Communications to the Editor

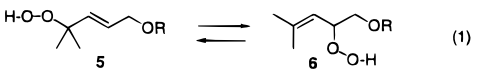
Preparation of an Unsymmetrically Labeled Allylic Hydroperoxide and Study of Its Allylic Peroxyl Radical Rearrangement

Jennifer R. Lowe and Ned. A. Porter*

Department of Chemistry, Duke University
Durham, North Carolina 27708

Received July 11, 1997

Allylic hydroperoxides are formed in the free radical and singlet oxygen oxidation of unsaturated compounds. Allylic hydroperoxides are also formed enzymatically, the prostaglandin G family being one example having this substructure. Allylic hydroperoxides undergo a rearrangement[1] thought to be free radical in nature (see eq 1) in which oxygen is transferred across the allyl group. The mechanism of the allylic rearrangement has been long debated with several mechanisms proposed.

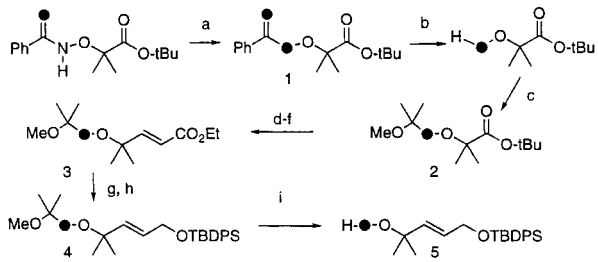


(1)

Evidence supports the notion that the rearrangement is free radical since it is initiated and inhibited with known radical initiators and inhibitors. While tracing the course of peroxyl oxygens during rearrangement would provide valuable mechanistic insight, experiments with compounds having a specific hydroperoxide oxygen labeled have not been possible because of the synthetic inaccessibility of the requisite hydroperoxides. We report here the preparation of an allylic hydroperoxide labeled with ^{18}O (shown as ●) only in the peroxide terminal position along with our first studies of the allylic rearrangement of this compound.

Reaction of the hydroxamate ester (Scheme 1), labeled in the carbonyl oxygen with 90% ^{18}O,[2] with nitrosyl chloride gives perester **1** in yields ranging from 28 to 40%.[3] Hydrolysis with lithium hydroxide affords the known hydroperoxide as a crystalline solid in 85% yield. Protection of the hydroperoxide as a perketal and reduction of **2** to the corresponding alcohol is realized with diisobutyllithium aluminum hydride (DIBAL-H), and the product alcohol is oxidized with pyridinium dichromate.[4] The crude aldehyde can be reacted with the stabilized ylide in benzene at room temperature for 48 h to give the unsaturated ester **3**. A second DIBAL-H reduction and derivatization with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) gives the allylic silyl ether **4.** Removal of the hydroperoxide protecting group with 4:2:1 THF/AcOH/H_2O at 0 °C gives allylic hydroperoxide **5**, formed in 47% overall yield in the six steps from **2**.[5] Reaction of **5** with triphenylphosphine gives triphenylphosphine oxide labeled with 44% ^{18}O and the structurally related alcohol that contains no label. This establishes the position of the oxygen label as being in the terminal oxygen[6] and furthermore is consistent with the presumed mechanism of the formation of **1** from a benzoyloxy radical in which the label scrambles between the two equivalent oxygens.

Scheme 1



a.) $NaNO_2$, HCl, K_2CO_3, CH_2Cl_2, -20 °C, then nujol, 0 °C to rt; 28-40%.
b.) LiOH:H_2O, THF:H_2O, 85%. c.) 2-Methoxypropene, CH_2Cl_2, cat PPTS, 97%.
d.) DIBAL-H, THF, -78 °C. e.) PDC, CH_2Cl_2. f.) $Ph_3P{=}CHCO_2Et$; C_6H_6; 65 % over 3 steps.
g.) DIBAL-H, THF, -78 °C, 79%. h.) TBDPS-Cl, DMF, imidazole, 96%.
i.) 4:2:1 THF:H_2O:AcOH, 0 °C, 95%.

Rearrangement of **5** in dodecane was initiated by di-*tert*-butyl hyponitrite at temperatures of 40 °C or below and by azobisisobutyronitrile (AIBN) at higher temperatures.[7] Rearrangements were carried out under air, aliquots were taken, and the product hydroperoxide **6** was separated from **5** by HPLC on silica gel. Isolated **5** and **6** were reacted with triphenylphosphine, and the phophine oxide and product alcohol were analyzed by GC-MS to determine the isotopic composition of the terminal and proximal oxygen of the two hydroperoxides. Data from a typical rearrangement are presented in Figure 1. Extrapolation of the normalized percent label present in the proximal and terminal positions of **6** to zero time gives information not only about the regioselectivity of the rearrangement but also provides a measure of the fraction of label lost during rearrangement. The data presented in the Figure 1 indicate that, at 60 °C in dodecane, 64% of the terminal label in **5** is transferred to the proximal position of **6** while 6.4% transfers to the product terminal position and 29.6% of the label is lost to the atmosphere.

