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The Stereochemistry of Carbonyl Oxides From Ozonolysis of Vinyl Ethers

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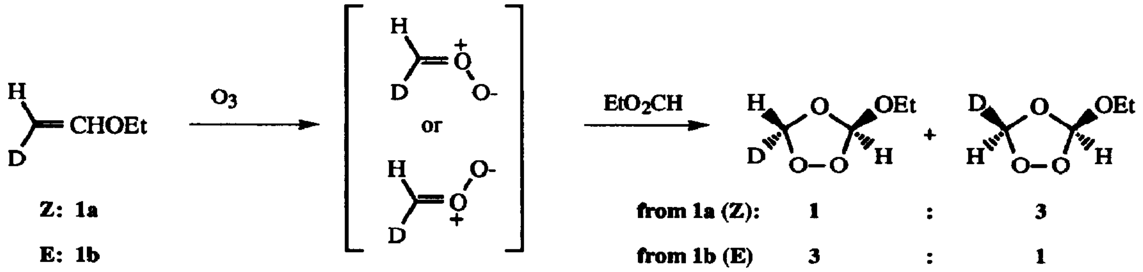
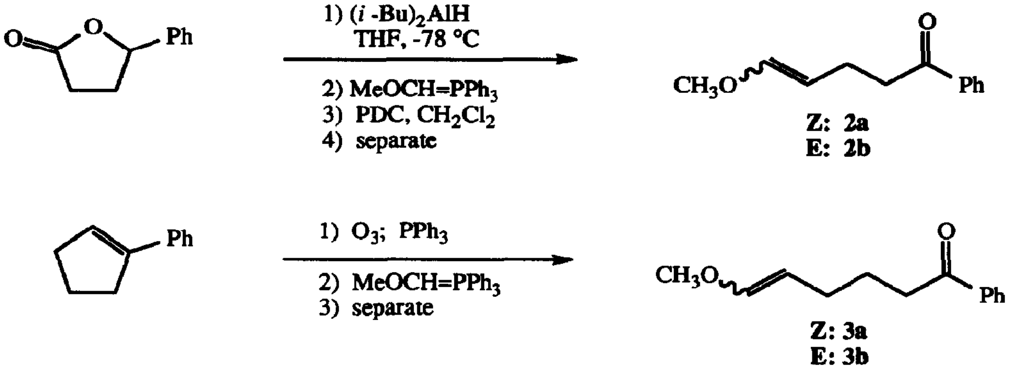
Abstract: *The geometries of the carbonyl oxides produced during ozonolysis of E- and Z-vinyl ethers have been assigned using the intramolecular trapping method. The alkoxy substituent exerts an anti-directive effect on formation of the carbonyl oxide; that is, the carbonyl oxide has a geometry opposite to that of the precursor vinyl ether.*

The elegant work of Kuczkowski and coworkers has established that the ozonolytic cleavage of vinyl ethers is highly regioselective and stereospecific.[2] Thus, the stereolabeled ethyl vinyl ethers **1a** and **1b** fragment to generate formaldehyde oxide and ethyl formate; recombination leads to the alkoxy ozonide with predominant retention of alkene stereochemistry. This requires that the intermediate labeled carbonyl oxide is formed stereospecifically from the vinyl ether. Since the final ozonide stereochemistry depends not only on the carbonyl oxide geometry, but also on the *exo-endo* topology of its cycloaddition with the ester, conclusions about the former are contingent on assumptions for the latter. For this reason, it has not been possible to assign the geometries of the intermediate carbonyl oxides. We have recently demonstrated that intramolecular trapping permits assignment of carbonyl oxide stereochemistry,[3] and report here the results of our studies on the intramolecular trapping of carbonyl oxides from ozonolyses of E and Z-vinyl ethers.



Carbonyl oxides are fleeting intermediates, and cannot be observed directly in ozonolysis reactions.[4] For a concerted, intramolecular cycloaddition of a carbonyl oxide with an aldehyde or ketone, the possible transition state geometries are limited by the length of the tether connecting the reactive groups. In the case of a short tether, cyclization is possible only if the carbonyl oxide has the geometry syn with respect to the trapping group. Therefore, the extent of intramolecular ozonide formation can be used to assess the carbonyl oxide geometry.

