.

The anilide acetals prepared were $\mathrm{XC_6H_4C(OMe)_2NMeC_6H_4Y}$ with X, Y, bp: H,H, 98 °C (0.1 mm Hg); 4-MeO, H, 132 °C (0.1 mm Hg); 4-Me, H; 115 °C (0.1 mm Hg); 4-Br, H, 130 °C (0.05 mm Hg); H, 4-MeO, 120 °C (0.05 mm Hg); H, 3-MeO, 115 °C (0.05 mm Hg); H, 4-Me, 125 °C (0.1 mm Hg); H, 3-Me, 117 °C (0.06 mm Hg); H, 4-Cl, 125 °C (0.1 mm Hg); H, 3-Cl, 120 °C (0.05 mm Hg). These had an appropriate NMR spectrum, with the characteristic OMe singlet at δ 3.1–3.2, and the NMe singlet at δ 2.7–2.9. Satisfactory elemental analyses were obtained.

Products. Products were determined by comparison of the UV spectra obtained upon complete hydrolysis of the anilide acetals with those obtained from authentic samples or mixtures of samples. In several cases the hydrolyzed solutions were extracted with ether, and after removal of solvent, an NMR spectra obtained. Good agreement was seen between the two methods.

Kinetics. Kinetics experiments at high pH were carried out on a Unicam SP 1800 spectrophotometer, and at low pH on a Durrum Gibson stopped-flow spectrophotometer. In the latter case, the experiments were conducted by adding the anilide acetal to an 0.005 M NaOH solution, which had been thermostated in an external water bath, and rapidly loading this into the stopped-flow instrument and mixing with excess buffer or HCl solution. Wavelengths employed corresponded to the λ_{max} of the methyl benzoate product: 232 nm, unsubstituted; 255 nm, 4-$\mathrm{MeOC_6H_4}$; 245 nm, 4-$\mathrm{MeC_6H_4}$; 248 nm, 4-$\mathrm{BrC_6H_4}$. With the exception of solutions near pH 7 (see later), plots of ln $(A_\infty - A)$ were excellently linear, and rate constants were obtained as their slopes.

Conditions for the kinetic experiments were 50% by volume dioxane:water, 25 °C, and ionic strength 0.1 maintained with NaCl. The pK_a values of the buffers were determined under these conditions, by measuring the pH of solutions made with different buffer ratios. The pH was measured on a Beckmann Research pH meter, and corrected by adding 0.15 to the meter reading. This factor is based on the observed meter reading of 2.15 of a 0.01 M HCl, 0.09 M NaCl solution in 50% dioxane. The hydroxide ion concentration was determined from the observed pH and a pK_w of 14.5, determined from the measured pH of 12.5 of a 0.01 M NaOH solution.

Results

Products. Initial Mode of Cleavage. Products can be accounted for in terms of an initial C–O cleavage reaction in base solutions (pH >10), producing an *O,N*-dimethyl-*N*-arylbenzimidatonium ion and methanol, and an initial C–N cleavage reaction in neutral and acid solutions (pH <9), producing an aryl dimethoxy carbocation and aniline (see eq 4). These cations are not stable, but are themselves hydrolyzed more rapidly than they are formed. The benzimidatonium ions yield products derived from both loss of amine (methyl benzoate and aniline) and loss of alcohol (*N*-methylbenzanilide and methanol).[4] The intermediacy of the benzimidatonium ion is established by the observation than an authentic sample of the cation as its trifluoromethanesulfonate salt hydrolyzes rapidly in base to the same product mixture.

In neutral and acid solutions the products are methyl benzoate, aniline, and methanol. These could in principle be derived from an initial C–O cleavage reaction forming imidatonium ion, since in nonbasic solutions this ion hydrolyzes only to ester and aniline. This can be ruled out, however, since with the exception of base solutions, the benzimidatonium ion undergoes hydrolysis considerably more slowly than the initial reaction of the anilide acetal,

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(1) McClelland, R. A. *J. Am. Chem. Soc.* **1978**, *100*, 1844–1849.