Scheme 2 presents time zero extrapolated product label information for the rearrangement of **5** → **6** as well as for rearrangements of **6** → **5** carried out at 20, 40, and 60 °C. The rearrangement is temperature dependent, reactions carried out at lower temperatures proceeding with less loss of label to the atmosphere and with more positional selectivity of the label

* Author to whom correspondence should be addressed at the following: tel (919) 660-1550, Fax (919) 660-1605, email porter@chem.duke.edu.

(1) (a) Schenck, G. D.; Neumuller, O. A.; Eisfeld, W. *Angew. Chem.* **1958**, *70*, 595. (b) Brill, W. F. *J. Chem. Soc., Perkin Trans. 2* **1984**, 621. (c) Porter, N.; Zuraw, P. *J. Chem. Soc., Chem. Commun.* **1985**, 1472. (d) Beckwith, A. L.; Davies, A. G.; Davison, I. G. E.; Maccoll, A.; Mruzek, M. H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 815. (e) Avila, D. V.; Davies, A. G.; Davison, I. G. E. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1847. (f) Mills, K. A.; Caldwell, S. E.; Dubay, G. R.; Porter, N. A. *J. Am. Chem. Soc.* **1992**, *114*, 9689. (g) Porter, N. A.; Caldwell, S. E.; Mills, K. A. *Lipids* **1995**, *30*, 277 and references cited therein.

(2) The hydroxamate ester was synthesized from ^{18}O-labeled benzoyl chloride and the corresponding alkoxyl amine. ^{18}O-labeled benzoyl chloride is prepared in one step from benzotrichloride and $H_2{}^{18}O$ in a modified procedure: Ponticorvo, L.; Rittenberg, D. *J. Am. Chem. Soc.* **1954**, *76*, 1705.

(3) (a) Koenig, T.; Deinzer, M. *J. Am. Chem. Soc.* **1966**, *88*, 4518. (b) Koenig, T.; Deinzer, M. *J. Am. Chem. Soc.* **1968**, *90*, 7014. (c) Koenig, T.; Deinzer, M.; Hoobler, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 938. (d) Koenig, T.; Hoobler, J. A.; Mabey, W. R. *J. Am. Chem. Soc.* **1972**, *94*, 2514. (e) Koenig, T.; Hoobler, J. A. *Tetrahedron Lett.* **1972**, 1803. (f) Koenig, T. *Tetrahedron Lett.* **1973**, 3487.

(4) For precedents for the transformations presented in Scheme 1, see: Dussault, P. *Synlett* **1995**, 997.

(5) Hydroperoxide **5** is stored as a dilute solution stabilized with 5% butylated hydroxytoluene (BHT) and is purified by HPLC on silica gel immediately before use.

(6) Caldwell, S. E.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 8676.

(7) In a typical rearrangement, hydroperoxide concentration is 0.01 M and initiator concentration is 0.001 M. Rearrangements are carried out over the course of 10−24 h with aliquots taken at regular intervals. During the first 5−10 h of rearrangement, only starting material and rearrangement hydroperoxide can be detected either by HPLC or by NMR. At later times, termination products corresponding to the alcohol and ketone structurally analogous to **6** can be observed by both HPLC and NMR. The hydroperoxide **6** and these termination products generally account for greater than 95% of consumed **5**, even at long reaction times (>24 h). An equilibrium mixture of **5**/**6** of 55:45 is approached for the rearrangement started from either hydroperoxide.

S0002-7863(97)02303-2 CCC: $14.00

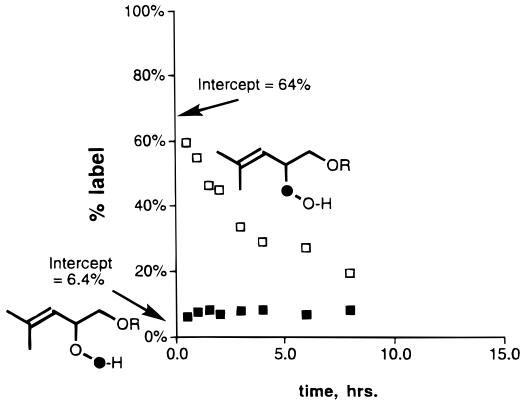
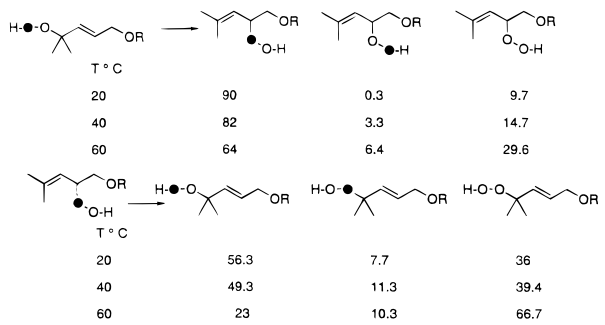


Figure 1. Normalized ^{18}O label in product **6** from the rearrangement of **5** labeled in the terminal peroxide oxygen. The rearrangement is at 60 °C in dodecane.

