

Anilide Acetal Hydrolysis. The Tetrahedral Intermediate of an Alcohol Interchange Reaction

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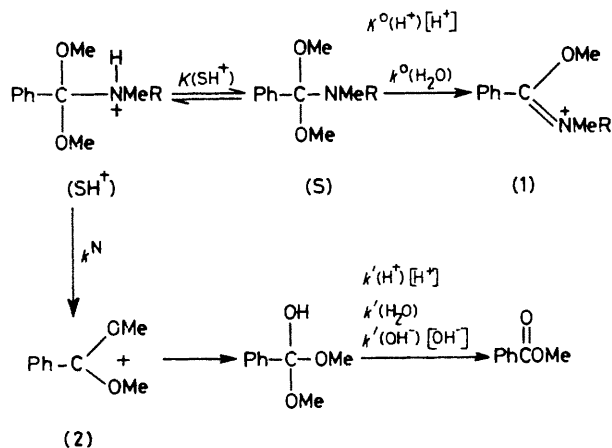
Summary The hydrogen ortho ester $\text{PhC}(\text{OMe})_2\text{OH}$ is detected as a transient intermediate in the hydrolysis of the anilide acetals $\text{PhC}(\text{OMe})_2\text{NMeAr}$.

HYDROLYSIS of the amide acetals $\text{ArC}(\text{OMe})_2\text{NMe}_2$ has recently been established to occur *via* the mechanism in the Scheme.¹ Its features are uncatalysed and H^+ -catalysed

reactions resulting in an imidate ion (1) (C–O cleavage), and C–N cleavage of the *N*-protonated amide acetal producing a dialkoxybenzylum ion (2). We report here a study of the anilide acetals $\text{PhC}(\text{OMe})_2\text{NMeAr}$. These show a similar pattern in their hydrolysis, with one important difference. In acid solutions there is a change in rate-determining step in the overall hydrolysis, and one of the more elusive metastable intermediates of mechanistic organic chemistry, $\text{PhC}(\text{OMe})_2\text{OH}$, is formed as a transient species.

The anilide acetals were prepared by reaction of the benzanilides with methyl trifluoromethanesulphonate, followed by treatment of the imidate salts so obtained with sodium methoxide in methanol. Products were analysed by u.v. spectral comparisons, and by isolation and n.m.r. spectroscopy. Kinetics were followed using conventional and stopped-flow u.v. spectroscopy, by monitoring the increase in absorbance at λ 232 nm, λ_{max} for methyl benzoate. Except in the region of the cross-over point (see later) accurate first-order kinetics were obtained. The Figure depicts first-order rate constants in 50% dioxan– H_2O mixtures. Buffer catalysis is observed at low pH (<6) and the points on the Figure are based on extrapolation to zero buffer concentration. No buffer catalysis is observed at high pH.

The pH independent region at high pH represents uncatalysed C–O cleavage, as before,¹ with $k_{\text{obs}} = k^0(\text{H}_2\text{O})$.



SCHEME

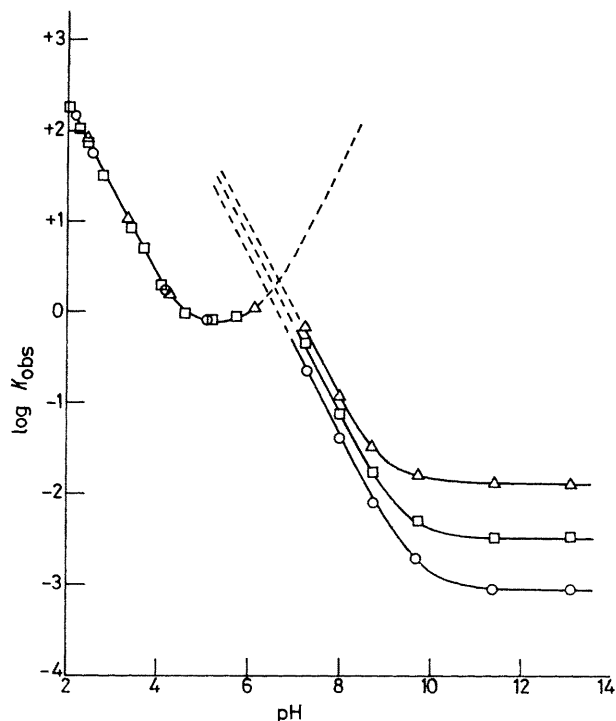


FIGURE. First-order rate constants in the hydrolysis of $\text{PhC}(\text{OMe})_2\text{NMeAr}$; Ar = $4\text{-ClC}_6\text{H}_4$ (O), Ph (\square), and $4\text{-MeOC}_6\text{H}_4$ (Δ). Conditions are 25°C , ionic strength = 0.1 , 50% dioxan-water.

