Communications to the Editor

Ozonolysis of Cyclic Vinyl Ethers. Formation of Anomalous Alkoxy Ozonides

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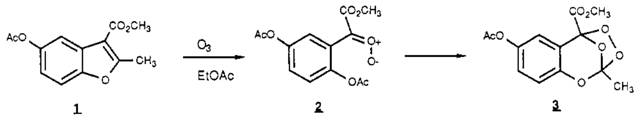
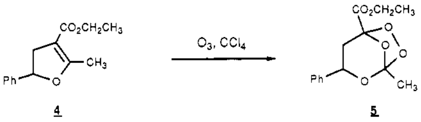
Alkoxy ozonides (3-alkoxy-1,2,4-trioxolanes) constitute an intriguing new class of cyclic peroxides which have generated much recent interest.[1-3] The pendant alkoxy group functions as an electron donor to the ozonide ring via an exo anomeric effect, as evidenced by structural studies on these compounds. In at least one case,[2] the electron-rich character of the ozonide is manifested in the stability of the peroxide system toward the nucleophilic reductant dimethyl sulfide. It is apparent, then, that alkoxy ozonides possess chemical properties which are quite different from simpler 1,2,4-trioxolanes. At present, however, only a few alkoxy ozonides are known. These have been prepared by cycloaddition of a carbonyl oxide, generated from alkene ozonolysis, with an ester. Although the process has been demonstrated for both intermolecular[1] and intramolecular[2,3] cases, in most instances the cyclization is quite inefficient, and only small amounts of ozonides can be obtained.

In this context we were intrigued by the work of Bernatek and co-workers in the mid-1950s, who showed that ozonation of certain benzofurans led to good yields of stable, crystalline peroxides.[4] These were formulated as the ozonides, although detailed structural evidence was not available. Since formation of these ozonides would most reasonably require intramolecular carbonyl oxide ester cycloaddition, we felt that it was important to reinvestigate this process. In the event, the Bernatek peroxide was obtained in 80% yield by ozonation (EtOAc, 20 °C) of benzofuran **1**.[4c] Spectral data for the crystalline product (**3**) was consistent with the ozonide structure but not compelling. Therefore, a single-crystal X-ray diffraction study was carried out, which fully confirmed the ozonide structure.[5]

The high efficiency of ozonide formation from **1** is surprising. Based on known directive effects in the cleavage of primary ozonides,[1b,c,6] **1** should produce the carbonyl oxide ester **2** as an intermediate. In the absence of special electronic and conformational controls, efficient cyclization of **2** to **3** is unexpected. In the case at hand, the fused benzene ring might serve as a conformational control element, enforcing a geometry favorable to cyclization in the carbonyl oxide ester tether. To test this, we ozonized the dihydrofuran **4**,[7] which lacks this rigidity. Surprisingly, the corresponding ozonide **5** was obtained as a single stereoisomer in 42% isolated yield, suggesting that conformational control within the tether is not necessary with these cyclic vinyl ethers.





The dihydrofuranyl ketone **6**,[8] on the other hand, led to a mixture of two ozonides in 60% and 10% yield (as determined by NMR). Initially, these were thought to be the stereoisomers of **7**, but upfield shifts of the methyl signals in the ^{1}H NMR spectrum of the major product[9] (isolated in 45% yield) led us to consider the alternative structure **8**, where the ozonide ring has "slipped" to the acetyl group of **6**. The difference in connectivity between **7** and **8** was exploited by a long-range (2–3 bond) heteronuclear polarization-transfer experiment (selective INEPT).[10] Thus, irradiation of the benzylic proton leads to enhancement of a ^{13}C NMR signal at 205.3 ppm, clearly the carbonyl group and not an acetal. This experiment establishes the major ozonide structure as **8**.

