The Mechanism of the [3,2] Allylperoxyl Rearrangement: A Radical–Dioxygen Pair Reaction That Proceeds with Stereochemical Memory†

Ned A. Porter,* Karen A. Mills, Sarah E. Caldwell, and George R. Dubay

Contribution from the Department of Chemistry, Duke University, Durham, North Carolina 27708

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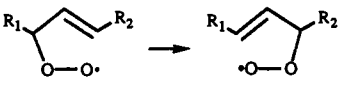
Abstract: The mechanism of the [2,3] allyl hydroperoxide rearrangement was investigated. The rearrangement proceeds with stereoselectivity and is promoted by free radical initiators. Recent theoretical investigations by Boyd *et. al.* support a β-fragmentation process involving an intermediate allyl radical for this rearrangement, and this mechanism was probed using solvent viscosity, isotopic labeling, and stereochemistry. These studies indicate that solvent viscosity and temperature affect the partitioning between escape and collapse of an intermediate allyl radical–dioxygen caged pair and support the dissociative mechanism. An increase in solvent viscosity results in a decrease in escape product and an identical increase in pair collapse product formed with stereocontrol.

Hydroperoxides are the main products in the autoxidation of organic compounds.[1] The hydroperoxide O–H bond is relatively weak ($D_{ROO-H} \sim 90$ kcal/mol),[2] and hydroperoxides readily react with organic free radicals such as alkoxyls to generate peroxyl radicals.[3] Allylperoxyl radicals, formed in the autoxidation of alkenes, are known to undergo [2,3] rearrangements in which the oxygen atoms, the two component, migrate across the allylic backbone, the three component (Scheme 1).[4] The free radical nature of the rearrangement is supported by experimental evidence; the rearrangement is catalyzed by free radical initiators or light, and the rearrangement is inhibited by phenolic antioxidants.[5]

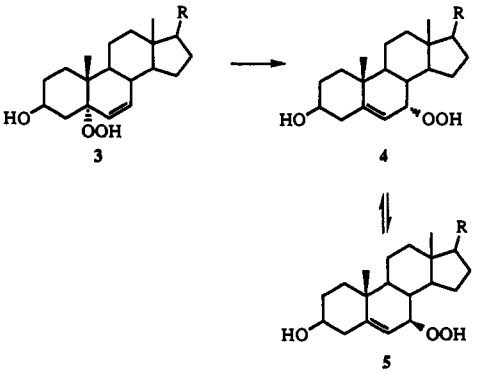
Despite the fact that [2,3] allylperoxyl rearrangements have been known since the late 1950s, the mechanism is still under debate.[4] In 1958, Schenck *et al.* reported on the rearrangement of cholesterol hydroperoxides in which the tertiary hydroperoxide 5α-hydroperoxy-3β-hydroxycholest-6-ene (**3**) slowly rearranges to its secondary allylic isomer **4** with complete retention of the α configuration (Scheme 2).[6]

Smith *et al.* showed that compound **4** undergoes a slower epimerization to the 7β-hydroperoxide **5**,[7] and in 1989, Beckwith and Davies performed the cholesterol allylperoxyl rearrangement under $(^{18}O)_2$ and observed no ^{18}O incorporation in the 7α-hydroperoxy-3β-hydroxycholest-5-ene (**4**). The epimerization of this product to 7β-hydroperoxy-3β-hydroxycholest-5-ene (**5**), a process that is also free radical in nature, involves 73–83% ^{18}O incorporation.[8] Beckwith and Davies suggested that the rearrangement of **3** to **4** involves a concerted [2,3] allylperoxyl rearrangement, whereas the second rearrangement of **4** to **5** proceeds through a dissociative mechanism.

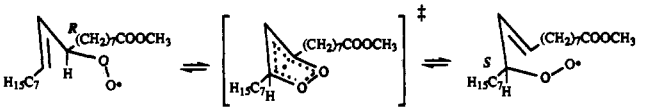
Scheme 1. The [2,3] Allylperoxyl Rearrangement



Scheme 2. Cholesterol [2,3] Allylperoxyl Rearrangement



Scheme 3. Concerted Mechanism for the Allylperoxyl Rearrangement



Acyclic allylperoxyls have also been investigated,[9] and the evidence from these studies is as follows: (1) the rearrangement proceeds with significant transfer of configuration from the stereogenic center of the starting hydroperoxide to that of the product,[9b] and (2) little atmospheric oxygen is incorporated into the product of rearrangement.[9c] These results suggest a concerted mechanism for the rearrangement, with transition state **6** as shown in Scheme 3 being consistent with the stereochemical data acquired.

† Taken, in part, from the dissertation of K. A. Mills, Duke University, 1994.

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(2) Benson, S. W. *J. Am. Chem. Soc.* **1965**, *87*, 972.

(3) For general and theoretical aspects of the peroxide group, see: Cremer, D. *The Chemistry of Functional Groups, Peroxides*; Patai, S., Ed.; John Wiley and Sons: New York, 1983.

(4) Porter, N. A. *Membrane Lipid Oxidation*; Vigo-Pelfrey, C., Ed.; CRC: Boca Raton, FL, 1990; Vol. 1, pp 33–62.

(5) Frimer, A. A. *Chem. Rev.* **1979**, *79*, 359.

(6) (a) Schenck, G. O. *Angew. Chem.* **1957**, *69*, 579. (b) Schenck, G. D.; Neumuller, O. A.; Eisfeld, K. C. *Angew. Chem.* **1958**, *70*, 595.

(7) Smith, L. L. *Cholesterol Autoxidation*; Plenum: New York, 1981.

(8) (a) Beckwith, A. L.; Davies, A. G.; Davison, I. G.; Macoll, A.; Mruzek, M. H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 815. (b) Davies, A. G.; Davison, I. G. *J. Chem. Soc., Perkin Trans 2* **1989**, 825.

(9) (a) Brill, W. F. *J. Chem. Soc., Perkin Trans. 2* **1984**, 621. (b) Porter, N. A.; Kaplan, J. K.; Dussault, P. H. *J. Am. Chem. Soc.* **1990**, *112*, 1266. (c) Porter, N. A.; Sullivan Wujek, J. *J. Org. Chem.* **1987**, *52*, 508.

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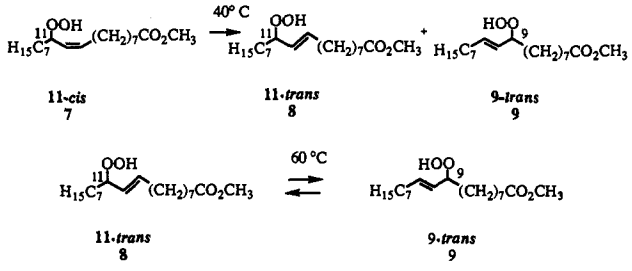
Scheme 4. Rearrangements of Methyl (*Z*)-11-Hydroxyperoxyoctadec-9-enoate (**7**) and Methyl (*E*)-11-Hydroperoxyoctadec-9-enoate (**8**)



Recent theoretical investigations initiated by Boyd, Boyd, and Barclay failed, however, to find a concerted transition state like **6** proposed for the rearrangement.[10] Calculations were performed at the unrestricted Hartree–Fock and *MP*2 levels on the simple allylperoxyl radical. Attempts to locate the concerted transition-state structure failed, but they revealed a localized cyclic dioxolanyl radical close in energy to that of the allylperoxyl radical but with a barrier in excess of 40 kcal/mol separating the cyclic carbon radical and the open peroxyl species. Furthermore, the calculations revealed that β-fragmentation of the allylperoxyl to an allyl radical–dioxygen pair requires only 22 kcal/mol and suggested that the [2,3] allylperoxyl rearrangement proceeds by this lower energy β-fragmentation process.

Stimulated by the apparent contradiction of experiment and theory, we undertook an investigation of the acylic rearrangement of allylperoxyls derived from methyl oleate. We sought to use stereochemistry, isotopic labeling, and solvent viscosity to probe the mechanism of the rearrangement, and we report here the results of this inquiry.

Results and Discussion

Two allyl hydroperoxides derived from methyl oleate were examined as reactants in the [2,3] allylperoxyl rearrangement. Methyl *(Z)*-11-hydroperoxyoctadec-9-enoate (**7**) and the geometric isomer methyl *(E)*-11-hydroperoxyoctadec-9-enoate (**8**), both prepared from the free radical autoxidation reaction of methyl oleate,[11] were used as starting materials in this study. The autoxidation of methyl oleate was run to 3–10% conversion to hydroperoxide products that were isolated by flash chromatography. The hydroperoxides **7** and **8** were separated from the mixture by preparative HPLC on silica.