Products here are methyl benzoate, substituted aniline, and substituted anilide, in proportions identical to those obtained starting directly with the imidate ion (which is not stable at high pH). In the region pH 7–10 the hydrolysis becomes first-order in H^+ concentration, and the nature of the products changes such that only methyl benzoate and aniline are formed. No imidate ion or products derived from its hydrolysis can be detected. The acid hydrolysis of the anilide acetals must therefore occur only with C–N cleavage, acid catalysed C–O cleavage [the $k^0(\text{H}^+)$ process] being unimportant. In this pH region $k_{\text{obs}} = k^{\text{N}}[\text{H}^+]/\{[\text{H}^+] + K(\text{SH}^+)\} = \text{ca. } \{k^{\text{N}}/K(\text{SH}^+)\} [\text{H}^+]$ since $[\text{H}^+] \ll K(\text{SH}^+)$.†

As the pH is further decreased methyl benzoate and aniline are still the only observable products, but a sharp break in the kinetic behaviour is observed, one of the more noteworthy features being that the rates become completely independent of the substituent in the aniline portion. We propose a change in the rate-limiting step in the overall C–N cleavage reaction. At $\text{pH} > 7$ the cleavage itself is slow, with the subsequent steps resulting in methyl benzoate being fast. At $\text{pH} < 6$ one of the steps which occurs after aniline departure becomes the slow step. The

cross-over‡ occurs at $\text{pH ca. } 6.5$, and is clearly seen by the intersection of the dotted lines in the Figure. Candidates for the slow step in acid are the hydration of the dialkoxy benzylium ion and the decomposition of the hydrogen ortho ester. The absence of a u.v. signal due to the ion, coupled with the actual form of the rate–pH profile, suggest the latter.

Thus, addition of anilide acetal to acid solutions results in the rapid accumulation of hydrogen ortho ester, and what is observed is its decomposition. The hydrogen ortho ester is the tetrahedral intermediate of a degenerate alcohol interchange reaction, the methanolysis of methyl benzoate. Cyclic hydrogen ortho esters are found as stable species in several instances;² they have also been observed as transient intermediates in the hydrolysis of suitable precursors.³ However, only two acyclic examples are known, the anionic species $\text{CF}_3\text{C}(\text{OMe})_2\text{O}^-$ which is formed when $\text{CF}_3\text{CO}_2\text{Me}$ is added to MeO^- – MeOH ,⁴ and $\text{HC}(\text{OMe})_2\text{OH}$ which is observed at low temperatures as an intermediate in the hydrolysis of $\text{HC}(\text{OMe})_2\text{OAc}$.⁵ Our example represents the first case of the detection of an acyclic hydrogen orthobenzoate, and has the important feature of providing a detailed kinetic analysis for its decomposition. The rate–pH profile (Figure) gives the rate law $k_{\text{obs}} = k'(\text{H}^+) [\text{H}^+] + k'(\text{H}_2\text{O}) + k'(\text{OH}^-) [\text{OH}^-]$, with $k'(\text{H}^+) = 1.9 \times 10^4 \text{ l mol}^{-1} \text{ s}^{-1}$, $k'(\text{H}_2\text{O}) = 0.6 \text{ s}^{-1}$, and $k'(\text{OH}^-) = \text{ca. } 5 \times 10^8 \text{ l mol}^{-1} \text{ s}^{-1}$ (50% dioxan-water, 25°C , $\mu = 0.1 \text{ M}$). The decomposition is also catalysed by general acids and bases.

Our results show that the breakdown of the tetrahedral intermediate is not exceedingly rapid, except in base. The failure to observe directly this type of intermediate in other systems stem from the fact that the steps leading to it are considerably slower, so that it can only exist in a low steady-state concentration. For example, the rate of hydrolysis of $\text{PhC}(\text{OMe})_3$ has the expected form, $\text{rate} = k''(\text{H}^+) [\text{H}^+] [\text{PhC}(\text{OMe})_3]$ with a value of $k''(\text{H}^+)$ in 50% dioxan of $7.0 \text{ l mol}^{-1} \text{ s}^{-1}$. This is three orders of magnitude smaller than the value of $k'(\text{H}^+)$ for $\text{PhC}(\text{OMe})_2\text{OH}$ decomposition. Therefore, $k''(\text{H}^+)$ must refer to the normal rate-limiting step, the generation of the intermediate dialkoxybenzylium ion from the ortho ester. Moreover $\text{PhC}(\text{OMe})_2\text{OH}$ decays at least three orders of magnitude more rapidly than it is formed, and cannot be detected. With the anilide acetals however, the apparent second-order rate constants for dialkoxybenzylium ion formation [$k^{\text{N}}/K(\text{SH}^+)$] are large, $\text{ca. } 10^7 \text{ l mol}^{-1} \text{ s}^{-1}$. Thus in acid solutions, where hydroxide ion catalysis of the breakdown of $\text{PhC}(\text{OMe})_2\text{OH}$ is unimportant, this intermediate is formed more rapidly than it decomposes.

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† Amide acetals are 4–6 pK units less basic than analogous amines (ref. 1). The value of pK_{SH^+} for an anilide acetal should therefore be $\text{ca. } 0$ – 2 .

‡ In the vicinity of the cross-over point the kinetic plots are in fact biphasic. The system is accurately described here by the kinetic equations for two consecutive first-order reactions with nearly equal rate constants.

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