Although **8**, obtained as a colorless oil, was rather unstable toward unimolecular rearrangement to the anhydride **9** (first-order half-life of 7 h at 25 °C), the ozonide was unreactive toward potential oxygen acceptors such as dimethyl sulfide and diethylamine. Thus, treatment of **8** with diethylamine led to the formation of diethylacetamide, at a rate commensurate with the conversion of **8** to **9** and with no apparent acceleration of this conversion. Remarkably, the ketone within **8** could be reduced with sodium borohydride,[11] leaving the ozonide system intact. The resulting 2:1 mixture of epimeric alcohols **10** is far more stable than **8**, reflecting the diminished propensity for migration of the carbinol center to the peroxide as compared to acyl migration. The alcohols were converted to the crystalline *p*-nitrobenzoates **11**. Three recrystallizations from methanol afforded a pure sample of the major isomer, suitable for X-ray diffraction. The structure[5] for **11** confirms the stereochemistry assigned to **8**, and an exo anomeric effect (with respect to the trioxolane ring) is evident in the differentiation of bond lengths to the pendant oxygen (see Scheme I).[12]

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(1) (a) Keul, H.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1984**, *106*, 3383. (b) Keul, H.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1984**, *106*, 5370. (c) Keul, H.; Choi, H.-S.; Kuczkowski, R. L. *J. Org. Chem.* **1985**, *50*, 3365. (d) LaBarge, M. S.; Keul, H.; Kuczkowski, R. L.; Wallasch, M.; Cremer, D. *J. Am. Chem. Soc.* **1988**, *110*, 2081.

(2) Bunnelle, W. H.; Schlemper, E. O. *J. Am. Chem. Soc.* **1987**, *109*, 612.

(3) (a) Odinokov, V. N.; Kukovinets, O. S.; Khalilov, L. M.; Tolstikov, G. A.; Kosnikov, A. Y.; Lindeman, S. V.; Struchkov, Y. T. *Tetrahedron Lett.* **1985**, *26*, 5843. (b) Odinokov, V. N.; Kukovinets, O. S.; Botsman, L. P.; Khalilov, L. M.; Tolstikov, G. A.; Kosnikov, A. Y.; Lindeman, S. V.; Struchkov, Y. T. *J. Org. Chem. USSR (Engl. Transl.)* **1987**, *23*, 897; *Zh. Org. Khim.* **1987**, *23*, 995.

(4) (a) Bernatek, E.; Thoresen, F. *Acta Chem. Scand.* **1955**, *9*, 743. (b) Bernatek, E.; Bø, I. *Acta Chem. Scand.* **1959**, *13*, 337. (c) Bernatek, E.; Hvatum, M. *Acta Chem. Scand.* **1960**, *14*, 836. (d) Bernatek, E. *Ozonation in the Naphthoquinone and Benzofuran Series*; Oslo University Press: Oslo, Norway, 1960. (e) Bernatek, E. *Acta Chem. Scand.* **1953**, *7*, 677.

(5) The details of these structure determinations will be published in the full paper. See also the Supplementary Material.

(6) (a) Fliszár, S.; Granger, M. *J. Am. Chem. Soc.* **1969**, *91*, 3330. (b) Fliszár, S.; Granger, M. *J. Am. Chem. Soc.* **1970**, *92*, 3361. (c) Fliszár, S.; Renard, J. *Can. J. Chem.* **1970**, *48*, 3002.

(7) Heiba, E. I.; Dessau, R. M. *J. Org. Chem.* **1974**, *39*, 3456.

(8) Vinogradov, M. G.; Kondorsky, A. E.; Nikishin, G. I. *Synthesis* **1988**, 60.