(2) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581–603.

(3) (a) A preliminary account of this work has been given.[3b] (b) McClelland, R. A.; Somani, R. *J. Chem. Soc., Chem. Commun.* **1979**, 407–408.

(4) (a) Two competing modes of cleavage in the base hydrolysis of tertiary imidatonium ions have been observed previously.[4b,c] (b) Deslongchamps, P.; Lebreux, C.; Taillefer, R. *Can. J. Chem.* **1973**, *51*, 1665–1669. (c) Smith, V. F.; Schmir, G. L. *J. Am. Chem. Soc.* **1975**, *97*, 3171–3177.

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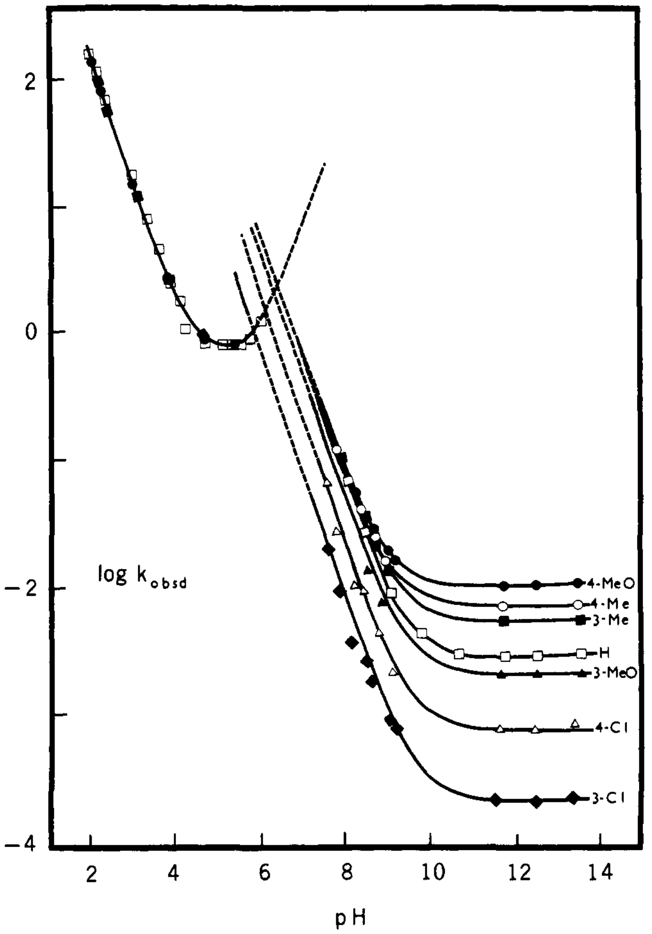


Figure 1. Observed rate constants for $PhC(OMe)_2NMeC_6H_4X$. Values in acid solution (pH <6) are based on extrapolation to zero buffer concentration. Conditions—50% dioxane:water, 25 °C, ionic strength 0.1.

Table I. Rate Constants for the Primary Cleavage of Anilide Acetals $XC_6H_4C(OMe)_2NMeC_6H_4Y$ (25 °C, 50% Dioxane:Water, Ionic Strength 0.1)

X	Y	k_0^{C-O}, s^{-1}	$k_{H^+}^{C-N}$, $M^{-1}\ s^{-1}$
4-MeO	H	0.0075	4.0×10^7
4-Me	H	0.0053	1.7×10^7
H	H	0.0034	7.5×10^6
4-Br	H	0.0017	1.1×10^6
H	4-MeO	0.013	8.6×10^6
H	4-MeO	0.0084	8.8×10^6
H	3-Me	0.0065	9.0×10^6
H	3-MeO	0.0024	5.6×10^6
H	4-Cl	0.00096	2.5×10^6
H	3-Cl	0.00025	8.6×10^5

and thus it would be detected if it were formed. The estimate can be made that less than 2% of imidatonium ion is formed at pH <8. This number is based on the observation that following the rapid UV spectral change associated with the anilide acetal reaction (see Kinetics), there is no further absorbance change which could be attributed to the imidatonium ion undergoing its slower hydrolysis. The ion $PhC^+(OMe)NMePh$ for example undergoes hydrolysis at pH <7 with a half-life of the order of 30 min, accompanied by a 150% absorbance increase at 232 nm. With $PhC(OMe)_2NMePh$, the products are formed within 30 s at pH 7 and no further slow absorbance increase at 232 nm is observed.