The Z- and E-vinyl ethers **2a,b** and **3a,b** were prepared as shown in Scheme 1.[5] Reduction of γ-phenyl-γ-butyrolactone with DIBAL-H, followed directly by reaction with methoxymethylenetriphenylphosphorane, afforded a 2 : 1 mixture of E and Z vinyl ethers in 84% yield. Oxidation of the mixture provided **2a** and **2b**, which could be separated efficiently by flash chromatography on $AgNO_3$-treated silica gel.[6] The synthesis of the higher homologs **3a,b** began with 1-phenylcyclopentene. Ozonation, followed by reduction with triphenylphosphine, provided the ketoaldehyde, which underwent selective olefination with methoxymethylenetriphenylphosphorane to yield a 1 : 7 mixture of **3a** and **3b**, respectively. As before, these isomers were easily separated on $AgNO_3$-treated silica gel.[6]

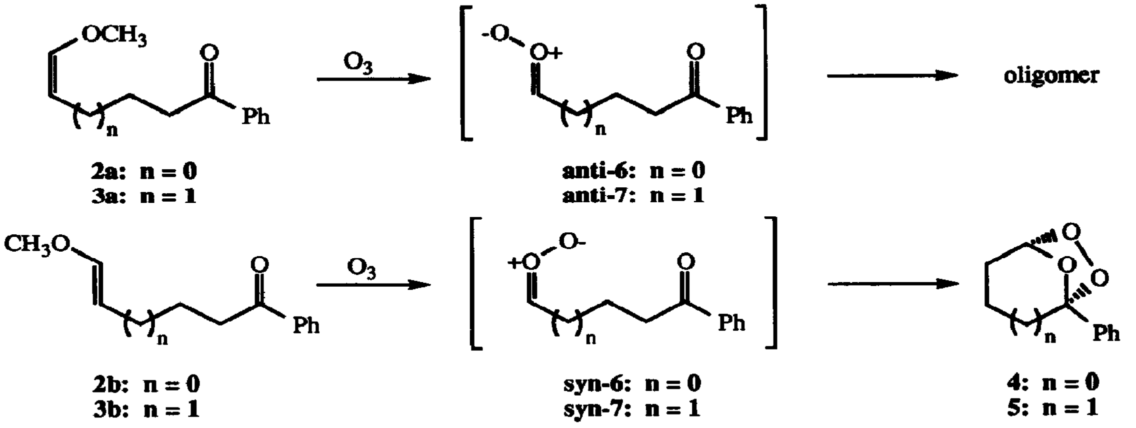


Scheme 1

Ozonolysis of **2b** was carried out in CD_2Cl_2 at -78 °C, and the NMR spectrum of the crude reaction mixture was recorded within 10 minutes at -70 °C. Diagnostic signals included the singlets for methyl formate (δ 8.68 and 3.68 ppm), and the bridgehead signal for ozonide **4** (br s, δ 6.22 ppm). Based on NMR integration (versus the total of the aromatic signals), a nearly quantitative amount of methyl formate was formed, along with 54 % of the ozonide **4**. It was essential to monitor the reaction mixture at low temperature, because **4** decomposes rapidly at higher temperature, presumably due to the strain in the bicyclo[2.2.1]heptane ring system.

When the Z-vinyl ether **2a** was ozonized under the same conditions, only a very small amount (< 3%) of ozonide **4** could be detected at -70 °C, along with a quantitative yield of methyl formate. The other signals were quite broad, suggesting the formation of oligomeric material.[7]

The lability of ozonide **4** prompted us to examine the ozonolyses of **3a,b**. The anticipated ozonide, **5**, was prepared in 84 % yield by ozonolysis of 1-phenylcyclopentene,[5] and was shown to be stable for weeks at room temperature. A solution of **3b** was ozonized at -78 °C in CD_2Cl_2, and the resultant solution warmed to room temperature. The yield of ozonide **5** was 52%, as determined by NMR analysis. Similar treatment of **3a** resulted in the formation of only 5-8 % of the ozonide **5**, along with methyl formate (98 %) and oligomeric peroxides.



Scheme 2

In each case, the formation of methyl formate indicates that regioselective fragmentation of the primary ozonides from **2** and **3** produces the carbonyl oxides **6** and **7**, respectively. Intramolecular cyclization to form the ozonides **4** and **5** can proceed only for **syn-6** and **syn-7**; the anti-carbonyl oxides cannot achieve a conformation for concerted intramolecular cycloaddition, and ultimately engage in intermolecular reaction to form oligomers. It must be noted that the yields of intramolecular ozonide represent the lower limits to the proportion of syn carbonyl oxide actually produced from the vinyl ethers, since intramolecular cyclization is probably not 100% efficient. For this reason, it is not possible to determine quantitative ratios of carbonyl oxide stereoisomers in each case. Nevertheless, the trend is clear: syn carbonyl oxides are produced as the major intermediate from the E-vinyl ethers **2a** and **3a**, while the Z-vinyl ethers **2b** and **3b** lead mainly to the anti-carbonyl oxides.

