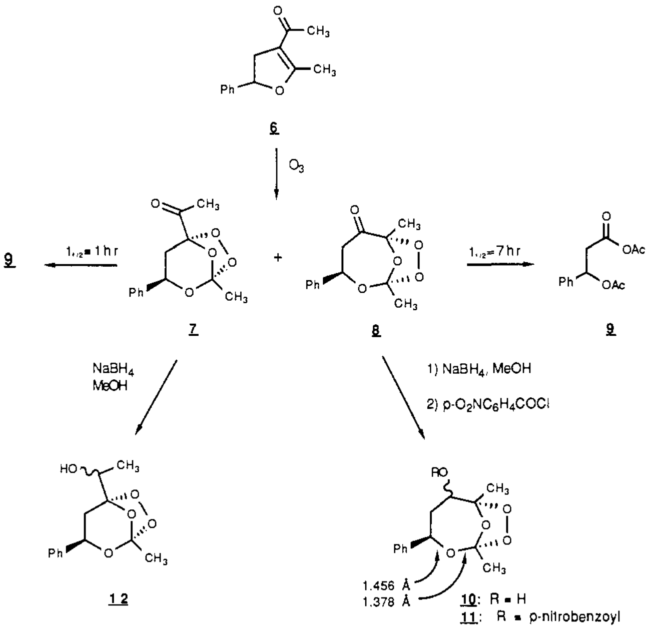
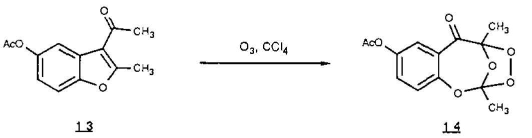
Scheme I



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.



13 14

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.

Acknowledgment. Support of this work by the University of Missouri Research Council and the National Science Foundation (CHE-8806198) is gratefully acknowledged. The NMR facilities at the University of Missouri are supported, in part, by the NSF (PCM-815599). We thank Dr. Hanna Gracz for her assistance with the NMR experiments.

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.

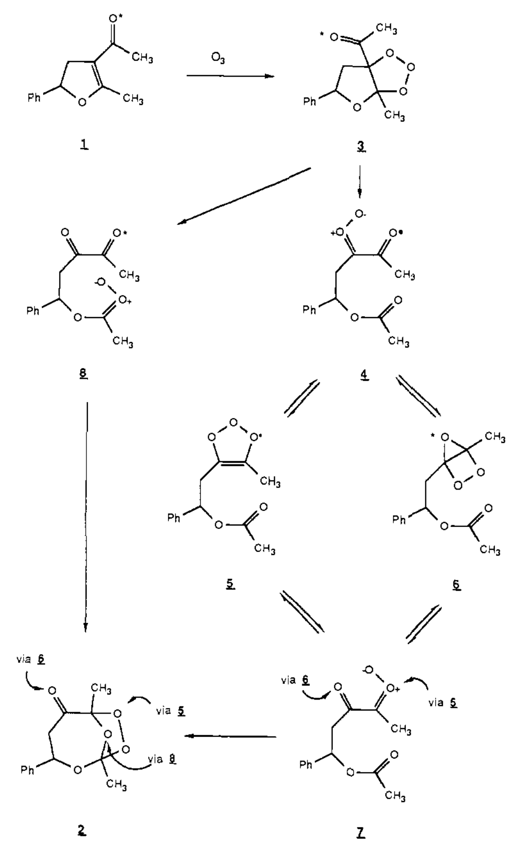
(2) (a) Fliszár, S.; Granger, M. *J. Am. Chem. Soc.* **1969**, *91*, 3330. (b) Fliszár, S.; Granger, M. *J. Am. Chem. Soc.* **1970**, *92*, 3361. (c) Fliszár, S.; Renard, J. *Can. J. Chem.* **1970**, *48*, 3002.

(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.

Scheme I



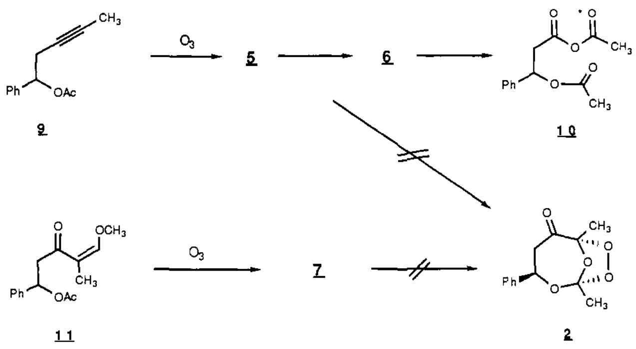
An alternate path proceeds through internal cyclization to the 2,4,5-trioxabicyclo[2.1.0]pentane **6**, which opens to **7**. Intermediates like **5** and **6** have been cited as intermediates in alkyne ozonolysis;[6] they should therefore be accessible by an independent route. The requisite alkyne is **9** (Scheme II). Ozonolysis of **9**, however, did not produce any of the expected ozonide **2**. The major product was the anhydride **10**, a known decomposition product of **2**,[4] but the rate of formation of **10** was greater than would be possible for a pathway involving **2**. In this case, it is likely that much of **10** results from cleavage of the dioxetane moiety within the trioxabicyclopentane **6**,[7] derived from **5** via **4** and/or **7**. Of course, this scenario implies that none of these intermediates are involved in the formation of alkoxy ozonide **2**.

