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First Experimental Evidence for a Synperiplanar Stereoelectronic Effect in the Acid Hydrolysis of Acetal

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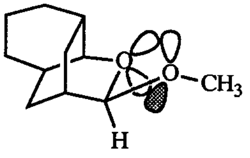
ABSTRACT: Tricyclic acetal 1 in which the ring oxygen has an electron pair synperiplanar to the C—OMe bond can be readily hydrolyzed with HCl 0.1N.

Acetals are readily hydrolyzed provided that one of the oxygen atom has an electron lone pair oriented antiperiplanar to the leaving group.[1-3] In principle, synperiplanar[4] oxygen lone pairs could play a similar role in influencing reaction rates and have been suggested to be operative in the hydrolysis of a rigid tricyclic β-glycoside[5] and in cyclic amidines.[6] Recent calculations by Grein[7] indicate that the *syn* and the antiperiplanar electronic effect are energetically similar, however the former process is sterically disfavored over the latter because eclipsed conformers (*syn* process) are energetically higher than gauche conformers (*anti* process).

In the preceding communication,[8] we have reported the synthesis and the ozonolysis of tricyclic acetal **1** and compared its reactivity with that of axial and equatorial methoxy bicyclic acetals **2** and **3**. This work has provided experimental evidence for the existence of a synperiplanar effect. We wish now to report that a similar synperiplanar stereoelectronic effect can be operative in the hydrolysis of acetals.



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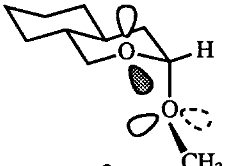

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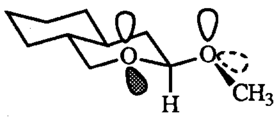

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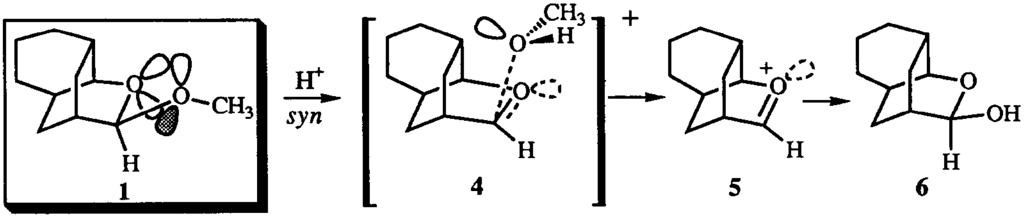
We have studied the hydrolytic behavior of tricyclic acetals **1-3**. Due to its bridged nature, tricyclic acetal **1** must exist in the conformation shown, where one lone pair of the endocyclic oxygen is synperiplanar to the C—OCH_3 bond.[9] By comparison, acetal **2** has one lone pair of the endocyclic oxygen antiperiplanar to the C—OCH_3 bond. On the other hand, the same oxygen in acetal **3** has neither a *syn* nor an *anti* lone pair periplanar to the C—OCH_3 bond.

Eikeren[10] has reported a detailed study on the acid hydrolysis of bicyclic acetals **2** and **3** and observed that the axial isomer **2** is hydrolyzed at a slightly faster rate than the equatorial isomer **3** by a factor of 1.5. The rates of hydrolysis of tricyclic acetal **1** and bicyclic acetal **2** were measured under the same conditions.[11] In competitive experiments, *the disappearance of 1 was found to be 25 times faster than that of acetal 2*. The reaction product of **1** is the expected lactol **6**. Acetal **1** being more readily hydrolyzed than acetal **2**, *this result clearly indicates that a synperiplanar stereoelectronic effect must be operative*. The higher reactivity of **1** is most likely a result of a ground state effect.[7] Considering that acetals are hydrolyzed via a late transition state,[12-14] the hydrolysis of **1** must follow the pathway **1**→**4**→**5**→**6** with transition state **4** having a geometry near the tricyclic oxenium ion **5**.



Hydrolysis of **1** could also take place via the cleavage of the tetrahydropyranyl ring. However, this pathway is not expected to compete significantly with the exocyclic cleavage shown; because recyclization of the $CH{=}OMe^+$ ion formed would be much faster than external attack by water.

Synperiplanar stereoelectronic effect being demonstrated, the hydrolysis of α and β-glycosides is presently being reexamined.[15]

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8. See following accompanying communication.
9. The preferred conformation of **1** is discussed in the following paper.
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11. Hydrolysis of acetals **1** and **2**: a mixture of 9.0 mg (0.05 mmol) of **1**, 8.5 mg (0.05 mmol) of **2** and 10.8 mg (0.1 mmol) of benzyl alcohol as an internal standard were mixed with acetone (5 mL) and water (4 mL). Hydrochloric acid (1 mL, 0.1 N) was added and the mixture was stirred at room temperature. Aliquots (5-10 µL) were analyzed by GC with a linear temperature program of 100-225°C at 25°C/min. The disappearance of acetals **1** and **2** follows first-order kinetics. Pseudo-first-order rate constants, k_1, were evaluated from the slopes of the semilogarithmic plots of normalized GC peaks. Eikeren[10]has shown that for the hydrolysis of acetals **2** and **3**, the variations of k_1 with increasing acid concentration are linear, so the second-order rate constants k_2 can be described as $k_1 = k_2[H^+]$, thus yielding the k_2 values of 12.8 $M^{-1}min^{-1}$ for acetal **1** and 0.51 $M^{-1}min^{-1}$ for acetal **2** at 25°C. This demonstrates that acetal **1** undergoes hydrolysis 25 times faster than acetal **2**.
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