

# Acetophenone Hemiacetal Build-Up Studied by Multi-Mixing Stopped-Flow

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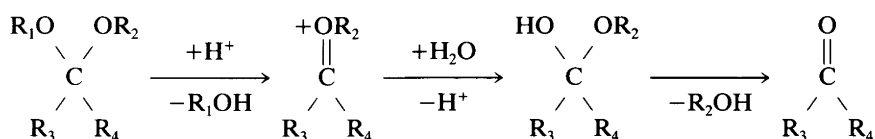
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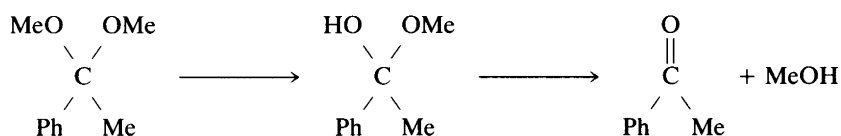
We wish to report on the potential of a new multi-mixing stopped-flow technique in the study of breakdown of hemiacetals in aqueous solution.

The hydrolysis of acetals is now well established to proceed via oxocarbenium and hemiacetal intermediates (Scheme 1).<sup>1</sup> While the hydration reaction of the oxocarbenium ion is normally very fast, there are several examples where the rates of the first stage and third stage are such that the hemiacetal form accumulates during the hydrolysis under some conditions, so that the third stage is partially or wholly rate-limiting in the overall hydrolysis. This situation has normally been demonstrated for mixed acetals where the presence of a good leaving group makes the first stage rapid,<sup>2,3</sup> or for highly strained cyclic acetals<sup>4</sup> and epoxy ethers.<sup>5</sup> For symmetrical dimethyl and diethyl acetals, hemiacetal build-up has only been shown with benzaldehyde derivatives.<sup>6,7</sup> In this paper, we show that it also occurs in a more reactive case, viz. the dimethyl acetal of acetophenone.

When this acetal is hydrolyzed at pH  $\approx$  6 in aqueous solution, with kinetics being followed via the appearance of acetophenone with absorption at 240 nm, excellent first-order behaviour is observed, with rate constants proportional to H<sup>+</sup> concentration and  $k_{H^+} = 8.0 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ . However, in HCl solutions there is a lag in the absorbance increase at the beginning of the reaction, and strict adherence to first-order kinetics is not observed. This behaviour is characteristic of the formation of a product of two consecutive first-order reactions whose rate constants are not substantially different (Scheme 2).<sup>8</sup> A double exponential equation describes this system, and indeed such an equation provides an excellent fit to the experimental data. This pattern of behaviour is observed in all HCl solutions (pH < 3.3). The two rate constants obtained in the fit are proportional to H<sup>+</sup> concentration, giving second-order rate constants at 25°C of  $(7.5 \pm 0.5) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$  and  $(1.0 \pm 0.2) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ . The smaller value can be assigned to H<sup>+</sup> catalysis of the first stage. This value is the same as



Scheme 1.



Scheme 2.

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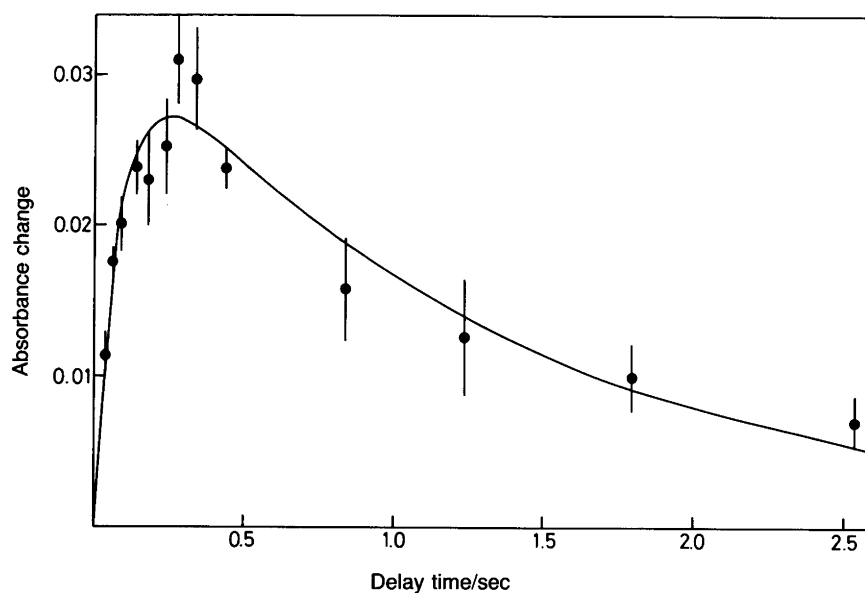