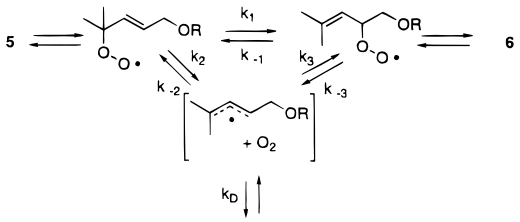
Scheme 2



transfer. This allows for the isolation of **6** from reactions at 20 °C that has label almost entirely at the proximal position. In fact, the reverse rearrangements (**6** → **5**) were carried out with **6** isolated from early aliquots of the **5** → **6** rearrangement at 20 °C and generally had a proximal/terminal label ratio of >100:1. Another feature of the rearrangement is that the **5** → **6** rearrangement (tertiary to secondary) is apparently more selective than the **6** → **5** process (secondary to tertiary). Thus, while the proximal to terminal product ratio for the 60 °C **5** → **6** process is 10:1 and 30% of the label is lost to the atmosphere, the **6** → **5** rearrangement occurs under identical conditions to give **5** with terminal/proximal label of 2:1 and with fully two-thirds of the label lost.

A mechanism for the rearrangement involving competitive pathways k_1 *vs* k_2 and k_{-1}*vs* k_{-3} is presented in Scheme 3. The k_1 pathways (forward and reverse) connect the peroxyl radicals directly by a process in which the terminal oxygen of **5** is transferred to the product proximal position, while the k_2 and k_3 pathways involve fragmentation of peroxyls to a pair species[8] which can collapse to peroxyl with scrambling of label or escape

Scheme 3



to give free allyl and oxygen. The data from Scheme 2 provide an estimate of the competition rate constants. Thus, at 40 °C, k_1/k_2 is approximated by $(82 - 3.3)/(2 \times 3.3 + 14.7) = 3.7$.[9] Estimation of k_1/k_2 at other temperatures followed by Eyring analysis[10] provides $\Delta\Delta H^{\ddagger}$, and $\Delta\Delta S^{\ddagger}$, for the competitive pathways. Thus, $\Delta H^{\ddagger}_2 - \Delta H^{\ddagger}_1 = 9.0$ kcal/mol and $\Delta S^{\ddagger}_2 - \Delta S^{\ddagger}_1 = 26$ eu by this analysis. Analysis of the reverse reaction in a similar way gives similar activation parameters, $\Delta H^{\ddagger}_{-3} - \Delta H^{\ddagger}_{-1} = 9.0$ kcal/mol and $\Delta S^{\ddagger}_{-3} - \Delta S^{\ddagger}_{-1} = 29$ eu. These data are consistent with a competition between an associated, ordered reaction (k_1) having a negative activation entropy with a dissociative process (k_2) having a positive activation entropy. The studies reported here do not distinguish between associative pathways involving a concerted oxygen transfer or a stepwise endocyclization−fragmentation. Experiments with analogous peroxyls do not, however, provide evidence for a carbon radical intermediate in the rearrangement,[1b−d] pointing to the concerted [3,2] oxygen transfer in those systems.

The availability of unsymmetrically labeled hydroperoxides by the synthetic strategy reported here permits other mechanistic issues, including the nature of the stereoselectivity of the associative and disociative pathways,[11] to be addressed with this powerful probe. The results of these studies will be reported in due course.

Acknowledgment. NSF support and the receipt of an NIH MERIT Award is gratefully acknowledged. J.R.L. acknowledges receipt of a C. R. Hauser Award. We thank Dr. Patrick H. Dussault of the University of Nebraska for helpful discussions.

Supporting Information Available: Synthetic procedures, analytical data, and Arrhenius plots for rearrangements (8 pages). See any current masthead page for ordering and Internet access instructions.

JA9723038

(8) The reversible addition of oxygen to resonance-stabilized radicals has been discussed extensively. See ref 1d. As an example, the equilibrium of the cumylperoxyl and cumyl radicals and dioxygen has been estimated to be 10^{-9} M^{-1} making carbon radical−carbon radical termination reactions unlikely. For a discussion of this point, see: Howard, J. A.; Chenier, J. H. B.; Yamada, T. *Can J. Chem.* **1982**, *60*, 2566. Nangia, P. S.; Benson, S. W. *Int. J. Chem. Kinet.* **1980**, *XII*, 19.

(9) Microscopic reversibility requires that $k_1/k_{-1} = (k_2/k_{-2})(k_3/k_{-3})$. See: Hammett, L. H. *Physical Organic Chemistry*, 2nd ed.; McGraw Hill: New York, **1970**; p 142.

(10) See the Supporting Information for Arrhenius plots.

(11) Porter, N. A.; Mills, K. A.; Caldwell, S. E.; Dubay, G. R. *J. Am. Chem. Soc.* **1994**, *116*, 6697.