In a typical preparative HPLC separation, 150–500 mg of the oleate hydroperoxide mixture obtained from a 5-g autoxidation was separated over the course of five injections on a normal-phase 41.4-mm × 25-cm column. Following this initial separation process, the isolated hydroperoxides were reinjected affording ~20–30 mg of pure compounds. Some rearrangement of the hydroperoxides occurs during the isolation process if free radical inhibitors are not present.[12] The radical inhibitor 2,4,6-tri-*tert*-butylphenol (TTBP) was added to the isolated hydroperoxide to suppress rearrangement prior to use. In a final HPLC purification step just before rearrangement studies, the hydroperoxide was separated from the inhibitor.

Rearrangements were performed on 0.01 M hydroperoxide in hexane at 22 and 40 °C for **7** or at 40 and 60 °C for **8**.[13] Di-*tert*-butyl hyponitrite (DTBN), was the free radical initiator used[14] for the 22 and 40 °C rearrangements, while 2,2′-azobisisobutyronitrile (AIBN) was used for rearrangements at 60 °C. Aliquots taken over the course of the rearrangement were quenched with the radical inhibitor TTBP. HPLC revealed that the 11-*(Z)* oleate hydroperoxide rearranges at 40 °C to give two hydroperoxide products. Analysis of the rearrangement mixture by HPLC–CIMS gives evidence that one of the products is the 11-*(E)* hydroperoxide **8** and the other is methyl *(E)*-9-hydroperoxyoctadec-10-enoate (**9**).[15] Rearrangement of the 11-*(E)* oleate hydroperoxide at 60 °C yields a mixture of the starting hydroperoxide and hydroperoxide **9**.

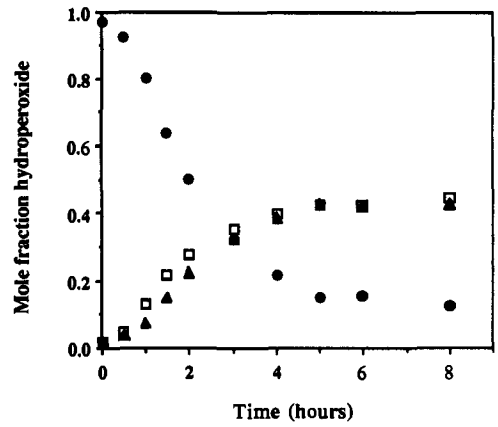


Figure 1. Mole fraction of hydroperoxide *vs* time for the 11-*cis*-allylperoxyl rearrangement at 40 °C (0.01 M 11-*cis*-hydroperoxide/0.001 M DTBN): circles for **7**, triangles for **8**, and squares for **9**.

Rearrangements were typically monitored for a 10-h period, and chromatograms for successive aliquots show the disappearance of the starting hydroperoxide and the formation of products. Peak areas were converted into mole fractions and plotted *vs* time. The course of rearrangement for the hydroperoxide **7** is shown in Figure 1. At long times of rearrangement, the hydroperoxide product consists of a 50:50 mixture of the *trans* hydroperoxides **8** and **9** for rearrangements starting from either **7** or **8**. Termination products[9c] become a significant component of the reaction mixture at long times of reaction.

Stereochemical Studies. Enantiomer resolution of **7** was achieved by the classical resolution method developed earlier for the *trans* compounds **8** and **9**.[16] By employing the resolving reagent *trans*-2-phenylcyclohexanol 2-propenyl ether (**10**), the racemic 11-*cis* hydroperoxide **7** was converted to a mixture of diastereomeric perketals **11** (Scheme 5).

While the perketals of the 9-*trans* and 11-*trans* oleate hydroperoxides had been previously resolved by normal-phase HPLC, the derivatized 11-*cis* oleate hydroperoxide perketals were not separated by this method. However, using preparative reverse-phase conditions, the perketals **11** were resolved to optical purities of greater than 99% diastereomeric excess. Removal of the perketal by mild acid hydrolysis gave the hydroperoxides in >99% enantiomeric excess. Proof of absolute stereochemistry of the hydroperoxides was achieved by the empirical technique developed by Gonella *et. al.* for secondary allylic alcohols.[17] The diastereomeric perketals were reduced with PBu_3 to the oleate alcohol that was subsequently converted to the *p*-bromobenzoate. CD spectroscopy was then used to assign the configuration of the *p*-bromobenzoates. As a double check, the *(S)*-11-*cis p*-bromobenzoate was photoisomerized to the *(S)*-11-*trans p*-bromoben-

(10) Boyd, S. L.; Boyd, R. J.; Barclay, R. C.; Porter, N. A. *J. Am. Chem. Soc.* **1993**, *115*, 687. See also: Boyd, S. L.; Boyd, R. J.; Barclay, R. C. *J. Am. Chem. Soc.* **1990**, *112*, 5724.

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(12) For a discussion of inhibition, see: Howard J. A. *Free Radicals*; Kochi, J. K., Ed.; John Wiley and Sons: New York, 1973; Vol II.

(13) A preliminary account of this work has appeared: Mills, K. A.; Caldwell, S. E.; Dubay, G. R.; Porter, N. A. *J. Am. Chem. Soc.* **1992**, *114*, 9690.

(14) (a) Traylor, T. G.; Kiefer, H. *Tetrahedron Lett.* **1966**, *49*, 6163. (b) Mendenhall, G. D. *Tetrahedron Lett.* **1983**, *24*, 451.

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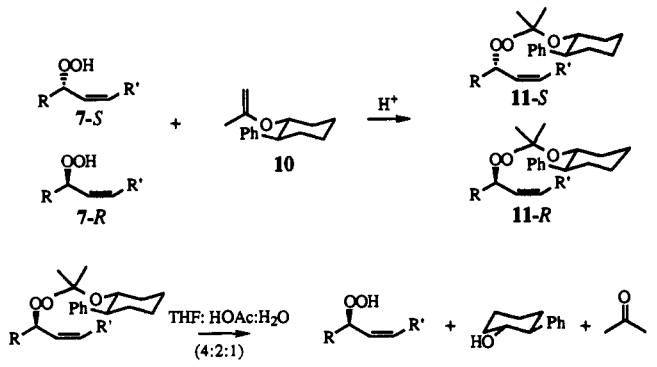
(16) (a) Porter, N. A.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 6276. (b) Porter, N. A.; Dussault, P. H.; Breyer, R. A.; Kaplan, J.; Morelli, J. *Chem. Res. Toxicol.* **1990**, *3*, 237.

(17) Gonella, N. C.; Nakanishi, K.; Martin, V. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3775.

Scheme 5. Resolution of Racemic Oleate Hydroperoxides



zoate analyzed previously by Dussault.[16] This photoreaction, carried out in the presence of triplet sensitizer benzophenone, generated a 60:40 *trans:cis* ratio of *p*-bromobenzoate products.

Rearrangement reactions were performed on 0.01 M *(R)*-11-*cis* hydroperoxide/0.001 M DTBN in hexane at 40 °C. The rearrangement progress was monitored by analytical normal-phase HPLC. Aliquots were taken periodically, and the hydroperoxides isolated by HPLC were perketalized with the chiral vinyl ether **10** to determine the enantiomeric excess of the recovered starting material and the product hydroperoxides. Rearrangement data are presented in Figure 2 with enantiomeric excess plotted *vs* the extent of rearrangement, 1 – [mole fraction of 11-*cis* hydroperoxide (χ_{11cis})], for each isomer.

Of further significance, Figure 2a illustrates that optical purity degrades over time for all three hydroperoxides. Comparison of these data with our earlier finding of high stereoselectivity in the 9-*trans* to 11-*trans* rearrangement[9b] leads to the conclusion that the rearrangement starting from the *cis* allyl hydroperoxide occurs with less stereoselectivity than rearrangements proceeding from a *trans* hydroperoxide. The rearrangement was also carried out at 22 °C. The data from this study, presented in Figure 2b, indicate substantially improved stereoselectivity for the rearrangement at the lower temperature.

Oxygen Labeling and Solvent Viscosity. The concerted mechanism shown in Scheme 3 is consistent with the data obtained in the stereochemical studies. The data are also consistent with a fragmentation pathway in which recombination of an initial radical pair occurs with stereochemical memory, as shown in Scheme 6. In this mechanism, fragmentation of the allylperoxyl radical occurs to give an allyl radical–dioxygen pair. Recombination of the allyl radical and dioxygen occurs to return to the starting peroxyl or to give the product peroxyl. Since the reaction of carbon radicals with dioxygen is very fast, at or near the diffusion-controlled limit,[18] one expects that recombination of the allyl radical with dioxygen would compete with separation of the initially-formed pair. That is to say, one expects a solvent cage effect in the rearrangement if the dissociative mechanism operates and if the reaction of dioxygen with the carbon radical is diffusion controlled. Collapse of the initially-formed pair to give reactant and product peroxyls should compete with diffusive separation of the pair.

