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Experimental Evidence for a Synperiplanar Stereoelectronic Effect in the Ozonolysis of a Tricyclic Acetal

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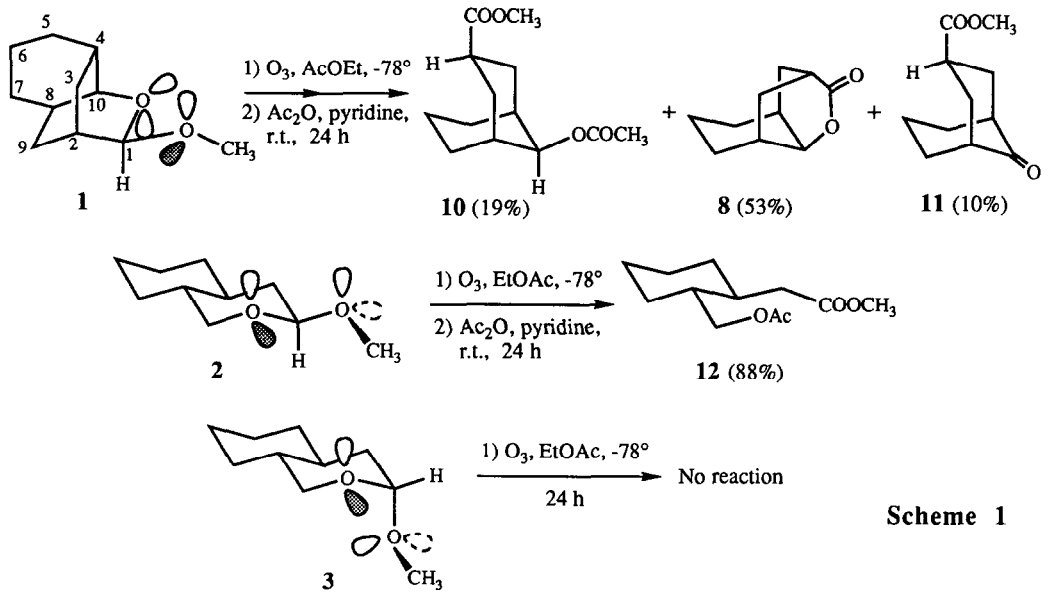
ABSTRACT: *Tricyclic acetal **1** in which the ring oxygen has one electron pair synperiplanar to the C—H bond is easily oxidized with ozone.*

Acetals react with ozone when they can take a conformation where each oxygen has an electron lone pair oriented antiperiplanar to the C-H bond.[1-2] In principle, synperiplanar[3] oxygen lone pairs could play a similar role in influencing this oxidation reaction. Recent calculations by Grein[4] indicate that the *syn* and the anti-periplanar electronic effect are energetically similar, however the former process is disfavored over the latter because eclipsed conformers (*syn* process) are higher energetically than gauche conformers (*anti* process) due to steric reasons. We wish now to report unambiguous experimental evidence for the existence of a synperiplanar effect in the oxidation of a conformationally rigid tricyclic acetal.



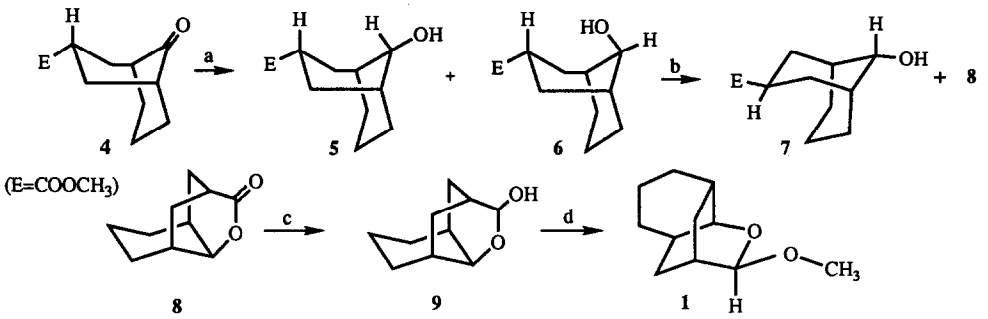
Scheme 1

We have studied the ozonolysis of methoxy tricyclic acetal **1** (Scheme 1) and compared its reactivity with that of bicyclic equatorial and axial methoxy acetals **2** and **3**. Due to its bridged nature, tricyclic acetal **1** exists in the conformation shown in Scheme 1 where the two lone pairs of the ring oxygen are oriented *syn* to the anomeric C_1—H and to the C_1—OCH_3 bonds respectively. The CH_3—O bond must also be antiperiplanar to

