the ^{1}H or ^{13}C NMR spectra of **3** over the temperature range -80–$+140$ °C, reflecting the thermodynamic stability of the oxygens "in" conformer relative to the unobserved oxygens "out" conformer.

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(22) Pauling, L. "The Nature of the Chemical Bond", 3rd ed.; Cornell University Press: Ithaca, NY, 1960; p 361. Flory, P. J.; Mark J. E. *Makromol. Chem.* **1964**, *75*, 11-21; *J. Am. Chem. Soc.* **1965**, *87*, 1415-1423.

Rearrangement of a Geometrically Restricted Triepoxide to the First Topologically Nonplanar Molecule: A Reaction Path Elucidated by Using Oxygen Isotope Effects on Carbon-13 Chemical Shifts

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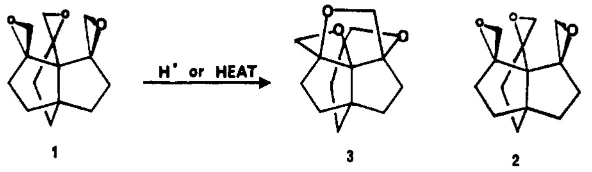
The symmetrical triepoxide trispiro[tricyclo[3.3.3.0^{1,5}]undecane-2,2′:8,2″:9,2‴-tris[oxirane]] (**1**[1]) cleanly undergoes rearrangement to the triether 2,5,14-trioxahexacyclo[5.5.2.1.2^{4,10}.0^{4,17}.0^{10,17}]heptadecane (**3**), both thermally and with acid catalysis (Scheme I).[2] To elucidate the reaction pathway for this novel rearrangement, we have developed and applied a new method of double-isotope labeling based on the perturbation of ^{13}C NMR chemical shifts by isotopes of oxygen.[3,4]

Triether **3** has been a target of our synthetic efforts because it is topologically unique. To our knowledge, it is the first organic molecule known which has a structure which cannot be represented as a planar graph.[5] In addition, the rearrangement that produces **3** was especially interesting, because it could proceed via an unprecedented $2\sigma + 2\sigma + 2\sigma$ to $2\sigma + 2\sigma + 2\sigma$ electrocyclic rearrangement[6] (Scheme II, path a). Consideration of the conformations of **1**, unsymmetrical triepoxide **2**, and the all-carbon analogue of **1**, trispiro[tricyclo[3.3.3.0^{1,5}]undecane-2,1′:8,1″:9,1‴-tris[cyclopropane]],[7] suggested that a conformation of **1** is possible which directs the lone pairs on each oxygen into the region of the antibonding orbitals of an adjacent C–O bond[8] (Figure 1). These considerations, combined with the fact that the electrocyclic reaction represented in path a is orbital-symmetry allowed,[9] made us optimistic that the rearrangement of **1** to **3** might be the first case of an electrocyclic reaction involving only σ bonds. However, an alternative route from **1** to **3** (path b) was also conceivable. Although unprecedented in its details, this route is more reminiscent of conventional epoxide chemistry.[10]

Scheme I



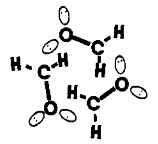


Figure 1. Schematic representation of **1** observed from the "top" along the C_3 axis.

The bonds broken and created in path a are different from those broken and created in path b, making the two paths distinguishable. To make this distinction, we have exploited the known ability of isotopic substitution of ^{18}O for ^{16}O to produce perturbations in the NMR chemical shifts of atoms directly attached to oxygen.[3,4] While the precise magnitude of this isotopic perturbation of chemical shift ($\Delta\delta$) depends on the nuclei involved and molecular structure, the ^{13}C NMR spectrum of a compound partially labeled with ^{16}O and ^{18}O at a position adjacent to a single ^{13}C-labeled atom will show two resonances, the downfield resonance arising from those ^{13}C atoms bonded to ^{16}O and the upfield resonance arising from those bonded to ^{18}O.[11] The relative intensity of the two resonances corresponds to the ratio of ^{16}O and ^{18}O labels in the adjacent position.[12] In contrast, should the ^{13}C

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(1) **1**–**3** are all chiral molecules. In our experiments, **1** is in fact a racemic mixture of the 2*S*,8*S*,9*S* enantiomer (shown) and the 2*R*,8*R*,9*R* enantiomer, while **2** is a racemic mixture of 2*R*,8*S*,9*S* enantiomer (shown) and the 2*S*,8*R*,9*R* enantiomer. The chirality of these species was established by NMR spectroscopy using the chiral shift reagent tris[3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]europium (III).

(2) Thermal reactions were carried out at 225 °C for 1 h in 0.3-i.d. × 12-cm sealed lead–potash glass tubes, prewashed with NH_4OH, distilled H_2O, MeOH, and EtOH, and then dried. Acid-catalyzed rearrangements were carried out in refluxing $CHCl_3$ over Amberlite 120 resin (sulfonic acid form) previously dried by azeotropic distillation of water with benzene.