To distinguish between a dissociative and caged pair mechanism, we performed the rearrangement in solvents of different viscosity under an atmosphere of $(^{18}O)_2$ to determine if a cage effect is operative in the process.[19] A method was developed to directly analyze the hydroperoxides for ^{18}O incorporation during rearrangement. This avoids tedious derivatization steps required for analysis by GC–MS. The method developed involves direct

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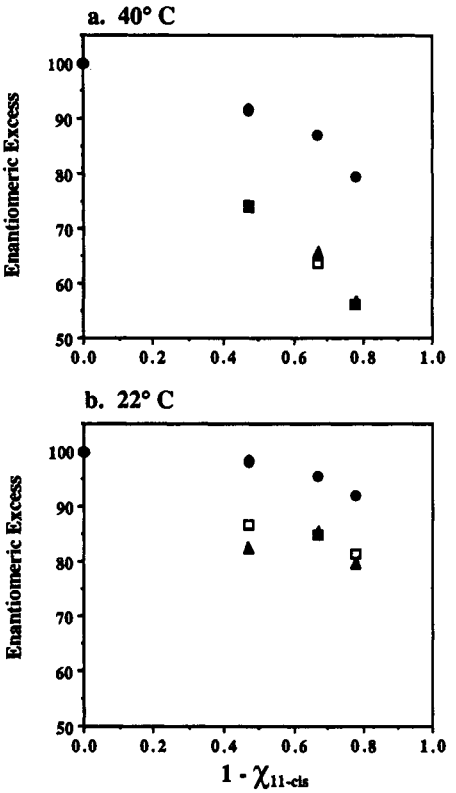
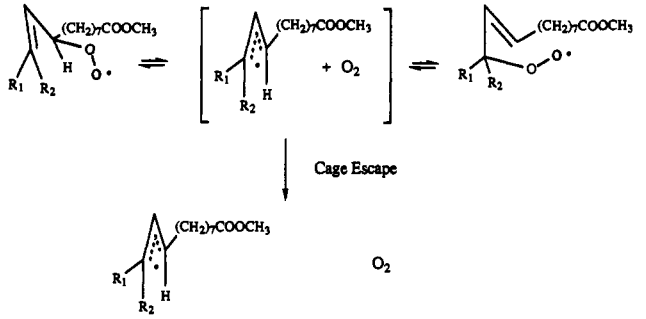


Figure 2. Stereochemical course of the *cis* allylperoxyl rearrangement. The mole fraction of 11-*cis* hydroperoxide (χ_{11cis}) **7** was determined by HPLC. The enantiomeric excess of hydroperoxide was determined by HPLC of the perketal derivative: circles for **7**, triangles for **8**, and squares for **9**.

Scheme 6. Pair Mechanism for the Allylperoxyl Rearrangement



analysis of the regioisomeric hydroperoxides by HPLC–CIMS. By this technique, the hydroperoxides are separated by HPLC, and the chromatographic peaks of the 11-*cis*, 9-*trans*, and 11-*trans* hydroperoxides are analyzed by CIMS to determine ^{18}O incorporation.

The amount of ^{18}O incorporated into the hydroperoxides was determined using two methods. The first involves analysis of the most abundant ion m/z = 311 ($MH^+ - H_2O$). Thus, the m/z = 311 and 313 (M + 2) ions for the hydroperoxides are compared. The second method involves the analysis of the ammonium adduct of the molecular ion where the m/z = 346 and 350 (M + 4) ions are compared.

The rearrangement was performed in hexane, dodecane, and octadecane at 0.01 M 11-*cis* hydroperoxide in hexane at 40 °C in a sealed vessel containing 99% $(^{18}O)_2$ at 1 atm. Aliquots were

(19) See, for example: (a) Pryor, W. A.; Smith, K. *J. Am. Chem. Soc.* **1970**, *92*, 5403. (b) Porter, N. A.; Marnett, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 4361. (c) Koenig, T.; Cruthoff, R. *J. Am. Chem. Soc.* **1969**, *91*, 2562. (d) Koenig, T.; Deinzer, M. *J. Am. Chem. Soc.* **1968**, *90*, 7014. (e) Koenig, T.; Huntington, J.; Cruthoff, R. *J. Am. Chem. Soc.* **1970**, *92*, 5413. (f) Pryor, W. A.; Morkved, E. H.; Bickley, H. T. *J. Org. Chem.* **1972**, *37*, 1999. (g) Nelson, S. F.; Bartlett, P. D. *J. Am. Chem. Soc.* **1966**, *88*, 145.

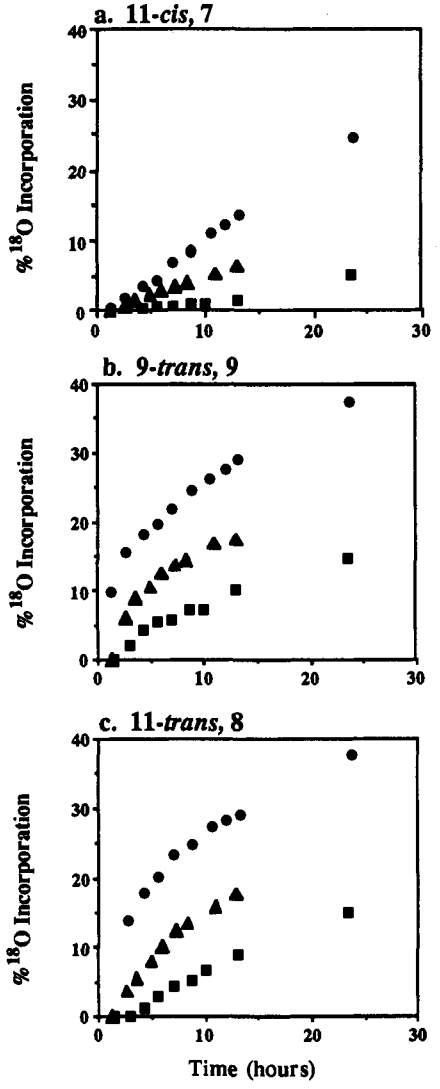


Figure 3. Viscosity dependence on labeled oxygen incorporation at 40 °C for (a) the starting hydroperoxide **7**, (b) hydroperoxide **9**, and (c) hydroperoxide **8**. Percentage of ^{18}O incorporation *vs* time for (a) 11-*cis*, (b) 9-*trans*, and (c) 11-*trans*-hydroperoxides. Circles indicate rearrangements carried out in hexane, triangles, in dodecane, and squares, in octadecane.

withdrawn periodically over 24 h. The overall rate of the disappearance of the starting hydroperoxide is nearly independent of solvent viscosity, the rate of rearrangement in octadecane being slightly retarded compared to those in hexane and dodecane. We note that both initiation and chain termination processes are solvent viscosity dependent, increasing viscosity leading to a cage effect in the initiation process and a decline in radical–radical termination reactions.

The percentage of ^{18}O incorporation into the hydroperoxides as a function of time is shown in Figure 3 for rearrangements of **7** carried out in hexane, dodecane, and octadecane. For rearrangements run in the more viscous solvents, the amount of ^{18}O incorporation is small relative to that for rearrangements carried out in less viscous solvents; hence, with octadecane (the most viscous solvent), there is relatively little ^{18}O incorporation. The same trends are observed for the starting hydroperoxide and each of the product hydroperoxides, **8** and **9**.

Rearrangement of the *trans* hydroperoxide **8** under an atmosphere of $(^{18}O)_2$ was also studied as a function of solvent viscosity. For this rearrangement carried out at 40 °C in hexane, there is less than 5% ^{18}O incorporation in the 9-*trans* rearrangement product; therefore, it is difficult to detect a viscosity dependence on ^{18}O incorporation with increasing solvent viscosity. Since an increase in temperature decreases solvent viscosity, it was proposed that increasing the temperature would result in an increase in the amount of escape (^{18}O) product and allow detection of a cage effect. Indeed, using 0.01 M 11-*trans* hydroperoxide **8**/0.001 M AIBN at 60 °C, significant levels of ^{18}O incorporation are observed for the product hydroperoxide and the starting compound (data not shown). The amounts of ^{18}O incorporated into the 11-*trans* and 9-*trans* hydroperoxides are similar and solvent viscosity dependent. Thus, at 8 h in the rearrangement, 42% of ^{18}O is incorporated into the product hydroperoxide **9** for the reaction carried out in hexane, while for the solvent dodecane the incorporation is 29% and for the solvent octadecane, at 8 h, the ^{18}O incorporation amounts to 13%.

The viscosity dependence observed gives evidence in support of a cage effect in the allylperoxyl rearrangement. As solvent viscosity increases, the only rate constant presumably affected is the rate of diffusional escape (k_D), and a decrease in this escape leads to more cage recombination and less atmospheric oxygen incorporation.