Kinetics. First-order rate constants for the hydrolysis of the anilide acetals were obtained by following the increase in absorbance at the λ_{max} of the benzoate ester product. (The anilide acetals have a UV spectrum which resembles that of the corresponding aniline, and kinetic studies using wavelengths near the aniline λ_{max} result in much smaller absorbance changes.) Observed rate constants are depicted as a function of pH in Figures 1 and 2. At high pH, the behavior of eq 1 is observed; values of k_0^{C-O} and $k_{H^+}^{C-N}$ are given in Tables I and II. We were unable to

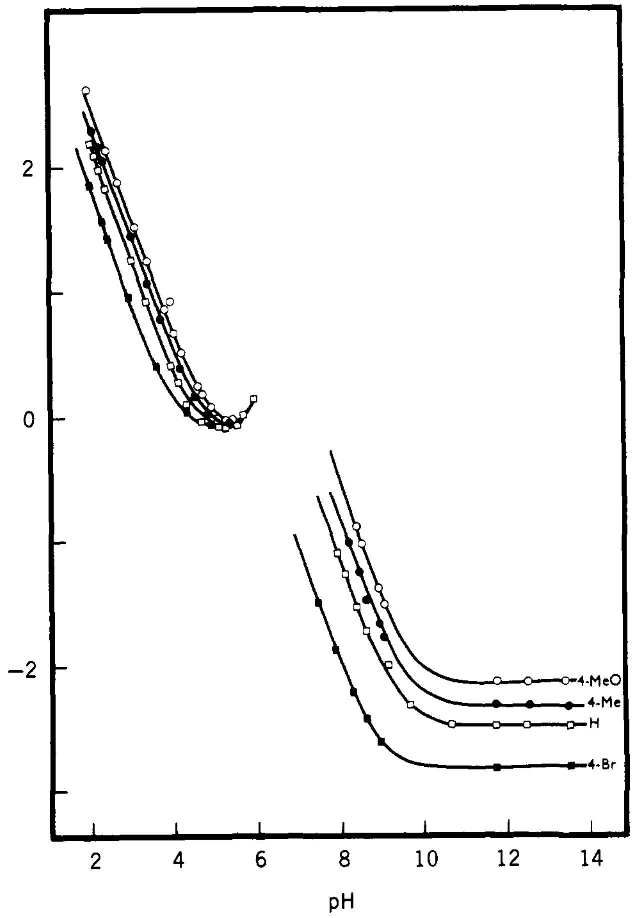


Figure 2. Observed rate constants for $XC_6H_4C(OMe)_2NMePh$.

Table II. Values of $k_{C-O}{}^0$ for $PhC(OMe)_2NMePh$ in Dioxane:Water Mixtures

% dioxane	$k_{C-O}{}^{0,a}$ s^{-1}	% dioxane	$k_{C-O}{}^{0,a}$ s^{-1}
30	5.0×10^{-2}	60	6.5×10^{-4}
40	1.6×10^{-2}	70	1.1×10^{-4}
50	3.4×10^{-3}	75	4.9×10^{-5}

[a] Value of k_{obsd} measured in 0.05 M NaOH, 0.05 M NaCl.

$$k_{obsd}(pH > 7) = k_0^{C-O} + k_{H^+}^{C-N}[H^+] \qquad (1)$$

observe buffer catalysis in this region. For example, with $PhC(OMe)_2NMeC_6H_4$-3Cl in 1 M Tris buffer and 1 M cacodylic acid buffer (1:1 buffer ratio), no significant decrease in rate is observed on buffer dilution. (If the estimate 0.001 $M^{-1}\ s^{-1}$ is made for the maximum rate constant for cacodylic acid catalysis, using the H_3O^+ rate constant, the Brønsted α must be greater than 0.9.)