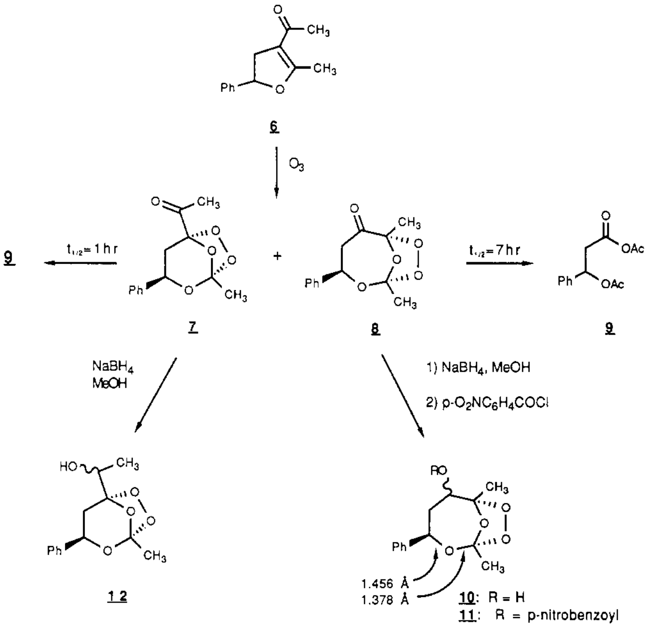
(9) NMR spectra of solutions in CDCl$_3$ were recorded on a JEOL FX-90Q spectrometer operating at 90 MHz (proton) and 22.5 MHz (carbon). IR spectra of neat liquid films or KBr pellets were obtained on a Nicolet 20DXB FTIR spectrometer. **8** (1,6-dimethyl-3-phenyl-2,7,8,9-tetraoxabicyclo[4.2.1]nonan-5-one): ^{1}H NMR δ 7.36 (m, 5 H), 5.36, (dd, J = 11.2, 1.1 Hz, 1 H), 3.51 (dd, J = 14.2, 11.2 Hz, 1 H), 2.64 (dd, J = 14.2, 1.1 Hz, 1 H), 1.83 (s, 3 H), 1.57 ppm (s, 3 H); ^{13}C NMR δ 205.3, 139.8, 128.7, 128.4, 126.1, 122.8, 107.0, 72.4, 51.1, 23.3, 16.4 ppm; IR ν 1735, 1224, 1159, 961 cm^{-1}. **14** (8-acetoxy-2,5-dimethyl-2,5-epoxy-1,3,4-benzotrioxocan-6-one): ^{1}H NMR δ 7.70 (d, J = 2.6 Hz, 1 H), 7.29 (dd, J = 9.0, 2.6 Hz, 1 H), 7.01 (d, J = 9.0 Hz, 1 H), 2.30 (s, 3 H), 1.99 (s, 3 H), 1.74 ppm (s, 3 H); ^{13}C NMR δ 192.0, 169.2, 149.4, 145.6, 129.5, 123.6, 122.7, 121.6, 121.4, 108.5, 23.0, 20.8, 15.9 ppm; IR ν 1765, 1695, 1195, 1164 cm^{-1}.

(10) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314.

(11) This result is reminiscent of the stability of the peroxide moiety of the antimalarial artemisinin. For a recent review, see: Luo, X.-D.; Shen, C.-C. *Med. Res. Rev.* **1987**, *7*, 29.

0002-7863/89/1511-7612$01.50/0

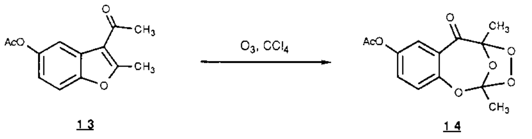
Scheme I



When dihydrofuranyl ketone **6** was ozonized in methanol at −70 °C, only a trace amount of **8** was obtained. Now the major product was the ozonide **7** (~70% yield, by NMR analysis of crude), identical with the minor component obtained in CCl_4. Because **7** degrades rapidly to the anhydride **9** (half-life at 20 °C = 1 h) it was not possible to characterize this compound cleanly. Instead, **7** was reduced to a 1:1 mixture of alcohols **12** with sodium borohydride; coupling of the carbinol proton to one of the methyl groups confirms the assigned structure. The stereochemistry for **7** is assigned on the basis of couplings to the benzylic proton (J = 11, 4 Hz) which are consistent with this hydrogen having the axial orientation.

The dramatic solvent effect on the ozonide distribution from **6** is not easily explained. No interconversion between **7** and **8** was observed in the solvents used, so the ozonide distribution appears to be kinetically controlled. Preliminary experiments suggest that decreased solvent polarity and lower temperatures lead to increased proportion of the "slipped" ozonide **8**. We have studied the mechanism for formation of **8**; this work is described in the following paper.[13]

The formation of "slipped" ozonides appears to be general for these acetyldihydrofurans. Thus, the benzofuran derivative **13**,



reported by Bernatek[4e] to give an unstable peroxidic product on ozonolysis, was found to provide a small yield (18%) of a relatively stable ozonide. Spectroscopic data, particularly the IR stretch at 1695 cm^{-1} for the ketone, led to assignment as the slipped ozonide **14**.[9] This assignment is further supported by sodium borohydride reduction to the corresponding alcohol, which shows no coupling from the carbinol methine to the methyl group.