Stereochemical, ^{18}O, and Solvent Viscosity Studies. Oxygen labeling studies were carried out on optically pure hydroperoxide to determine the stereochemistry of the cage (^{16}O) product and escape (^{18}O) product. If a planar *cis* allyl radical escapes the initial solvent cage and undergoes reaction with atmospheric oxygen (^{18}O), this would presumably occur to give racemic ^{18}O incorporated products. The experimental strategy for these stereochemical/oxygen labeling studies to determine the $^{16}O/^{18}O$ composition of the hydroperoxide enantiomers involved the following: (1) the rearrangement was performed on optically pure 11-*cis* hydroperoxide under an atmosphere of $(^{18}O)_2$, and the rearrangement progress was monitored for the loss of 11-*cis* hydroperoxide with time by HPLC; (2) for each aliquot taken, the regioisomeric hydroperoxides (11-*cis*, 9-*trans*, and 11-*trans*) were isolated using normal-phase analytical HPLC; (3) the isolated regioisomeric hydroperoxides were perketalized with the chiral vinyl ether **10** by the standard method; (4) the enantiomeric excess of the derivatized hydroperoxides (11-*cis*, 9-*trans*, and 11-*trans*) was determined by reverse-phase HPLC; and (5) the $^{16}O/^{18}O$ composition in the major and minor enantiomers of the derivatized hydroperoxides was determined by reverse-phase HPLC–CIMS. The ions selected for $^{16}O/^{18}O$ quantitation were $m/z = 311$ (^{16}O incorporation) and 313 (^{18}O incorporation) ions, $MH^+ - H_2O$. Unfortunately, minimal molecular ion for the derivatized hydroperoxide $m/z = 545$ (MH^+) or 562 ($M + NH_4^+$) was detected; therefore, the M + 4 could not be analyzed for ^{18}O incorporation. The experiments started with 5 mg of hydroperoxide at step 1, and by step 5, analysis was performed on microgram quantities of derivatized hydroperoxide. Therefore, sensitivity was a more important issue, and "selected ion monitoring" (SIM) analysis was applied to this system.

During the rearrangement, three aliquots were taken at 4, 6, and 8 h for reactions carried out in hexane, dodecane, and octadecane. For each aliquot, the hydroperoxides were separated by HPLC and converted to the corresponding diastereomeric perketals. The perketal samples were then analyzed by standard reverse-phase HPLC to determine the stereoselectivity of the products formed in the reactions. The results of the stereochemical analyses are presented in Table 1 for rearrangement starting with methyl (*R*)-(*Z*)-11-hydroperoxyoctadec-9-enoate (**7**).

In this stereoselectivity analysis, the (*R*) and (*S*) enantiomers for each hydroperoxide were isolated for further analysis by HPLC–CIMS to quantitate the amount of ^{18}O and ^{16}O incorporated in the major and minor enantiomers. Table 2 presents the data obtained for the three aliquots, while the results from aliquot 3 are presented in graphical form in Figure 4. The histogram in Figure 4 shows the percentages of ^{16}O and ^{18}O for (*R*)- and (*S*)-11-*cis*, -11-*trans* and -9-*trans* hydroperoxides for rearrangements carried out in solvents hexane, dodecane, and

Table 1. Viscosity Effects on the Stereoselectivity of the 11-*cis* Rearrangement

aliquot	solvent	1 – [mole fraction of 11-*cis*][a]	% enantiomer of recovered 11-*cis*[b]	% enantiomer of product 9-*trans*	% enantiomer of product 11-*trans*
1 (4 h)	hexane	0.444	97.9% (*R*)	91.7% (*R*)	90.7% (*S*)
	dodecane	0.461	98.5% (*R*)	94.6% (*R*)	93.1% (*S*)
	octadecane	0.462	99.9% (*R*)	97.6% (*R*)	96.3% (*S*)
2 (6 h)	hexane	0.583	96.3% (*R*)	88.9% (*R*)	87.9% (*S*)
	dodecane	0.592	97.4% (*R*)	92.0% (*R*)	91.0% (*S*)
	octadecane	0.562	99.0% (*R*)	96.0% (*R*)	94.8% (*S*)
3 (8 h)	hexane	0.655	93.5% (*R*)	83.6% (*R*)	83.4% (*S*)
	dodecane	0.661	96.4% (*R*)	89.8% (*R*)	88.6% (*S*)
	octadecane	0.630	97.6% (*R*)	94.3% (*R*)	92.4% (*S*)

[a] Determined by HPLC. [b] Percent of the major enantiomer ± 0.6 (configuration) of the hydroperoxide as determined by HPLC of the perketal derivative. The starting material was the (*R*)-11-*cis* hydroperoxide. Rearrangement was performed at 40 °C.

Table 2. Composition of ^{16}O and ^{18}O Labeled Products

a. (*R*)- and (*S*)-11-*cis* Hydroperoxide **7**

aliquot	solvent	$1-\chi_{11cis}$[a]	%^{16}O (*R*)-**7**[b]	%^{16}O (*S*)-**7**	%^{18}O (*R*)-**7**	%^{18}O (*S*)-**7**
1	hexane	0.444	96.3	0.3	1.9	1.8
	dodecane	0.461	97.7	0.4	0.8	1.1
	octadecane	0.462	99.7	0.0	0.2	0.0
2	hexane	0.583	94.0	0.9	2.3	2.8
	dodecane	0.592	95.6	1.6	1.8	1.0
	octadecane	0.562	98.4	0.4	0.6	0.6
3	hexane	0.655	89.0	1.1	4.5	4.5
	dodecane	0.661	94.1	1.0	2.3	2.3
	octadecane	0.630	96.3	1.3	1.3	1.3

b. (*R*)- and (*S*)-11-*trans* Hydroperoxide **8**

aliquot	solvent	$1-\chi_{11cis}$[c]	%^{16}O (*R*)-**8**[d]	%^{16}O (*S*)-**8**	%^{18}O (*R*)-**8**	%^{18}O (*S*)-**8**
1	hexane	0.444	2	85	8	6
	dodecane	0.461	2	89	5	5
	octadecane	0.462	2	93	2	3
2	hexane	0.583	2	78	10	10
	dodecane	0.592	2	84	7	7
	octadecane	0.562	2	91	3	3
3	hexane	0.655	2	68	14	15
	dodecane	0.661	4	80	8	8
	octadecane	0.630	3	89	4	3

c. (*R*)- and (*S*)-9-*trans* Hydroperoxide **9**

aliquot	solvent	$1-\chi_{11cis}$[e]	%^{16}O (*R*)-**9**[f]	%^{16}O (*S*)-**9**	%^{18}O (*R*)-**9**	%^{18}O (*S*)-**9**
1	hexane	0.444	86	1	6	7
	dodecane	0.461	90	1	4	4
	octadecane	0.462	96	1	2	2
2	hexane	0.583	79	1	10	10
	dodecane	0.592	85	2	7	6
	octadecane	0.562	91	1	4	3
3	hexane	0.655	69	2	14	15
	dodecane	0.661	82	2	8	8
	octadecane	0.630	90	2	4	4

[a] Mole fraction of the 11-*cis* hydroperoxide as determined by HPLC–UV detection. [b] Percentages of ^{16}O and ^{18}O (*R*)- and (*S*)-11-*cis* hydroperoxide **7** calculated from the mole fractions of each enantiomer as determined by HPLC of the perketal derivative and the mole fractions of ^{16}O and ^{18}O labeled **7** as determined by HPLC–CIMS. [c] Mole fraction of the 11-*cis* hydroperoxide (χ_{11cis}) as determined by HPLC–UV detection. [d] Percentages of ^{16}O and ^{18}O (*R*)- and (*S*)-11-*trans* hydroperoxide **8** calculated from the mole fractions of each enantiomer as determined by HPLC of the perketal derivative and the mole fractions of ^{16}O and ^{18}O labeled **8** as determined by HPLC–CIMS. Rearrangements were performed on 0.01 M (*R*)-11-*cis* hydroperoxide/0.001 M DTBN at 40 °C. [e] Mole fraction of the 11-*cis* hydroperoxide (χ_{11cis}) as determined by HPLC–UV detection. [f] Percentages of ^{16}O and ^{18}O (*R*)- and (*S*)-9-*trans* hydroperoxide **9** calculated from the mole fractions of each enantiomer as determined by HPLC of the perketal derivative and the mole fractions of ^{16}O and ^{18}O labeled **9** as determined by HPLC–CIMS. Rearrangements were performed on 0.01 M (*R*)-11-*cis* hydroperoxide/0.001 M DTBN at 40 °C.