In acid solutions a break in kinetic behavior is observed, and the rate constants now obey eq 2. Significant catalysis by both

$$k_{obsd}(pH < 6) = k_{H^+}{}^d[H^+] + k_0{}^d + k_{OH^-}{}^d[OH^-] \qquad (2)$$

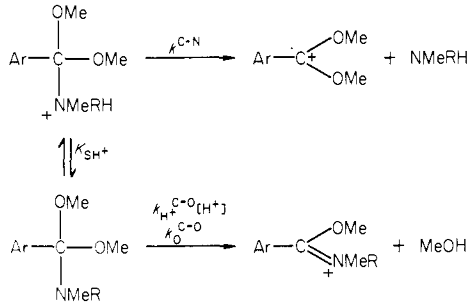
the acid and base component of the buffer is also observed. A further key observation is that in the series $PhC(OMe)_2NMeAr'$ values of k_{obsd} at low pH are within experimental error independent of the nature of Ar′ (Figure 1). For $PhC(OMe)_2NMeAr'$ values of the rate constants $k_{H^+}{}^d$, $k_0{}^d$, and $k_{OH^-}{}^d$ are respectively 1.9×10^4 $M^{-1}\ s^{-1}$, 0.6 s^{-1}, and 4×10^8 $M^{-1}\ s^{-1}$.

Near pH 7 non-linear first-order kinetic plots are observed. Analysis reveals that the absorbance–time data can be fit by the equation[5,6] for formation of product C in two consecutive first-order reactions with nearly equal rate constants, where the rate constants are extrapolated from high pH and low pH (eq 3).

$$\mathrm{A} \xrightarrow{k_{\mathrm{obsd}}(\mathrm{pH}>8)} \mathrm{B} \xrightarrow{k_{\mathrm{obsd}}(\mathrm{pH}<6)} \mathrm{C} \qquad (3)$$

Discussion

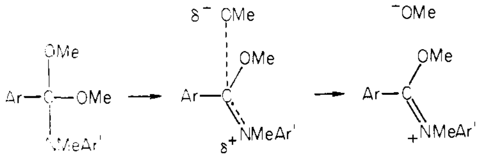
Anilide Acetal. Primary Cleavage. Depicted in eq 4 is the



(4)

general scheme previously proposed[1] for the primary decomposition pathways of an amide acetal. The general features are, in base, a pH independent C–O cleavage reaction, probably occurring by simple ionization of the C–O bond,[1,7] and in acid, two competing reactions, C–N cleavage of the N-protonated substrate and H$^+$-catalyzed C–O cleavage of the neutral substrate. The latter reactions are kinetically equivalent, their relative importance being given by $(\mathrm{C{-}O/C{-}N})_{\mathrm{acid}} = k_{\mathrm{H^+}}{}^{\mathrm{C-O}}(K_{\mathrm{SH^+}}/k^{\mathrm{C-N}})$. One of the more interesting observations made with ArC(OMe)$_2$NMe$_2$ is that there is a close competition between these acid reactions. The unsubstituted system for example has a $(\mathrm{C{-}O/C{-}N})_{\mathrm{acid}}$ ratio near unity.

We propose that the general features of this mechanism also apply with the anilide acetals. A pH independent C–O cleavage reaction resulting in imidatonium ion is observed at high pH. The heterolytic nature of this reaction is suggested by the accelerating effect of electron donors in both aromatic rings. For ArC(OMe)$_2$NMePh the ρ value based on $k_{\mathrm{C-O}}{}^0$ is -1.3, while for PhC(OMe)$_2$NMeAr′ a plot of log $k_0{}^{\mathrm{C-O}}$ vs. pK_a(Ar′NH$_2$) has a slope of 0.92. This latter observation in particular suggests a relatively late transition state with a substantial development of positive charge on nitrogen. Also of significance is the observation



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that a plot of log $k_{\mathrm{C-O}}{}^0$ (Table II) vs. the solvent Y value[8] is linear with a slope of 1.05. It can also be noted that in this reaction PhC(OMe)$_2$NMePh is about 10^4 less reactive than PhC(OMe)$_2$NMe$_2$.[9] This difference is obviously associated with the decreased availability of the nitrogen lone pair in the aniline derivative.

