Stereoselective Acyclic 3,2 Peroxyl Radical Rearrangements

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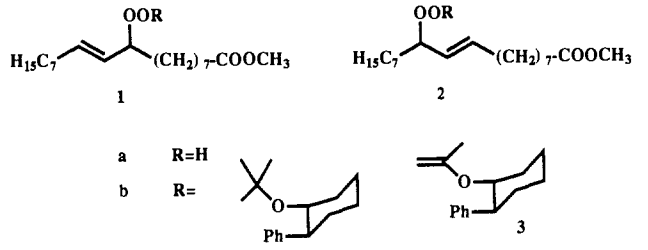
The rearrangement of allylic hydroperoxides has been known for over 30 years,[1] and several mechanisms for allylic hydroperoxide rearrangements have been proposed.[2-7] Recent studies in cyclic[6] and acyclic[7] systems suggest that the rearrangement proceeds by a concerted 3,2 free-radical pathway in contrast to dienyl hydroperoxides where a dissociative mechanism involving intermediate pentadienyl radicals has been supported by experiment.[8-10] The evidence for a concerted rearrangement should imply specific stereochemical consequences, and we report here that optically pure acyclic allylic peroxyl radicals rearrange in a highly stereoselective process.

The resolution of hydroperoxides has been previously described,[11] and we find that oleate hydroperoxides can be resolved to optical purities of greater than 99% enantiomeric excess by using normal-phase chromatography on silica (solvent:2% ethyl acetate in hexane). Thus, the perketal derivative of (*S*)-methyl 9-hydroperoxyoctadec-10(*E*)-enoate, **1b**, elutes before the corresponding 9*R* diastereomer on normal-phase chromatography, and multimilligram quantities can be readily prepared.[12] Deprotection with acid gives the optically pure hydroperoxide, which is chromatographed on silica before use. We find that some rearrangement of the hydroperoxide **1a** (2-8%) occurs during solvent removal if free-radical inhibitors are not present, and 0.1 mM 2,4,6-tri-*tert*-butylphenol was added to the hydroperoxide after purification on silica to suppress this rearrangement.



Rearrangement of the optically pure hydroperoxide **1a** in hexane was initiated by di-*tert*-butyl hyponitrite, and after an induction period (in which inhibitor is consumed), the 11-hydroperoxide **2a** formed. The increase in **2a** was monitored by HPLC, and fractions of **1a** and **2a** were taken and converted to the perketals **1b** and **2b** by reaction with **3**. Analysis of the perketals allows determination of the configuration at the stereocenters of the starting hydroperoxide and the rearrangement product throughout the course of the rearrangement. The configuration of both hydroperoxides was determined by reduction to the corresponding alcohol, conversion of the alcohol to the *p*-bromobenzoate, and measurement of the CD spectrum of the *p*-bromobenzoate.[13] The rearrangement was carried out on both the 9(*R*)- and 9(*S*)-hydroperoxides and in Table I is presented data for for rearrangements carried out at 20, 40, and 55 °C.

Table I. Stereochemical Course of Oleate Hydroperoxide Rearrangement

config of starting 9-ROOH[a]	temp, °C	9-ROOH/ 11-ROOH[b]	% enantiomer of product 11-ROOH[c]	% enantiomer of recovered 9-ROOH[c]
S (>99)	40	2.6	96 ± 1 (*R*)	98.5 ± 0.5 (*S*)
R (>99)	40	11	96 ± 1 (*S*)	>99 (*R*)
S (>99)	22	1.7	97.2 ± 0.5 (*R*)	98.5 ± 0.5 (*S*)
S (>99)	50	1.5	94 ± 1 (*R*)	97 ± 1 (*S*)

[a] Configuration at C-9 of starting hydroperoxide (enantiomeric excess). [b] Ratio of 9- and 11-hydroperoxides as determined by HPLC. [c] Percent major enantiomer ± standard error (configuration) of hydroperoxide as determined by HPLC of perketal derivative.