(3) Cohn, M.; Hu, A. *Proc. Natl. Acad. Sci.* U.S.A. **1978**, *75*, 200-203. Batiz-Hernandez, H.; Bernheim, R. *Prog. Nucl. Magn. Reson. Spectrosc.* **1967**, *3*, 63-85.

(4) While this work was in progress, other examples of ^{18}O perturbation of ^{13}C chemical shifts were reported: Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252-254; *Ibid.* **1980**, *102*, 4609-4614; *Ibid.* **1980**, *102*, 6699-6702. Vederas, J. C. *Ibid.* **1980**, *102*, 374-376.

(5) Balaban, A. T., Ed., "Chemical Applications of Graph Theory"; Academic Press: New York, 1976; p 84. Simmons, H. E., III; Maggio, J. E. *Tetrahedron Lett.* **1981**, 287-290. For a molecule to have a topologically nonplanar graph, it is necessary (but not sufficient) that no planar representation of the molecule exists that has no bonds crossing. The catenanes (two interlocked rings) would be considered simply as two disconnected graphs in graph theory and are therefore planar. For a graph theoretical discussion of this, see: Busacker, R. G.; Saaty, T. L. "Finite Graphs and Networks: An Introduction with Applications"; McGraw-Hill: New York, 1965; p 7. Because double-bond isomerization (geometry) is not considered in graph theory, the more recent "betweenanenes" can be drawn without edge crossings and are also planar.

(6) A reaction similar to that reported here, although almost certainly not "electrocyclic" in nature, has been reported: Weitemeyer, C.; deMeijere, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 686-687.

(7) Maggio, J. E.; Simmons, H. E., III; Kouba, J. K. *J. Am. Chem. Soc.*, preceding paper in this issue.

(8) Deslongchamps, P. *Heterocycles* **1977**, *7*, 1271-1317.

(9) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Academic Press: New York, 1970.

(10) Pritchard, J. G.; Siddiqui, I. *J. Chem. Soc., Perkin Trans. 2* **1973**, 452-457.

(11) In this work, the downfield and upfield resonances were assigned to the ^{16}O- and ^{18}O-labeled molecules, respectively, by comparing the intensities of the resonances with the amounts of M and M + 2 ions appearing in the mass spectrum. All observed isotope effects on chemical shifts over one chemical bond are in this direction; upfield signals arise from the nuclei bound to the heavier isotope.[3,4] A single example of a two-bond effect (0.004 ppm) has been reported by Vederas.[4]

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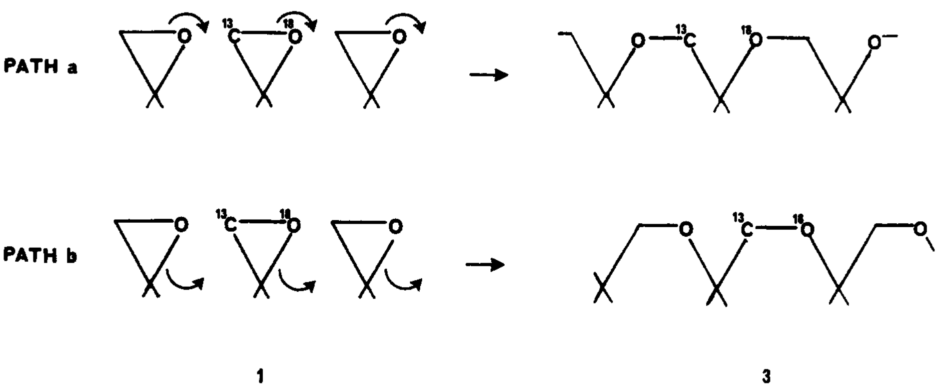
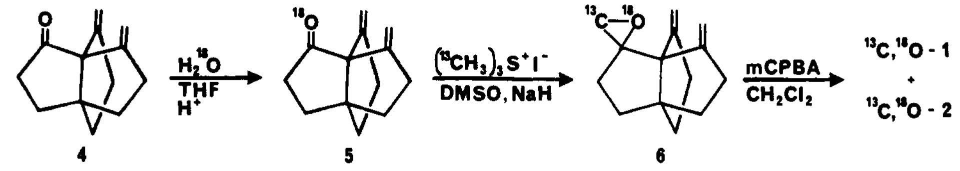
Scheme II



Scheme III



atom be directly bonded to an unlabeled oxygen, it will appear as a single NMR resonance.

Triepoxide **1** labeled with both ^{13}C (90%) and ^{18}O (45%) in one of the three epoxide groups was prepared by the route shown in Scheme III.[13-15] The ^{13}C NMR spectrum[16] of ^{13}C, [^{18}O]-**1** showed two resonances (46.77 and 46.74 ppm downfield of Me_4Si) having relative intensities of 55:45 (downfield:upfield). The isotopic perturbation of the ^{13}C chemical shifts ($\Delta\delta$ 0.030)[17] is the largest that has been reported to date for ether bonds. Rearrangement by path a, breaking the ^{13}C–^{18}O bond in labeled **1** would produce triether **3** having a single ^{13}C NMR resonance. Path b would retain the ^{13}C–^{18}O bond, producing triether **3** showing two resonances with relative intensities of 55:45.