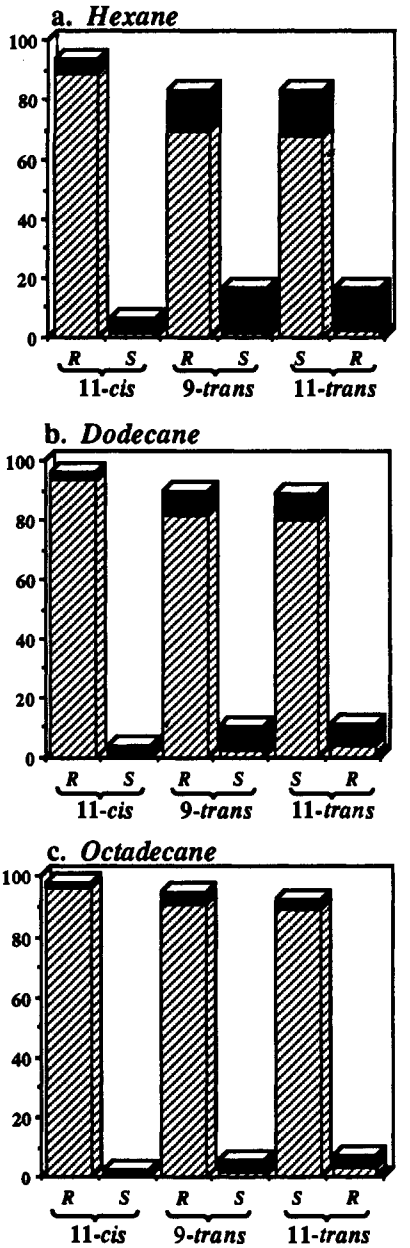


Figure 4. Percentages of $^{16}O/^{18}O$ (*R*)- and (*S*)-11-*cis*, -11-*trans*, and -9-*trans* hydroperoxides at 8 h (aliquot 3) for solvents (a) hexane, (b) dodecane, and (c) octadecane. Solids represent ^{18}O labeled product, and diagonals, ^{16}O labeled product.

octadecane for aliquot 3 (8 h). The cage (^{16}O) product is represented in the cross hatch pattern, and the escape (^{18}O) product is represented in solid black. The cage (^{16}O) products are formed with a high degree of stereoselectivity (*i.e.*, with the enantiomeric excess being close to 98% for the 9-*trans* hydroperoxide). For the escape (^{18}O) product, ^{18}O incorporation occurs with complete loss of configuration.

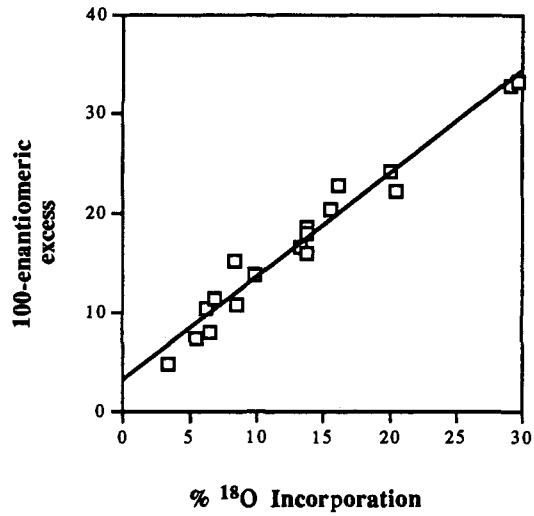


Figure 5. Relationship between enantiomeric excess and the percent of ^{18}O incorporation. All data are for products of rearrangement of **7**, hydroperoxides **8** and **9**, least squares fit: $100 - ee = 1.0(\%^{18}O) + 3.2$.

Consistent with our hypothesis, the stereoselectivity of the cage (^{16}O) product is apparently independent of solvent viscosity. Cage product stereochemistry is not related to the diffusional rate constant (k_D) that varies with solvent viscosity. To illustrate this point, for the 9-*trans* hydroperoxide **9** at 4 h (aliquot 1), the percentages of enantiomeric excess for the cage (^{16}O) product for hexane, dodecane, and octadecane are 97, 97, and 98, respectively.

In agreement with the results obtained in the racemic 11-*cis* hydroperoxide oxygen labeling studies, the amount of escape (^{18}O) product decreases as solvent viscosity increases. These results are also in accord with the *cis* allyl radical–dioxygen pair mechanism (Scheme 6). Moreover, as solvent viscosity increases from hexane to octadecane, ^{18}O is still incorporated with racemization of configuration. These results give additional evidence that a planar *cis* allyl radical escapes the solvent cage and reacts with $(^{18}O)_2$.

The data also show that the overall enantiomeric excess determined is inversely proportional to the percent of ^{18}O incorporation (Figure 5). An increase in solvent viscosity results in a decrease in the amount of escape (^{18}O) product formed with loss of stereochemistry and an identical increase in the amount of cage (^{16}O) product formed with retention of stereochemistry. Hence, the percent of ^{18}O incorporation that occurs during rearrangement is proportional to the escape product and the percent of enantiomeric excess of the rearrangement is proportional to the cage product. A linear regression analysis of data for the products of rearrangement of **7** gives a good fit to the equation $100 - ee = 1.0(\%^{18}O) + 3.2$. Loss of optical purity correlates directly with ^{18}O incorporation. Furthermore, the intercept of 3.2 suggests that, at the limit of no ^{18}O incorporation, the peroxide products are formed with an enantiomeric excess of close to 97% (100 − 3.2). This factor represents the loss of stereochemistry occurring in the formation of the cage (^{16}O) product. The cage collapse products are formed with small, but measurable, loss of stereochemical configuration.

Consider again the mechanistic question of the allylperoxyl rearrangement in light of the data presented in Table 2 and in Figures 4 and 5. More pair escape occurs in hexane solvent than in viscous solvents during the course of rearrangement. The pair collapse (^{16}O) products are formed with high stereoselectivity independent of the solvent (Figure 5). The marginal collapse product formed in a more viscous solvent relative to hexane is formed stereoselectively. Product **9**, for example, is formed within the cage ~70% of the time in hexane, while in octadecane, the in-cage product amounts to ~92% of the product mixture. The increased cage product in octadecane compared to hexane is, however, formed stereoselectively. The simplest mechanism consistent with these data is one involving an intermediate allyl radical–dioxygen pair that collapses stereoselectively at the diffusion-controlled rate.

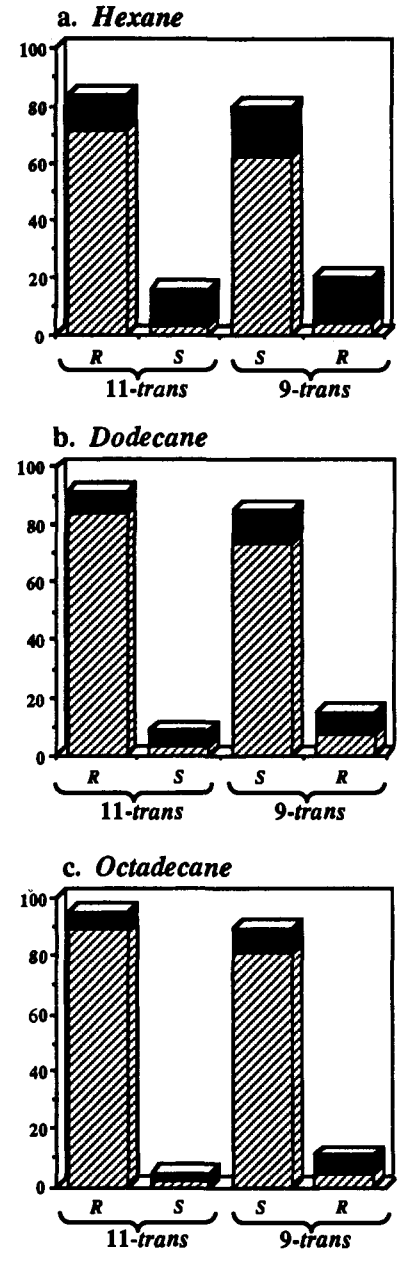
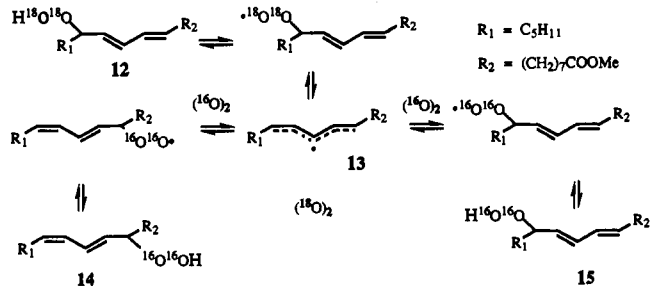


Figure 6. $^{16}O/^{18}O$ (*R*)- and (*S*)-11-*trans* and -9-*trans* hydroperoxides at 4 h (aliquot 3) for solvents (a) hexane, (b) dodecane, and (c) octadecane. Solids represent ^{18}O labeled product, and diagonals, ^{16}O labeled product.

For additional evidence of the cage mechanism for rearrangement of a *trans* hydroperoxide precursor, the viscosity test was applied to the optically pure 11-*trans* hydroperoxide **8**. The rearrangement was performed on 0.01 M *(R)*-11-*trans* hydroperoxide/0.001 M AIBN at 60 °C in hexane, dodecane, and octadecane, and the reactions were analyzed as reported above for the *cis* hydroperoxide.