The changeover to the acid reaction occurs with ArC(OMe)$_2$NMeAr′ near pH 9–10, and unlike the situation with ArC(OMe)$_2$NMe$_2$, only C–N cleavage occurs. The reason for this is fairly obvious. As noted above substitution of a methyl group by aryl slows the C–O cleavage reaction (decreases $k_{\mathrm{H}}{}^{\mathrm{C-O}}$). In the C–N cleavage reaction, nitrogen protonation is made more difficult with the aryl group present, but once protonated the neutral aniline is a much better leaving group than a neutral amine. The net result is difficult to predict. The following analysis shows that the cleavage step is the more affected, and the overall C–N cleavage is faster for ArC(OMe)$_2$NMeAr′ than for ArC(OMe)$_2$NMe$_2$.

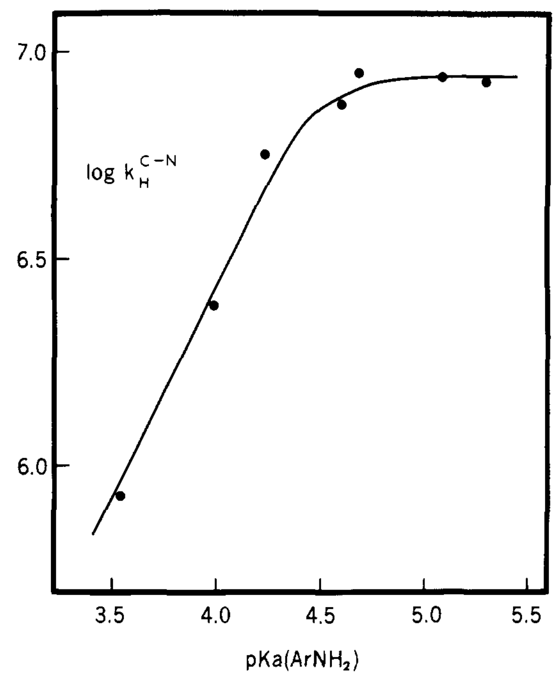

Figure 3. Plot of log $k_{\mathrm{H^+}}{}^{\mathrm{C-N}}$ for PhC(OMe)$_2$NMeAr vs. pK_a (ArNH$_2$).

The apparent H$^+$ catalyzed C–N cleavage is a specific acid catalyzed reaction on the neutral substrate, and the observed second-order rate constant $k_{\mathrm{H^+}}{}^{\mathrm{C-N}}$ is equal to $k^{\mathrm{C-N}}/K_{\mathrm{SH^+}}$. For PhC(OMe)$_2{}^+NMe_2$H p$K_{\mathrm{SH^+}}$ is around 4 in 50% dioxane:water,[1] and if the assumption is made that the substitution of Me by Ph has the same effect in an amide acetal as in an amine, p$K_{\mathrm{SH^+}}$ for PhC(OMe)$_2{}^+$NMePhH should be of the order of -1. This produces a value of $k^{\mathrm{C-N}}$ of the order of 10^8 s^{-1}, while a value of 1–10 s^{-1} can be estimated for PhC(OMe)$_2{}^+$NMe$_2$H.[10] Thus, substitution of methyl by phenyl produces about a five order of magnitude decrease in the amount of protonated anilide acetal available for C–N cleavage, but this is more than overcome by a seven–eight order of magnitude increase in the cleavage rate.