the C_1—C_2 bond as a result of the *exo* anomeric effect[5] (one lone pair of the OCH_3 group antiperiplanar to the ring C_1—O bond) and minimal steric interaction between the CH_3 group and the tetrahydropyran ring. Thus, by comparison, acetal **1** has one lone pair synperiplanar and one lone pair antiperiplanar to the C_1—H bond, acetal **2** has two lone pairs antiperiplanar to the C—H bond whereas acetal **3** has only the oxygen lone pair of the OCH_3 group antiperiplanar to the C—H bond in its most stable conformation.

Synthesis of acetals 1, 2, and 3

Tricyclic acetal **1** was prepared in four steps (Scheme 2) from the known bicyclic ketoester **4**.[6] Reduction of **4** with sodium borohydride gave an unseparable mixture of hydroxyesters **5** and **6** in a 2:3 ratio. Treatment of this mixture with sodium methoxide in methanol at reflux gave a mixture of **7**[7] and **8**[7] which were separated by chromatography with silica gel. Reduction of lactone **8** with diisobutylaluminium hydride provided the crystalline lactol **9**[7] which was transformed into the desired bicyclic acetal **1**[7] by the acid catalyzed reaction with methanol. Due to symmetry reasons, only racemic lactol **9** can be produced from lactone **8**. The isomeric bicyclic acetals **2** and **3** have been previously reported by Eikeren.[8]

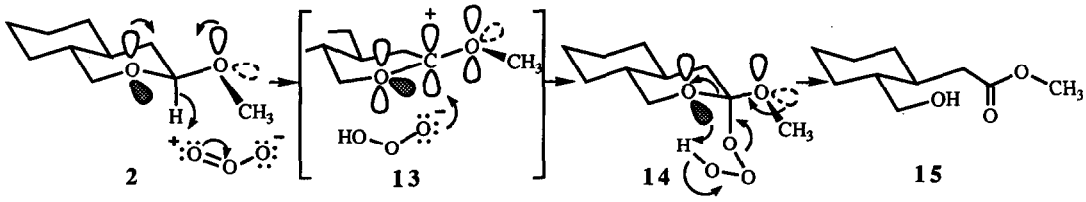


Scheme 2. a) $NaBH_4$, CH_3OH, 1 h, 87%; b) CH_3ONa, CH_3OH, reflux, 16 h, and chromatography, 20% of **7** and 57% of **8**; c) DIBAL, CH_2Cl_2, -78°C, 2 h, 92%; d) CH_3OH, $(CH_3O)_3CH$, $PTSO_3H$, 24 h, r.t., 90%.

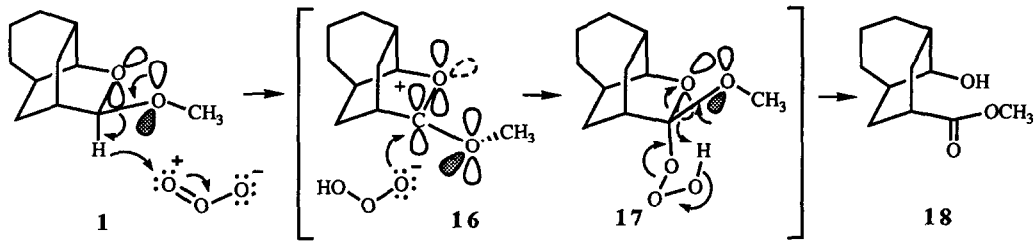
Ozonolysis: results and discussion

The ozonolysis reactions were carried out as previously reported.[1] The acetals were treated with excess ozone in ethyl acetate at -78°C, the reaction was monitored by tlc. The reaction mixture were then treated with acetic anhydride and pyridine at room temperature to isolate the corresponding hydroxyesters as their more stable acetate derivatives. The results are summarized in Scheme 1. Acetals **1** and **2** are both readily oxidized within 20 minutes at -78°C whereas acetal **3** was found to be unreactive even after 24 h (>85% recovery of starting material).[9] The ozonolysis of a 1:1 mixture of **1** and **2** monitored by G.C. showed that the rate of disappearance of **1** is 1.25 times faster than that of **2**.