The histogram in Figure 6 shows the percentages of ^{16}O and ^{18}O incorporation for the *(R)*- and *(S)*-11-*trans* and -9-*trans* isomers for each solvent (hexane, dodecane, and octadecane) for aliquot 3 (4 h). Data for aliquots 1 and 2 are not shown. As is the case for the *cis* allylperoxyl system, the stereoselectivity of the cage (^{16}O) product is independent of solvent viscosity. For the 9-*trans* hydroperoxide product of rearrangement at 4 h (aliquot 3), the percentages of enantiomeric excess for the cage product

Scheme 7. Proposed Mechanism of the Dienylperoxyl Rearrangement



for hexane, dodecane and octadecane are 85, 83, and 88, respectively, with an experimental uncertainty of ±3.3. The escape (^{18}O) product decreases, as expected, with increasing solvent viscosity. Trends observed for the 9-*trans* hydroperoxide are also seen for the 11-*trans* starting material. The composition of ^{16}O and ^{18}O (*R*)- and (*S*)-11-*trans* and -9-*trans* hydroperoxides is presented as a function of the extent of rearrangement in tabular form in the supplementary material.

The data also show that the overall enantiomeric excess is inversely proportional to the percent of ^{18}O incorporation. As in the *cis* allylperoxyl system, there appears to be some loss of stereochemistry occurring in the formation of the cage (^{16}O) product, which is formed with >97% enantiomeric excess.

Solvent Viscosity Studies of the Linoleate Peroxyl Rearrangement. Studies by Chan have established that the rearrangement of dienylperoxyl radicals derived from linoleate proceeds by a β-fragmentation mechanism.[20] This was determined through investigations of the thermal rearrangement of dienyl hydroperoxide **12** derived from methyl linoleate (Scheme 7). It was demonstrated that ^{18}O labeled dienyl hydroperoxides undergo rearrangement with incorporation of atmospheric oxygen into the rearrangement products **14** and **15**, giving evidence in support of a β-fragmentation mechanism involving pentadienyl radical intermediate **13**. Since the evidence for this rearrangement clearly points to a dissociative–recombination mechanism, it is of interest to apply the solvent viscosity test to this rearrangment. The dienylperoxyl radical has 24–28 kcal/mol of resonance stabilization energy and has a significantly larger driving force for fragmentation than an allylperoxyl radical which has only 13–14 kcal/mol of resonance stabilization energy.[21] The reaction of the stabilized pentadienyl radical with oxygen may be slower than that of the presumably more reactive allyl radical, *i.e.* the viscosity effects may be dramatically different for dienyl and allyl radicals if the dienyl radical reacts with oxygen at a rate substantially below the diffusion-controlled limit.

Rearrangement reactions were carried out in hexane, dodecane, and heptadecane under $(^{18}O)_2$ on the linoleate 13-*trans,trans* hydroperoxide **15**. Conditions of the rearrangement were essentially the same as those used for the oleate hydroperoxide rearrangements; one of the product hydroperoxides, the 9-*trans*,-*trans* compound, was isolated, and oxygen incorporation for this product was determined by HPLC/CIMS. The oxygen isotopic composition of the product of the rearrangement of **15** is >95% ^{18}O for samples taken throughout the rearrangement. Atmospheric oxygen incorporation is nearly complete for rearrangements carried out in all of the solvents. There is a small difference between solvents used in the rearrangement, but the difference is close to the uncertainty of the analysis. These data support the dissociative mechanism for this rearrangement and indicate that solvent viscosity has a marginal effect on the rearrangement.

If the reaction of carbon radicals with dioxygen is close to the diffusion-controlled limit, the structure of the intermediate carbon radical will play a critical role in determining the solvent viscosity dependence of rearrangement reactions. For the pentadienyl radical, the data suggest that diffusion of the initial pair dominates combination, while for simple allyls, combination must be faster than diffusion.

Stereochemistry of Reactive Pairs. The proposal that allyl radical–dioxygen pairs collapse without significant loss of stereochemical configuration invites comparison of this system with other pair collapse processes reported. Radical–radical coupling reactions generally result in loss of stereochemistry of the radical precursor.[22] In 1970, Greene *et al.* reported on the stereochemistry of coupling products formed from decomposition of *meso*- and (–)-(*S,S*)-azobis(phenylethane) in benzene at 105 °C.[22b] These studies indicate that radical pair reorientation is fast relative to radical coupling in solution; consequently, there is substantial loss of stereochemistry of the radical precursor in the coupling products formed.

The lack of stereochemical control has made radical recombination reactions undesirable for use in many synthetic conversions. However, this problem is circumvented by generating radicals in molecular aggregates such as micelles or lipid bilayers or in crystals. The high microviscosities in these media reduce the mobility of the radicals and enhance the stereoselectivity of radical–radical coupling reactions.[23] Radical–radical coupling reactions in biological systems have also been suggested to occur with control of stereochemistry. Oxygen insertion reactions of cytochrome P-450, for example, proceed with significant control of stereochemistry, and these reactions have been suggested to involve reactive pair species.

We conclude that the simplest mechanism for the *cis* and *trans* allylperoxyl rearrangements based on the experimental results and theoretical investigations[10a] involves an allyl radical–dioxygen caged pair that collapses with stereochemical memory at a rate comparable with that of diffusion. The results do away with the need of assuming a bridged species as an intermediate in the rearrangement. Allyl radicals that diffuse into solution incorporate $(^{18}O)_2$ with racemization of configuration. This gives evidence of a planar allyl radical intermediate that escapes from the initial solvent cage. The pair collapse (^{16}O) product apparently forms with a high degree of stereoselectivity compared to that for other known radical pair reactions. The stereochemical oxygen labeling studies indicate that solvent viscosity affects the partitioning between escape and collapse of the allyl radical–dioxygen caged pair. An increase in solvent viscosity results in a decrease in escape product and an identical increase in pair collapse product. Pentadienyls, radicals that are more stablilized than simple allyls, apparently successfully escape from the initial pair. Complete atmospheric oxygen incorporation and loss of stereochemistry attend rearrangements involving pentadienyl intermediates.

Comparing the *cis* and *trans* allylperoxyl rearrangements, the *trans* system shows higher stereoselectivity and lower ^{18}O incorporation than the *cis* rearrangement. Since the stereoselectivity is defined in the pair collapse step, we conclude that the *trans* allyl radical–dioxygen reaction is faster than the *cis* allyl radical–dioxygen reaction or that diffusion of the *trans* allyl radical–dioxygen reaction is slower than the *cis* allyl radical–dioxygen reaction.

We note that the stereochemical oxygen labeling methodology developed here might be applicable to other peroxyl radical systems of interest. The results also demonstrate that solvent viscosity plays an important role in peroxyl radical rearrangements; therefore, viscosity might affect peroxyl radical rearrangements in biological systems of high microviscosity (*i.e.*, lipid bilayers).

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(21) Korth, H.-G.; Heinrich, T.; Sustmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483.

(22) (a) Porter, N. A.; Krebs, P. J. *Topics in Stereochemistry*; Eliel, E., Wilen, S., Eds.; John Wiley and Sons: New York, 1988; p 97. (b) Greene, F. D.; Berwick, M. A.; Stowell, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 867.

(23) Brittain, W. J.; Porter, N. A.; Krebs, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 7652.

We have presented the rearrangement in terms of a dioxygen–allyl radical pair, but we note that substantial charge transfer could attend the formation of this pair. In the limit, the intermediate would be an allyl cation–superoxide radical pair, and Brill[9a] has pointed out that molecular orbital symmetry is appropriate for this process. Furthermore, the strength of this interaction would depend on the solvent and particular structure of the carbon fragment.

Experimental Section

Methyl oleate (>99%) was purchased from Nu Chek Prep (Elysian, MN). Labeled oxygen, $(^{18}O)_2$ (99.5%), was purchased from Icon Services, Inc. (Mount Marion, NY) and MSD Isotopes (Montreal, Canada). Sodium hyponitrite was purchased from Michigan Technological University (Houghton, MI). All other reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI). HPLC solvents were purchased from Mallinckrodt (St. Louis, MO).