Unusual reactivity associated with a neutral aniline leaving group as compared to a neutral amine leaving group has been observed previously[11,12] where it was suggested to be due to the delocalization of the lone pair into the aromatic ring in the transition state for the cleavage. The rate constant $k^{\mathrm{C-N}}$ estimated above is in fact sufficiently large that the possibility exists, particularly when electron withdrawing substituents are present in the aniline, that a cation such as PhC(OMe)$_2{}^+$NMeAr′H may undergo breakdown at a rate faster than the diffusion limit. An indication that something unusual is occurring with the present system is seen in the plot of log $k_{\mathrm{H^+}}{}^{\mathrm{C-N}}$ for PhC(OMe)$_2$NMeAr′ vs. pK_a(Ar′NH$_2$) which is significantly curved (Figure 3). Electron-donating substituents have little effect on the rate while electron-withdrawing substituents show a significant rate retardation, with the limiting slope approaching unity. This behavior suggests a change in rate-determining step or a change in mechanism. A simple explanation[13] involves a change from

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

(6) Ahmad, M.; Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *J. Am. Chem. Soc.* **1979**, *101*, 2669–2677.

(7) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476–1488; Ferraz, J. P.; Cordes, E. H. *Ibid.* **1979**, 1488–1491.

(8) Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846–854; Fainberg, A. H.; Winstein, S. *Ibid.* **1956**, *78*, 2770–2777.

(9) PhC(OMe)$_2$NMe$_2$ is not sufficiently stable in basic 50% dioxane:water for a value of $k_0{}^{\mathrm{C-O}}$ to be measured directly (by conventional spectroscopy), although an estimate of 10 s^{-1} can be made based on the behavior of 4-NO$_2$C$_6$H$_4$(OMe)$_2$NMe$_2$.[1]

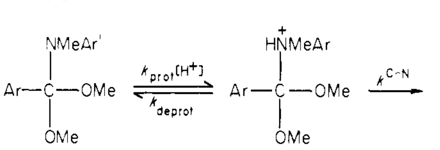
(10) See: McClelland, R. A.; Potter, J. P. *Can. J. Chem.* **1980**, *58*, 2318–2325.

(11) Klüger, R.; Chin, J.; Choy, W. W. *J. Am. Chem. Soc.* **1979**, *101*, 6976–6980.

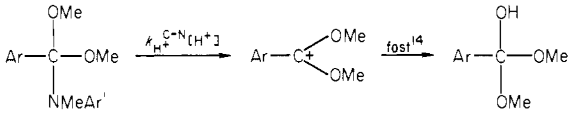
(12) Ewing, S. P.; Lockshon, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 3072–3084.

(13) This simple explanation has the drawback that since p$K_{\mathrm{SH^+}}$ is less than zero, deprotonation is likely to be diffusion limited. Other possibilities include a change to a rate-determining diffusion apart from the aniline and the dialkoxy carbocation, or a change to a concerted proton transfer and C–N cleavage.[12]

rate-determining breakdown of the protonated anilide acetal to rate-determining protonation as k^{C-N} becomes greater than k_{deprot}.



Change in Slow Step. In more acidic solutions the reaction products remain the same as those observed at pH 7-9, but there is a significant change in the nature of the kinetics. This behavior can be explained by a change in the rate-determining step for product formation. At high pH the formation of the aryl dimethoxy carbocation (eq 6) is slower than the subsequent steps leading to product, and the kinetics refer to that process. At low pH, however, the decomposition of the hemiorthoester (eq 7) becomes slower, the steps leading to this species being more rapid. Addition of anilide acetal to acid solutions results in the rapid formation of hemiorthoester, and the kinetics of product formation refer to the kinetics of hemiorthoester decomposition.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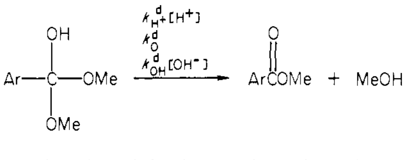
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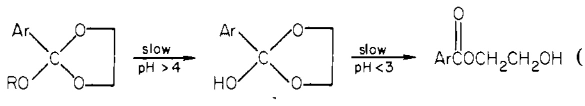
The principal piece of evidence for the changeover is the observation that in acid solutions rates are independent of the aniline portion of the anilide acetal. This implies that the aniline group is not present in the kinetically observed step, as is obviously the case if eq 7 is rate determining. This argument has previously been applied to dioxolane ortho ester hydrolysis,[6] where a cyclic hemiorthoester accumulates in acid solutions, and the rate becomes independent of the exocyclic alkoxy group.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Corroborative evidence with both systems comes in the observation of a changeover region, near pH 7 in the present case, where the rates of the two stages crossover, as indicated in Figure 1 for example by the intersections of the dashed lines. In this crossover region product formation is not a first-order process, but the data can be fit by the equations for two consecutive first-order reactions. It can also be pointed out that the kinetic behavior observed in acid solutions is fully consistent with a process of hemiorthoester decomposition. These kinetics should be similar to those associated with the decomposition or formation of carbonyl hydrates or hemiacetals, where general catalysis by both acids and bases is observed.[15,16]