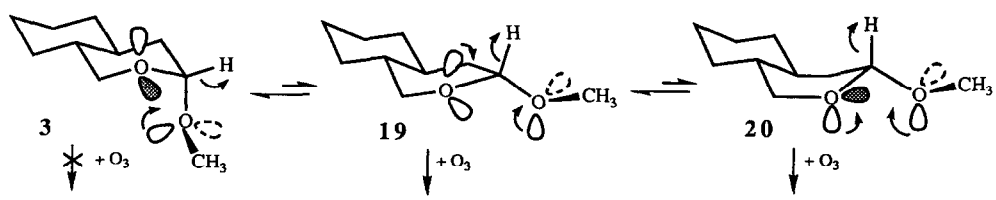
The results obtained with acetal **2** is consistent with previous reports on equatorially oriented β-glycosides[1-2] and further confirmed that when an acetal can have two lone pairs (one on each oxygen) antiperiplanar to the C-H bond, it is very reactive towards ozone. Product formation is thus explained by the formation of the hydrotrioxide intermediate **14** which breaks down to give the corresponding hydroxyester **15** isolated as the acetate derivative **12**.[9] The formation of **14** probably takes place via a hydride transfer of the anomeric hydrogen to ozone producing *in situ* the lactonium ion **13** and HO_3^- which react together.[1-2]



The successful ozonolysis of acetal **1** demonstrates that one oxygen lone pair synperiplanar and another antiperiplanar to the C—H bond is also an equally powerful stereoelectronic effect. Product formation is thus also explained by the formation of a hydrotrioxide intermediate **17** (via **16**) which collapses to give the corresponding hydroxyester **18**. This compound is then further oxidized in part to give ketoester **11**, lactonized to give lactone **8** or esterified to yield acetate ester **10**.[9] Lactone **8** could also directly come from the breakdown of intermediate **17** (again assisted by a *syn* stereoelectronic effect).



As previously reported[1-2] for axially oriented α glycosides, acetal **3** is unreactive towards ozone. This result is explained by the fact that the hydride transfer to ozone cannot take place because the ring oxygen does not have a lone pair properly oriented to expel a hydride ion, also the inductive effect of the endocyclic C—O bond should slow down the hydride transfer. The non reactivity of acetal **3** further indicates that the population of other conformers such as the half-chair **19** which has one lone pair *syn* and one lone pair *anti* to the C—H bond, or the twist-boat conformer **20** which has two lone pairs *anti*, must be extremely low at -78°C. Indeed, conformers **19** and **20** having each two lone pairs properly oriented should be reactive toward ozone. However, the ozonolysis reaction being a bimolecular process, the rate of oxidation which depends on the effective concentration of these high energy reactive conformers is thus extremely slow. In the case of **1**, the situation is completely different because this compound naturally adopts an eclipsed conformation, the effect of a synperiplanar lone pair orientation can thus be readily observed. The previously reported[1] ozonolysis of α and β-methyl 2,3,5-tri-O-acetyl-ribofuranosides may also take place with the help of a *syn* (ring oxygen) and an *anti* (OMe oxygen) lone pair.



In conclusion, the above work constitutes rigorous evidence that when an acetal can take a conformation with one oxygen lone pair synperiplanar and one antiperiplanar to the C—H bond, the ozonolysis reaction takes place with ease. This work provides also unequivocal evidence for the existence of a synperiplanar stereoelectronic effect.[10]