Thus, the alkoxy substituent steers formation of the carbonyl oxide to the remote alkene position, with a geometry opposite to that of the precursor vinyl ether. This *anti* directive effect of the alkoxy group, in conjunction with Kuczkowski's results for ozonolysis of **1a** and **1b**,[2] implies a preferred endo-transition state for cycloaddition of carbonyl oxides with esters. For example, ozonolysis of **1a** will proceed to the anti-carbonyl oxide, which must add to methyl formate in an endo fashion to produce the observed cis-ozonide as the major product. Likewise, the E-vinyl ether **1b** leads, via endo-cycloaddition of the syn-formaldehyde oxide, to the trans-ozonide. Finally, it can be noted that the directive effect of the alkoxy group reported here confirms that suggested for ozonolysis of Z and E-1-methoxypropene.[2b]

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References:

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5. Characterization data for new compounds: **2a**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (m, 2H), 7.53 (m, 1H), 7.44 (m, 2H), 5.89 (dt, J = 6.2, 1.3 Hz, 1H), 4.44 (dt, J = 6.2, 7.3 Hz, 1H), 3.56 (s, 3H), 3.03 (t, J = 7.4 Hz, 2H), 2.47 ppm (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.9, 146.9, 136.7, 132.8, 128.4, 127.9, 104.9, 59.4, 38.6, 18.9 ppm; IR (neat film) ν 1684, 1597, 1390, 1180 cm^{-1}. **2b**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.95 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 6.37 (dt, J = 12.6, 1.1 Hz, 1H), 4.79 (dt, J = 12.6, 7.4 Hz, 1H), 3.49 (s, 3H), 3.01 (t, J = 7.3 Hz, 2H), 2.37 ppm (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.5, 147.9, 136.9, 132.9, 128.5, 127.9, 101.4, 55.8, 39.7,22.5 ppm; IR (neat film) ν 1689, 1600, 1382, 1175 cm^{-1}; Anal. C,H. **3a**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.95 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 5.90 (dt, J = 6.3, 1.2 Hz, 1H), 4.36 (dt, J = 6.3, 7.4 Hz, 1H), 3.55 (s, 3H), 2.97 (t, J = 7.3 Hz, 2H), 2.17 (m, 2H), 1.78 ppm (tt, J = 7.4, 7.3 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 200.5, 146.8, 137.2, 132.8, 128.5, 128.0, 105.8, 59.4, 37.4, 24.3, 23.4 ppm; IR (neat film) ν 1675, 1597, 1259, 1104 cm^{-1}; Anal. C,H. **3b**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.95 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 6.30 (dt, J = 12.6, 0.8 Hz, 1H), 4.72 (dt, J = 12.6, 7.4 Hz, 1H), 3.50 (s, 3H), 2.96 (t, J = 7.3 Hz, 2H), 2.04 (m, 2H), 1.80 ppm (tt, J = 7.4, 7.3 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 200.4, 147.6, 137.0, 132.9, 128.5, 128.0, 102.9, 55.9, 37.6, 27.2, 25.1 ppm; IR (neat film) ν 1675, 1590, 1442, 1125 cm^{-1}. **4**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.58 (m, 2H), 7.43 (m, 3H), 6.22 (br s, 1H), 2.56 (m, 1H), 2.23 (m, 2H), 2.08 ppm (m, 1H). **5**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.54 (m, 2H), 7.38 (m, 3H), 5.97, (brs, 1H), 2.37 (m, 1H), 2.25 (m, 1H), 1.86 (m, 2H), 1.79 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 135.8 (s), 129.4 (d), 128.5 (d), 125.8 (d), 108.0 (s), 103.6 (d), 33.1 (t), 29.0 (t), 16.1 (t) ppm; IR (KBr) ν3035, 1452, 1356, 1103, 1041, 933, 761 cm^{-1}; Anal. C,H.

6. AgNO$_3$-silica gel was prepared by adding 100 g of silica gel (Merck Si 60; 230-400 mesh) to a solution of 5 g AgNO$_3$ in methanol (50 mL) and distilled water (50 mL). The volatiles were removed under vacuum, and the silica gel dried for 24 h at 120 °C. This material could be stored for limited periods under N$_2$ in the refrigerator.

7. For studies of the structures of oligomeric 'ozonides,' see: Murray, R. W.; Su, J.-S. *J. Org. Chem.* **1983**, *48*, 817-822, and references therein.

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