Fig. 1. Absorbance change when a solution of acetophenone dimethyl acetal in 0.001 M HCl is quenched with an equal volume of phosphate buffer (total concentration = 0.4 M) of pH 7.3. The delay time is the interval between the initial mixing of acid and base to prepare the 0.001 M HCl solution, and the mixing with quenching buffer. The points are experimental, with vertical lines representing two standard deviations. The line is theoretical (see text).

that obtained at higher pH where base catalysis of the breakdown of the hemiacetal makes that stage very fast. The larger rate constant therefore corresponds to  $H^+$  catalysis of hemiacetal breakdown.

This analysis predicts that the hemiacetal accumulates to a maximum of about 6% of the initial concentration of acetal in the HCl solutions. To verify this, partially hydrolyzed solutions were neutralised to pH 6.5–9.5 by the addition of an appropriate buffer. This has the effect of quenching the first stage, which is only  $H^+$ -catalyzed, while hemiacetal that has accumulated goes on to product. A multi-mixing stopped-flow spectrophotometer (Hi-Tech Scientific SF 53) was employed. This provided the mixing of a solution of the acetal in base (0.002 M NaOH) with excess acid (0.004 M HCl) to initiate the hydrolysis. After a short time delay the neutralising buffer was mixed with the reaction solution. This experiment did result in small, first-order, absorbance increases representing the formation of ketone from the hemiacetal that had accumulated before the quench. The dependency of the amplitude of this increase on the time delay is shown in Fig. 1. The amplitude increases rapidly to a maximum at about 0.3 seconds and then falls off more slowly. This increase gives a measure of the amount of hemiacetal in the acid at the time of quenching. As shown by the solid line in Fig. 1, the behaviour is that expected on the basis of the two  $H^+$  catalytic coefficients. This curve was calculated from the equation for the intermediate of two consecutive reactions,<sup>8</sup> absorbance =  $A(e^{-k_1t} - e^{-k_2t})$  using rate constants  $k_1 = 0.75 \text{ s}^{-1}$  and  $k_2 = 10 \text{ s}^{-1}$  appropriate to 0.001 M HCl, and adjusting the single pre-exponential factor  $A$ .

In the experiments described above, the rate constant for each time-delay was the same. This is expected, since this represents the breakdown of whatever amount of hemiacetal is present. Rate constants did, however, vary with pH and buffer concentration, showing the expected catalysis by the base component of the buffer and  $OH^-$ . At the high pH required to quench the first stage, catalysis by buffer acids and water was not observed. Catalytic coefficients are listed in Table 1. A Brønsted plot passes satisfactorily through all the points, with the exception of hydroxide, which shows its normal small positive deviation.<sup>9</sup> The  $\beta$  value is 0.61, similar to values for the base-catalyzed breakdown of  $\alpha$ -bromoacetophenone hemiacetals.<sup>10</sup>

Table 1. Rate constants (25.0°C, ionic strength = 0.5) for the base-catalyzed breakdown of acetophenone methyl hemiacetal.

Catalyst	$k_B/M^{-1} \text{ s}^{-1}$
$MeCO_2^-$	~0.3
$Me_2AsO_2^-$	2.6
$HPO_4^{2-}$	18
$MePO_3^{2-}$	26
$(HOCH_2)_3CNH_2$	69
$H_2BO_3^-$	$3.8 \times 10^2$
$NH_3$	$1.02 \times 10^3$
$OH^-$	$6.4 \times 10^6$

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