Clearly, ozonolysis of cyclic vinyl ethers provides a rich hunting ground for the preparation of new alkoxy ozonides. Chemical manipulation of these systems has been demonstrated and offers possibilities for increasing their stability. We are continuing our efforts to delineate the mechanistic features of this process, in particular to understand the origin of the solvent effect on ozonide distribution.

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Supplementary Material Available: Computer-generated plots and tables of positional parameters, thermal parameters, interatomic distances, interatomic angles, and dihedral angles for non-hydrogen atoms for **3** and **11** (12 pages). Ordering information is given on any current masthead page.

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[12] This bond distance criterion has been used to assess the anomeric effect in carbohydrates: Jeffrey, G. A.; Pople, J. A.; Binkley, J. S.; Vishveshwara, S. *J. Am. Chem. Soc.* **1978**, *100*, 373. See, also: references 1 and 2.

[13] Bunnelle, W. H., following paper in this issue.

Ester Oxide Intermediates in the Ozonolysis of Cyclic Vinyl Ethers

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According to the Criegee mechanism for alkene ozonolysis,[1] a primary ozonide (1,2,3-trioxolane), formed by addition of ozone to the alkene, fragments to give a carbonyl compound from one end of the starting alkene and a carbonyl oxide from the other. Substituent effects on the regioselectivity of primary ozonide fragmentation have been reported.[2] Thus, while an acyl substituent tends to favor proximal production of the carbonyl oxide, alkoxy groups direct carbonyl oxide formation to the remote fragment. Kuczkowski[3] has recently demonstrated, in fact, that ozonation of ethyl vinyl ether leads to nearly exclusive production of formyl oxide and ethyl formate—these recombine, albeit inefficiently, to ethoxy ozonide (3-ethoxy-1,2,4-trioxolane). We have reported that ozonation of cyclic vinyl ethers can lead efficiently to alkoxy ozonides.[4] In some cases, notably the dihydrofuranyl ketone **1**, the ozonide obtained was not that from the expected carbonyl oxide ester cycloaddition. Thus, ozonation of **1** in CCl_4 gave, as the major product, alkoxy ozonide **2**, where the trioxolane ring includes what had been the acetyl carbon of the starting material. We have investigated the mechanism of this conversion and report here evidence that primary ozonides from these cyclic vinyl ethers cleave regioselectively in a manner contrary to literature precedent, forming a ketone and an ester oxide. Little is known of the chemistry of ester oxides. A few have been trapped with alcohol solvents,[5] but their cyclization with carbonyl partners to form alkoxy ozonides has apparently not been described previously.

The mechanistic possibilities for ozonation of **1** are outlined in Scheme I. According to literature precedent, the primary ozonide **3** should cleave regioselectively to the carbonyl oxide ester **4**.[2] Since **2** cannot result directly from cyclization of this intermediate, we considered the possibility of oxygen transfer to provide the isomeric carbonyl oxide ester **7**. A priori, there are two likely pathways. The first involves an electrocyclic closure to the 1,2,3-trioxolene **5**, followed by opening in the regioisomeric sense.

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(1) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic: New York, 1978; Vol. 1; 1982; Vol. 2.

(2) (a) Fliszár, S.; Granger, M. *J. Am. Chem. Soc.* **1969**, *91*, 3330. (b) Fliszár, S.; Granger, M. *J. Am. Chem. Soc.* **1970**, *92*, 3361. (c) Fliszár, S.; Renard, J. *Can. J. Chem.* **1970**, *48*, 3002.

(3) (a) Keul, H.; Choi, H.-S.; Kuczkowski, R. L. *J. Org. Chem.* **1985**, *50*, 3365. (b) Keul, H.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1984**, *106*, 5370.

(4) Bunnelle, W. H.; Meyer, L. A.; Schlemper, E. O., preceding paper in this issue.

(5) Kopecky, K. R.; Molina, J.; Rico, R. *Can. J. Chem.* **1988**, *66*, 2234.

0002-7863/89/1511-7613$01.50/0