Independent access to the carbonyl oxide ester **7** was explored by ozonation of enol ether **11**, prepared by condensation of benzaldehyde with the enolate from 3-methyl-4-methoxy-3-buten-2-one.[8] In the event, only trace amounts of the ozonide **2** were detected. At this juncture, it seemed quite unlikely that ozonide **2** resulted from intramolecular carbonyl oxide ester cycloaddition, and the involvement of intermediates **4**–**7** could not be supported.

If, however, the primary ozonide decomposition proceeded in the opposite regiochemical sense, the dione ester oxide **8** would result. Intramolecular cyclization of the ester oxide with the remote ketone would lead directly to **2**. Since intramolecular carbonyl oxide ketone cycloadditions are facile processes, this is expected to proceed efficiently.

The mechanistic scenario outlined in Scheme I is well-suited to an oxygen labeling experiment. Unlike most ozonolyses, where the ozonide oxygens are derived from ozone and consequently cannot be selectively labeled, the situation at hand involves scrambling of oxygens, in particular the ketone oxygen of **1**. A label at this oxygen is delivered differently for each of the three mechanistic pathways, as indicated in Scheme I. Thus, ketone-labeled **1** is an ideal probe for the mechanism for formation of **2**.

Scheme II



Crucial to success of this method is the identification of the label position in the product. In the present case, distinction between a carbonyl, peroxide, and ether sites must be possible. The large chemical shift dispersion of ^{17}O NMR, along with the low natural abundance of this isotope, makes this technique well-suited for such studies. The chemical shift regions for ketones (~500 ppm), peroxides (~300 ppm), and ethers (~100 ppm) are sufficiently well-separated to permit location of the label.[9] Ketone-labeled **1** (~10% ^{17}O enrichment) was readily prepared by acid-catalyzed exchange with $^{17}OH_2$;[10] ^{17}O NMR established that only labeling at the carbonyl oxygen occurred (δ 523 ppm). The crude material after ozonolysis gave several lines in the ^{17}O NMR spectrum: δ 573, 367, 330, and 136 ppm. The first three of these arise from unidentified impurities, and they remain unchanged over time, as the ozonide is converted to **10**. In contrast, the largest signal, at 136 ppm, diminished as new lines appeared at 413 and 268 ppm, as expected for the anhydride. Repetition of the ozonolysis, followed by purification of the ozonide by flash chromatography, afforded a product which gave a single absorbance at 138 ppm. This signal, as for the mixture, was replaced by new lines at 413 and 272 ppm over a period of several hours.[11] The chemical shift of the ozonide signal identifies the label as the ozonide ether oxygen, which must result from intermediacy of the ester oxide **8**.

It is likely that ester oxides are involved in the ozonolysis of other cyclic vinyl ethers. Thus, the efficiency of alkoxy ozonide formation from benzofurans and dihydrofurans, in contrast to intramolecular carbonyl oxide ester cycloadditions, is readily explained if the former processes actually involve intramolecular ester oxide ketone cyclization. Less easily rationalized is the apparent preference for cyclization of the ester oxide within **8** to the more remote keto group, to form a seven- rather than a six-membered ring. Several factors may be involved, including conformational preferences and the syn–anti disposition of the ester oxide, for which data are not yet available, so that it is premature to speculate on this point.

Acknowledgment. Support of this research by the University of Missouri Research Council and the National Science Foundation (CHE-8806198) is gratefully acknowledged. The NMR facilities at the University of Missouri are supported, in part, by the NSF (PCM-815599). I thank Professor Tuck Wong and Dr. Hanna Gracz for their help with the ^{17}O NMR experiments.

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(6) (a) Ando, W.; Miyazaki, H.; Ito, K.; Auchi, D. *Tetrahedron Lett.* **1982**, *23*, 555. (b) Pryor, W. A.; Govindan, C. K.; Church, D. F. *J. Am. Chem. Soc.* **1982**, *104*, 7563.

(7) Yang, N. C.; Libman, J. *J. Org. Chem.* **1974**, *39*, 1782.

(8) Mishra, S.; Shrivastava, R. D. *J. Indian Chem. Soc.* **1978**, *105*, 1273.

(9) (a) Kintzinger, J. NMR, Oxygen-17 NMR Spectroscopy. In *NMR, Basic Principles and Progress*; Springer-Verlag: Berlin, 1981; Vol. 17. (b) Wong, T. C.; Guziec, F. S., Jr.; Moustakis, C. A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1471. (c) Zagorski, M. G.; Allan, D. S.; Salomon, R. G.; Clennan, E. L.; Heah, P. C.; L'Esperance, R. P. *J. Org. Chem.* **1985**, *50*, 4484.

(10) Obtained from Cambridge Isotope Laboratories, Woburn, MA.

(11) In principle, the rearrangement of **2** to **10** should place the label at the anhydride acetyl oxygen, but scrambling with the anhydride ether oxygen occurs rapidly, long before the eventual disproportionation of **10** to a statistical composition of mixed and symmetric anhydrides. This aspect will be discussed in the full paper.