Methods. HPLC was carried out using a Waters M600 E pump with either a Waters 481 or 486 variable-wavelength UV detector or a Waters R401 differential refractometer. Analytical HPLC used Beckman Ultrasphere 5-μm silica 2 (4.6 × 25 cm) columns for normal-phase (NP) conditions and Altex-Beckman 5-μm ODS 2 (4.6 × 25 cm) columns for reverse-phase (RP) conditions. A flow rate of 1 mL/min was used for analytical HPLC. Preparative HPLC used a Rainin Dynamax 60A 8-μm 83-121-C5 silica (21.4 mm × 25 cm) column or a Rainin Dynamax 60 A 8-μm 83-141-C silica (41.4 mm × 25 cm) column for NP conditions and a Rainin Dynamax 60 A 8-μm C-18 (21.4 mm × 25 cm) column for RP conditions. A flow rate of 10 mL/min was used for the 21.4-mm diameter columns and 25 mL/min for the 41.4-mm diameter column. All HPLC columns were equipped with guard columns, and HPLC solvents were filtered through Rainin Nylon 66 (0.45-μm pore size) filters. Integration of chromatograms was carried out with a Hewlett Packard 3390A integrator, and chromatograms were recorded on a Fisher Recordall Series 5000. HPLC–CIMS was carried out using a Waters M590 pump/5988A mass spectrometer with a Hewlett Packard 59880A particle beam LC/MS interface. The reagent gases used for chemical ionization were CH_4/4% NH_3 and i-C_4H_{10} at a source pressure of (0.8–1.6) × 10^{-3} atm.

Synthesis of Oleate Hydroperoxides. Methyl oleate (50 g, 0.17 mol) and DTBN[14] (5 mg, 0.029 mmol) were stirred as air was bubbled into the reaction flask for 3–10 days at 40 °C. The reaction was monitored for formation of oleate hydroperoxides *via* TLC (15% EtOAc/hexane), R_f(oleate-OOH) 0.17. The reaction mixture was purified by flash column chromatography (15% EtOAc/hexane) to afford ~2.5 g (5%) of the regioisomeric oleate hydroperoxides. Tri-*tert*-butylphenol (TTBP), a few crystals, was added to the oleate hydroperoxide mixture to inhibit rearrangement.

Methyl (*Z*)-11-Hydroperoxyoctadec-9-enoate (7). The 11-*cis* oleate hydroperoxide **7** was isolated by preparative NP–HPLC–RI (1% *i*-PrOH/hexane, 41.4-mm diameter column, 80 mg/injection), HPLC t_R 40 min. The 11-*cis* hydroperoxide was purified by reinjection to afford ~250 mg. TLC: R_f 0.17 (15% EtOAc/hexane). Analytical NP–HPLC–UV: t_R 18 min (1% *i*-PrOH/hexane, λ = 254 nm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (s, 1H, OO*H*), 5.72 (dt, *J* = 11.1, 7.8 Hz, 1H, C*H*=CH—CHOOH), 5.31 (dd, *J* = 10.9, 9.4 Hz, 1H, CH=C*H*—CH—OOH), 4.70 (dt, *J* = 9.0, 5.7 Hz, 1H, C*H*OOH), 3.66 (s, 3H, CO_2CH_3), 2.35 (t, *J* = 7.2 Hz, 2H, $CH_2CO_2CH_3$), 2.11 (m, 2H, CH_2C=), 1.71–1.10 (22H), 0.85 (t, *J* = 7.2 Hz, 3H, terminal CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.39 (C=O), 136.26 (CH=CH—CHOOH), 128.34 (CH=CH—CHOOH), 81.19 (CHOOH), 51.49, 34.03, 32.59, 31.77, 30.38, 29.55, 29.43, 29.16, 28.97, 28.94, 27.75, 25.20, 24.84, 14.08. FTIR ($CHCl_3$): 3524, 3156, 2931, 2858, 2261, 1727 (ester), 1650, 1096 cm^{-1}. MS (CI, CH_4/NH_3): *m/z* 346 (12, M + NH_4^+), 328 (25, M – H_2O + NH_4^+), 312 (47, M – H_2O_2 + NH_4^+), 311 (100, MH^+ – H_2O), 295 (44, MH^+ – H_2O_2), 230 (63), 213 (66).[24]

Methyl (*E*)-11-Hydroperoxyoctadec-9-enoate (8). The 11-*trans* oleate hydroperoxide **8** was isolated by preparative NP–HPLC–RI, t_R 43 min (1% *i*-PrOH/hexane, 41.4-mm diameter column, 80 mg/injection). The 11-*trans* hydroperoxide was purified by reinjection to afford ~300 mg. TLC: R_f 0.17 (15% EtOAc/hexane). Analytical NP–HPLC–UV: t_R = 19 min (1% *i*-PrOH/hexane, λ = 254 nm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (s, 1H, OO*H*), 5.75 (dt, *J* = 15.6, 6.6 Hz, 1H, C*H*=CH—CHOOH), 5.35 (dd, *J* = 15.3 Hz, 8.3 Hz, 1H, CH=C*H*—CHOOH), 4.24 (dt, *J* = 8.1, 6.1 Hz, 1H, C*H*OOH), 3.63 (s, 3H, CO_2CH_3), 2.29 (t, *J* = 7.5 Hz, 2H, $CH_2CO_2CH_3$), 2.04 (br q, *J* = 6.6 Hz, 2H, CH_2C=), 1.71–1.12 (22H), 0.85 (t, *J* = 7.2 Hz, 3H, terminal CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.39 Hz (C=O), 136.80 (CH=CH—CHOOH), 128.67 (CH=CH—CHOOH), 87.00 (CHOOH), 51.47, 34.01, 32.40, 32.22, 31.74, 29.45, 29.14, 28.98, 28.95, 28.87, 28.83, 25.30, 24.82, 22.61, 14.06. FTIR ($CHCl_3$): 3524, 3156, 2933, 2858, 1729 (ester), 1664, 1097 cm^{-1}. MS (CI, CH_4/NH_3): *m/z* = 346 (291, M + NH_4^+), 328 (32, M – H_2O + NH_4^+), 312 (44, M – H_2O_2 + NH_4^+), 311 (100, MH^+ – H_2O), 295 (32, MH^+ – H_2O_2), 230 (61), 213 (61).

2-Propanone, *O,O*-1-(Methoxycarbonyl)octadec-9-en-11-yl *O*-*trans*-2-Phenylcyclohexyl Peracetal (11-*S*). To a solution of 170 mg (0.52 mmol) of 11-*cis* oleate hydroperoxide **7** in 2 mL of CH_2Cl_2 were added 1–2 mg (2.5 mol %) of PPTS and 124 mg of (1*R*,2*S*)-*trans*-2-phenylcyclohexyl 2-propen-2-yl ether **10**[16] (0.57 mmol ~ 1.1 equiv). Upon completion of the reaction, the solution was quenched with $KHCO_3$ to neutralize excess PPTS. The solution was concentrated and subjected to flash column chromatography on 10 g of silica gel using 5% EtOAc/hexane as the eluent to afford 255 mg (90%) of a colorless oil **11**.

The mixture of diastereomers **11** was resolved by RP–HPLC. Analytical RP–HPLC–UV: t_R 32 and 34 min, k_1 = 3.6, k_2 = 3.9, α = 1.1 (CH_3CN/trace NEt_3, dual ODS columns, λ = 254 nm, 2 mg/injection). Preparative RP–HPLC–UV: t_R 72 and 78 min, k_1 = 6.2, k_2 = 6.8, α = 1.1 (CH_3CN/trace NEt_3, λ = 254 nm, 50 mg/injection). Mixed fractions (20 mg) were reinjected, and the leading and tailing fractions were individually repurified to afford 89 mg of the leading diastereomer which was shown to be >99% pure. TLC: R_f 0.43 (15% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.21 (5H, Ar), 5.52 (dt, *J* = 11.1, 7.2 Hz, 1H, C*H*=CH—CHOOR), 5.27 (dd, *J* = 10.8, 9.0 Hz, 1H, CH=C*H*—CHOOR), 4.57 (q, *J* = 8.1 Hz, 1H, CHOOR), 3.66 (s, 3H, CO_2CH_3), 3.53 (m, 1H, HCO), 2.51 (m, 1H, HCPh), 2.38 (m, 1H), 2.27 (t, *J* = 7.5 Hz, 2H, $CH_2CO_2CH_3$), 2.01 (m, 2H, CH_2C=), 1.95–1.18 (29H), 1.14 (s, 3H, CH_3), 0.88 (t, *J* = 6.8 Hz, 3H, terminal CH_3), 0.46 (s, 3H, CH_3). MS (CI, CH_4/NH_3): 562 (5, M + NH_4^+), 346 (5, oleate-OOH + NH_4^+), 328 (28), 312 (67), 311 (81), 295 (57), 236 (86), 217 (86), 194 (100), 159 (95).[16]

The trailing diastereomer was shown to be >99% pure. TLC: R_f 0.43 (15% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.20 (5H, Ar), 5.52 (dt, *J* = 11.1, 7.5 Hz, 1H, C*H*=CH—CHOOR), 5.27 (t, *J* = 9.9 Hz, 1H, =C*H*—CHOOR), 4.61 (m, 1H, CHOOR), 3.68 (s, 3H, CO_2CH_3), 3.59 (m, 1H, HCO), 2.55 (dt, *J* = 9.6, 3.9 Hz, 1H, HCPh), 2.42 (m, 1H), 2.32 (t, *J* = 7.5 Hz, 2H, $CH_2CO_2CH_3$), 2.05 (m, 2H, CH_2C=), 1.98–1.19 (29H), 1.21 (s, 3H, CH_3), 0.89 (t, *J* = 6.8 Hz, 3H, terminal CH_3), 0.51 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.05 (ester), 144.63 (Ar), 133.22 (olefin), 129.58, 128.38, 127.48, 125.78, 104.34 (perketal), 78.40 (CHOO), 75.60 (C—O), 51.26, 50.62, 35.82, 33.90, 32.06, 31.67, 29.43, 29.11, 29.00, 28.94, 27.60, 25.88, 25.45, 25.27, 25.18, 24.77, 22.53, 21.27, 13.97. FTIR: 2932, 2857, 1729, 1648, 1381, 1097 cm^{-1}.