In fact, both thermal and acid-catalyzed rearrangement[2] of [^{13}C,^{18}O]-**1** produced [^{13}C,^{18}O]-**3**, displaying two ^{13}C resonances ($\Delta\delta$ 0.023),[17] with peak intensities in a ratio of 55:45. Thus, to within experimental error, none of **3** was formed from **1** via path a.[18]

Although the approach we have outlined here should be useful for mechanistic studies, it was disappointing to find that reaction along path a was not observed in competition with that along path b. Despite many efforts to exclude traces of acid from both the substrate and the reaction vessel we cannot exclude the possibility that the rearrangement from **1** to **3** by path b is catalyzed by contaminants. Removing the influence of any contaminants, for example, by using a laser for multiphoton excitation,[19] might permit us to observe the elusive $2\sigma + 2\sigma + 2\sigma$ to $2\sigma + 2\sigma + 2\sigma$ electrocyclic reaction. It is also possible that there exists no low-energy electrocyclic pathway, either because the conformation shown in Figure 1 is not energetically accessible or because additional geometric requirements exist for electrocyclic reactions that make and break only σ bonds. One such requirement may be that the three atoms involved at any one reaction center must be collinear.[20] Thus, the apparent difficulty in achieving such linearity in electrocyclic rearrangements involving only σ bonds may account for their scarcity in organic chemistry. Interestingly, if we interpret the mode of rearrangement observed in terms of a rate-limiting heterolysis of the side C–O bond, molecular models suggest that there is an accessible conformation for the subsequent steps which, although not "concerted", permits each to proceed via a transition state having a linear arrangement of attacking oxygen, carbon, and leaving oxygen.

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(12) Both ^{16}O and ^{18}O nuclei have zero spin; thus the relaxation times and line widths of the adjacent ^{13}C nuclei are negligably affected by this isotopic substitution, and peak integrals accurately reflect the ^{16}O:^{18}O ratio at the position adjacent to the labeled carbon. This experiment cannot be done with ^{17}O; scalar spin–spin relaxation of the quadrupolar nucleus severely broadens resonances of adjacent ^{13}C nuclei.

(13) Ketodiolefin[14] labeled with ^{18}O (**5**) was prepared by exchange of 4 (110 mg) in THF with $H_2{}^{18}O$ (80 μL) catalyzed by a small amount (2 μL) of concentrated HCl. Trimethylsulfonium iodide labeled with ^{13}C was synthesized from $^{13}CH_3I$ and freshly prepared Na_2S. The sulfonium ylide was prepared and reacted with **5** by the method of Corey[15] (Scheme III) to produce the monoepoxide **6**. Epoxidation with *m*-chloroperbenzoic acid produced a mixture of symmetrical **1** and unsymmetrical **2** triepoxides labeled with ^{13}C and ^{18}O; the mixture was separated by preparative thin-layer chromatography (silica gel, eluant 2:1 hexane:ether). All products were characterized by NMR, IR, and mass spectroscopies and gave satisfactory analyses.

(14) Drouin, J.; Leyendecker, F.; Conia, J. *Tetrahedron Lett.* **1975**, 4053–4056; *Tetrahedron* **1980**, *36*, 1203–1208.

(15) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.

(16) ^{13}C spectra at 25.2 and 67.9 MHz were recorded on instruments fitted with 5-mm probes. Typical experimental line widths were 0.5 Hz, with a digital resolution of 0.1 Hz.

(17) The magnitude of the chemical-shift isotope effect ($\Delta\delta$) in **1** and **3** is consistent with that observed in model compounds which were prepared as described above.[13] Values for the isotopic perturbation of chemical shift ($\Delta\delta$) were obtained for the following ketones, cyclohexanone (0.053), cyclopentanone (0.050), cyclobutanone (0.051), acetone (0.049), and 4 (0.051); the epoxides, 1-oxaspiro[2.5]octane (0.033), **1** (0.030), and **6** (0.030); and tetrahydrofuran (0.024) and **3** (0.023). Resolution in these cases was ±0.002 ppm. The isotopic perturbations seen in epoxides are uniformly larger than those seen in other ethers.[4] This may be understood in terms of an expected difference in anharmonicity in the carbon–oxygen bond potential wells of these two classes of compounds. Jameson, C. J. *J. Chem. Phys.* **1977**, *66*, 4977–4982; 4983–4988.

(18) Experimental uncertainty is a function of the signal/noise ratio of the spectra (about 40:1 in these experiments). The contribution of path a to the conversion from **1** to **3** is 0.5 ± 1.2%.

(19) Olzyna, K. J.; Grunwald, E.; Keehn, P. M.; Anderson, S. P. *Tetrahedron Lett.* **1977**, 1609–1612. Berman, M. R.; Comita, P. B.; Moore, C. B.; Bergman, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 5692–5694.

(20) This geometric requirement is well-known for displacement reactions at saturated carbons: Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059–2069.