Table III. Rate Constants for $PhC(OMe)_2OH$ Decomposition and Formation from $PhC(OMe)_2NMePh$

pH	$k_{formation}$,[a] s^{-1}	k_{decomp},[b] s^{-1}	$k_{formation}/k_{decomp}$
1	7.5×10^5	1.9×10^4	390
3	7.5×10^3	19	380
5	75	0.9	80
7	0.75	13	0.06
9	0.0075	1.3×10^3	6×10^{-6}

[a] $7.5 \times 10^6[H^+]$; see also ref 17. [b] $1.9 \times 10^4[H^+] + 0.6 + 1.26 \times 10^{-6}/[H^+]$.

The changeover occurs for the same reason here as it does in the dioxolane system of eq 8. Hemiorthoester decomposition involves hydronium ion catalysis, water catalysis, and hydroxide ion catalysis, while its formation from anilide acetal involves only hydronium ion catalysis.[17] Given a situation where the value of k_{H^+} for formation is larger than the value of k_{H^+} for decomposition, a changeover will occur in the relative overall rates because of the additional modes of decomposition. This is illustrated in numerical terms in Table III where the rates of $PhC(OMe)_2OH$ decomposition and its formation from $PhC(OMe)_2NMePh$ are compared at various acidities.

It can also be noted that unlike the dioxolane ortho esters of eq 8, a trimethyl orthobenzoate does not exhibit a changeover, the dialkoxy carbocation forming stage being rate determining throughout. This was suggested previously from the fact that there is no change in the kinetic behavior of $PhC(OMe)_3$ between pH 7 and 1,[18] and with a number now available for $PhC(OMe)_2OH$ decomposition it can be demonstrated unequivocally. The second-order rate constant k_{H^+} for the formation of methyl benzoate from trimethyl orthobenzoate is 7 M^{-1} s^{-1} in 50% dioxane:water.[19] This number is three orders of magnitude smaller than the value of k_{H^+} for $PhC(OMe)_2OH$ decomposition. Thus even in strong acid solutions, the hemiorthoester forms for trimethyl orthobenzoate 1000 times more slowly than it decomposes, and the formation process is rate determining. The feature of the anilide acetal which makes possible the observation of a change in rate-determining step is the extreme lability of the C-N bond in the presence of acid.

Acknowledgment. Financial support of the Natural Sciences and Engineering Research Council of Canada and the Research Corporation is gratefully acknowledged.

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(14) (a) The rate of hydration of $PhC^+(OMe)_2$ has been estimated to be 10^5 s^{-1}.[14b] (b) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7031-7036.

(15) Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1-29.

(16) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444-5459.

(17) The rate of formation of hemiorthoester from anilide acetal will not be first order in H^+ concentration in all solutions, but will level off when the anilide acetal becomes protonated.

(18) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7027-7031.

(19) (a) This was measured in 0.1 M HCl, using stopped-flow spectroscopy. The value in water is 56 M^{-1} s^{-1}.[19b] (b) Bull, H. G.; Koehler, K.; Pletcher, T. C.; Ortiz, J. J.; Cordes, E. H. *J. Am. Chem. Soc.* **1971**, *93*, 3002-3011.