The leading 11-*cis* perketal **11a** (89 mg, 0.16 mmol) was dissolved in 5 mL of 4:2:1 THF/HOAc/H_2O in the presence of 1 mol % TTBP. The reaction was stirred for 24 h at room temperature, and 75 mL of cyclohexane was added to remove the acetic acid (C_6H_{12}:HOAc = 98:2, bp = 79 °C). The mixture was then concentrated to dryness. The crude product was subjected to preparative NP–HPLC–UV, t_R 26 min (1% *i*-PrOH/hexane, 21.4-mm diameter column, λ = 254 nm, 20 mg/injection), to afford 41 mg of 7-*R* (75%). TLC: R_f 0.17 (15% EtOAc/hexane). The *S* enantiomer was similarly prepared. The resolution of **8** and the stereochemical proof of the configurations of the enantiomers of **7** and **8** are presented in the supplementary material.

Allylperoxyl Rearrangements. All rearrangement reactions were performed at 0.01 M hydroperoxide using 0.001 M initiator (DTBN/AIBN). The hydroperoxide was prepared as a stock solution at 0.01 M (3.3 mg/1 mL of hexane). The initiator was prepared as a stock solution (3.5 mg DTBN/1 mL of hexane, 22 °C and 40 °C rearrangements, or 3.5 mg AIBN/1 mL of benzene, 60 °C rearrangements). All stock solutions were stored at –78 °C prior to use. Aliquots taken were quenched with TTBP (a few crystals).

The rearrangement of **7** is illustrative. The 11-*cis* hydroperoxide **7** (3.3 mg, 0.01 mmol) was subjected to rearrangement at 40 and 22 °C. The rearrangement was monitored by analytical NP–HPLC for 8 h. HPLC revealed two hydroperoxide products, the 11-*trans* oleate hydroperoxide **8** (section 3.2.4.) and the 9-*trans* oleate hydroperoxide **9** (methyl (*E*)-9-hydroperoxyoctadec-10-enoate). The 11-*trans* hydroperoxide **8** (3.3

(24) The 9-*trans* oleate hydroperoxide has been previously characterized, refs 9c and 16.

mg, 0.01 mmol) was subjected to rearrangement conditions at 40 °C. The rearrangement was monitored by analytical NP–HPLC for 8 h. HPLC revealed one hydroperoxide product, the 9-*trans* hydroperoxide **9**.

Stereochemical Studies. All stereochemical studies were carried out on >99% pure hydroperoxide. Aliquots were withdrawn and quenched with TTBP (a few crystals), and the regioisomeric hydroperoxides were isolated by analytical NP–HPLC. The isolated hydroperoxides were subjected to perketalization conditions (section 3.3.1.), and the diastereomeric perketals were analyzed for enantiomeric excess *via* analytical RP–HPLC–UV (CH_3CN/trace NEt_3, dual ODS columns, $\lambda = 254$ nm). The experimental uncertainty for the oleate hydroperoxide enantiomers is ±0.6%.

Oxygen Labeling Experiments. All oxygen labeling experiments were performed in a sealed vessel containing 99.5% $(^{18}O)_2$ at 1 atm. A rearrangement apparatus was designed for work performed under an atmosphere of $(^{36}O)_2$. Oleate hydroperoxide at 0.01 M (3.3 mg/1 mL of hexane) was placed in the 3.8-mL reaction vessel. The solution was degassed of $(^{32}O)_2$ *via* a series of freeze–pump–thaw cycles with a high-vacuum system (1.3×10^{-5} atm). The solution in the reaction vessel was frozen with liquid N_2 (stopcock 1 open, stopcock 2 closed) followed by evacuation of the chamber *in vacuo* by opening stopcock 2. The chamber was then sealed by closing stopcock 2, and the solution was allowed to thaw. This sequence was repeated eight times. The labeled oxygen was cautiously added from the lecture bottle until the system pressure gauge read 0 psi. The reaction vessel was then detached from the lecture bottle at the glass–metal fitting (stopcocks 1 and 2 closed) and transported to a constant-temperature bath. The rearrangement was monitored by analytical NP–HPLC. Aliquots (~100 μL) were withdrawn from the reaction vessel at the vacuum septum and quenched with TTBP (a few crystals). The samples were preserved at −78 °C for further analysis by HPLC–CIMS to determine the amount of ^{18}O incorporation.

Stereochemical Oxygen Labeling Experiments. The rearrangements were performed on 0.01 M optically pure 11-*cis* or 11-*trans* (>99%) hydroperoxide (5 mg/1.5 mL of hexane, >99% ee)/0.001 M initiator (0.27 mg/75 μL). These experiments were performed using the apparatus in section 3.7.1. The *cis* allylperoxyl rearrangements were performed at 40 °C (DTBN added in hexane), and the *trans* allylperoxyl rearrangements were performed at 60 °C. For each aliquot taken (~500 μL), the solution was quenched with a few crystals of TTBP and the regioisomeric hydroperoxides were isolated by analytical NP–HPLC–UV, t_R (11-*cis*) 18 min; HPLC t_R (11-*trans*), 19 min; and HPLC, t_R (9-*trans*) 21 min (1% *i*-PrOH/hexane, $\lambda = 254$ nm). The isolated regioisomeric hydroperoxides were derivatized with the chiral vinyl ether **10** derived from (1*R*,2*S*)-*trans*-2-phenylcyclohexanol to the corresponding diastereomeric perketals, *vide supra*. The perketals (microgram quantities) were then analyzed by RP–HPLC–UV (5% THF/CH_3CN/trace NEt_3, dual ODS columns, $\lambda = 254$ nm) to determine the enantiomeric excess (±1.2%). This procedure was repeated for optically pure rearrangements performed in dodecane and octadecane.

The $^{16}O/^{18}O$ composition in the major and minor enantiomers was determined by RP–HPLC–MS (10% THF/CH_3CN/trace NEt_3; 5-μm ODS column (4.6 mm × 25 cm); CI, *i*-C_4H_{10}). The ions selected for $^{16}O/^{18}O$ incorporation were the $m/z = 311$ and 313 ($MH^+ - H_2O$). The reagent gas was switched to *i*-C_4H_{10} (g) since an abundant $m/z = 312$ ($+NH_4^+$) ion was produced using CH_4/NH_3 (g) that complicated quantitation of the relative amounts of the $m/z = 311$ and 313 ions. A minimal amount of the perketal $m/z = 545$ (MH^+) or 562 ($M + NH_4^+$) was detected; therefore, the M + 4 ion could not be analyzed for ^{18}O incorporation. To obtain optimum sensitivity on the microgram quantities of oleate perketals, selected ion monitoring (SIM) was used in these experiments. The selected ions were $m/z = 313$ (8), 311 (100), 309 (1), 296 (12), and 295 (60), relative ion abundance determined at 1×10^6 ion counts. To calculate $^{16}O/^{18}O$ in the *R*- and *S*-regioisomeric oleate hydroperoxides, the fraction of the major and minor oleate hydroperoxide enantiomers determined by HPLC–UV ($\lambda = 254$ nm), ±0.006, was multiplied by the percentages of ^{18}O incorporation determined by CIMS, ±0.9% (major enantiomer) and ±1.2% (minor enantiomer). This procedure was repeated for ^{16}O incorporation. The experimental uncertainty of the percent of $^{18}O/^{16}O$ data is ±1.5% for the major enantiomer and ±1.8% for the minor enantiomer.

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Supplementary Material Available: The compositions of ^{16}O and ^{18}O (*R*)- and (*S*)-11-*trans* and -9-*trans* hydroperoxides are presented as a function of the extent of rearrangement of **8** in tabular form, and figures showing the disappearance of starting hydroperoxides as a function of time and solvent for rearrangement of **7** and **8**, the resolution of **8**, and the stereochemical proof of the configuration of the enantiomers of **7** and **8** and histograms for aliquots 1–3 for rearrangement of **7** and **8** are also given (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page.