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7. Compound **7**: mp 75-77°C (from AcOEt); IR ($CHCl_3$): 3610, 1725, 1225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 3.77 (m, 1H, $_{10}C\underline{H}$), 3.66 (s, 3H, $-OCH_3$), 3.05 (m, 1H, $_2C\underline{H}$), 2.10-1.45 (m, 12H, CH and CH_2); ^{13}C NMR ($CDCl_3$): 176.66 (C_1), 71.80 (C_{10}), 51.60 ($-OCH_3$), 38.19 (C_2), 34.02 (C_4 and C_8), 33.72 (C_3 and C_9), 23.77 (C_5 and C_7), 20.82 (C_6); MS (m/e): 198 (M^+), 180 (M^+-H_2O).
   Compound **8**: m.p. 150-151°C (from AcOEt-hexane); IR ($CHCl_3$): 1745, 1225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 4.11 (t, J=3.7 Hz, 1H, $_{10}C\underline{H}$), 2.48 (m, 1H, $_2C\underline{H}$), 2.28 (br, 2H, $_4C\underline{H}$ and $_8CH$), 1.93 (m, 2H, $_3C\underline{H}H$ and $_9C\underline{H}H$), 1.60-1.30 (m, 8H, CH_2); ^{13}C NMR ($CDCl_3$): 176.73 (C_1), 80.28 (C_{10}), 34.24 (C_2), 30.26 (C_4 and C_8), 28.13 (C_3 and C_9), 27.35 (C_5 and C_7), 13.38 (C_6); MS (m/e): 166 (M^+), 122 (M^+-CO_2).
   Compound **9**: mp 54-56°C; IR ($CHCl_3$): 3600, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): 5.14 (br, 1H, $_1C\underline{H}$), 4.00 (d, J=3.9 Hz, 1H, O$\underline{H}$), 3.39 (t, J=3.5 Hz, 1H, $_{10}C\underline{H}$), 2.25 (m, 1H, $_2C\underline{H}$), 2.17 (m, 2H, $_4C\underline{H}$ and $_8C\underline{H}$), 1.80-1.10 (m, 10H, CH_2); ^{13}C NMR ($CDCl_3$): 94.30 (C_1), 72.68 (C_{10}), 31.12, 30.78 (C_4, C_8), 29.98, 28.04 (C_2, C_3, C_9), 29.39, 21.67 (C_5, C_7), 14.17 (C_6); MS (m/e): 168 (M^+), 151 (M^+-OH).
   Compound **1**: IR (film): 2925, 1110 cm^{-1}; ^1H NMR (C_6D_6): 4.63 (dd, J=2.35 Hz, 0.90 Hz, 1H, $_1C\underline{H}$, anomeric hydrogen), 3.42 (s, 3H, $-OCH_3$), 3.37 (t, J=3.80 Hz, 1H, $_{10}C\underline{H}$), 2.32 (m, 2H, $_4C\underline{H}$ and $_8C\underline{H}$), 2.03 (m, 1H, $_2C\underline{H}$), 1.70-0.90 (m, 10H, CH_2); ^{13}C NMR (C_6D_6): 101.19 (C_1), 72.12 (C_{10}), 54.56 ($-OCH_3$), 31.83, 31.60 (C_4, C_8), 30.25 (C_2), 30.45, 28.45 (C_3, C_9), 29.74, 23.01 (C_5, C_7), 14.66 (C_6); MS (m/e): 182 (M^+), 151 (M^+-OCH_3).
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9. Compound **10**: IR (film): 1735, 1235, 1200, 1175 cm^{-1}; ^1H NMR ($CDCl_3$): 4.74 (br, 1H, $_{10}C\underline{H}$), 3.64 (s, 3H, $-OCH_3$), 3.05 (m, 1H, $_2C\underline{H}$), 2.05 (s, 3H, $C\underline{H}_3Ac$), 2.03 (m, 2H, $_4C\underline{H}$ and $_8C\underline{H}$), 1.80-1.50 (m, 10H, CH_2); ^{13}C NMR ($CDCl_3$): 176.49 (C_1), 170.54 (C=OAc), 74.37 (C_{10}), 51.54 ($-OCH_3$), 37.74 (C_2), 31.39 (C_4 and C_8), 30.72 (C_3 and C_9), 27.73 (C_5 and C_7), 21.36 ($C\underline{H}_3Ac$), 20.86 (C_6); MS (m/e): 180 (M^+-CH_3COOH).
   Compound **11**: is a known compound: Ooslerhout, H. van; Kruk, C.; Speckamp, W.N.; *Tetrahedron Lett.* **1978**, 653.
   Compound **12**: IR (film), 1735, 1240, 1165 cm^{-1}; ^1H NMR ($CDCl_3$): 3.97 (d, J=5.3 Hz, 2H, $_9C\underline{H}_2$), 3.61 (s, 3H, $-OCH_3$), 2.49 (dd, J=14.8 Hz, 4.6 Hz, 1H, $_2C\underline{H}H$), 2.10 (dd, J=14.9 Hz, 7.8 Hz, 1H, $_2CH\underline{H}$), 2.00 (s, 3H, $C\underline{H}_3Ac$), 1.80-1.00 (m, 10H, CH and CH_2); ^{13}C NMR ($CDCl_3$): 173.32 (C_1),171.03 (C=OAc), 67.18 (C_9), 51.33 ($-OCH_3$), 41.16, 38.83, 36.27 (C_2, C_3, C_4), 32.32, 29.64, 25.63, 25.49 (C_5, C_6, C_7, C_8), 20.82 (CH_3Ac); MS (m/e): 196 (M^+-CH_3OH), 185 (M^+-CH_3CO).

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