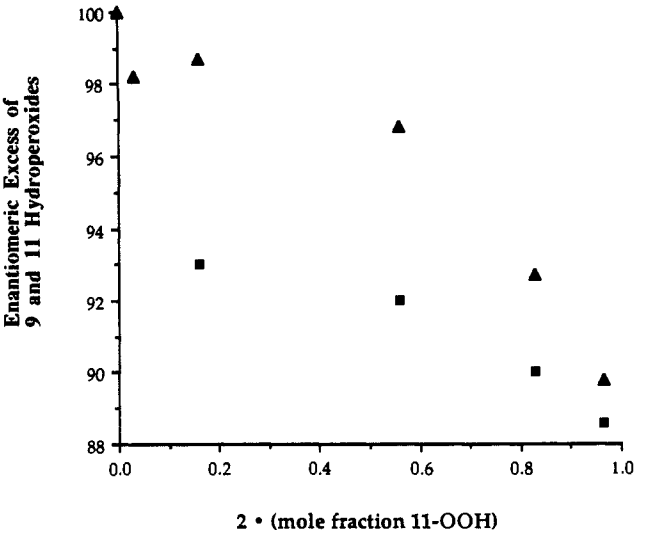
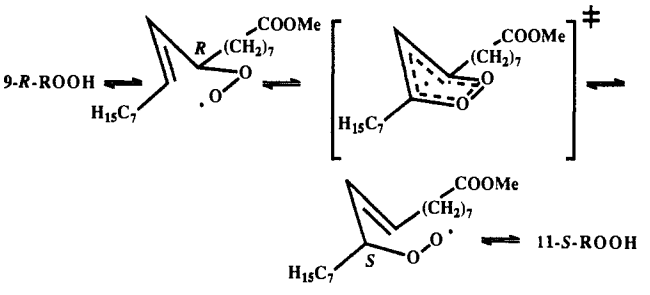


Figure 1. Enantiomeric excess vs extent of rearrangement of **1a**: ▲, 9-hydroperoxide **1a**; ■, 11-hydroperoxide **2a**.

Scheme I



The rearrangement is highly stereoselective, the rearrangement product is of the opposite configuration from the starting material, and even after extensive rearrangement when the 9- and 11-hydroperoxides are present in nearly equal amounts, both hydroperoxides are still significantly enriched in one enantiomer. There is a temperature dependence on the observed selectivity, with product hydroperoxide being isolated with optical purities approaching 98% when the rearrangement is carried out at 20 °C while 50 °C rearrangements lead to products with a greater loss of stereochemical integrity. Enantiomeric excess for starting and rearranged hydroperoxide is presented in Figure 1 as a function of extent of rearrangement at 40 °C.

The stereochemical course of the rearrangement of acyclic allylic hydroperoxides supports the proposal that the rearrange-

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(12) We find normal-phase chromatography to be more convenient than reverse-phase for the preparation of quantities of hydroperoxides. We have reported that the *R* diastereomer elutes before the *S* on reverse-phase chromatography for all hydroperoxides studied, but this rule does not apply for normal-phase chromatography.
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ment proceeds by a concerted 3,2 peroxyl radical mechanism. Furthermore, the transfer of chirality across the allyl system during rearrangement suggests a model for the rearrangement in acyclic peroxyls in which substituents on the allyl system occupy pseudoequatorial positions in an envelopelike transition-state structure. The proposed mechanism for rearrangement and the suggested transition-state structure are shown in Scheme I. Such a transition-state model suggests that the stereochemistry of the product stereogenic center should depend on the geometry of the double bonds in the reactant and product hydroperoxides.

The observed stereochemical course of the concerted 3,2 peroxyl radical rearrangement is of interest with regard to eicosanoid biosynthesis. Allyl and dienyl hydroperoxides are important intermediates in the arachidonic acid cascade, and the observation of highly stereoselective allyl hydroperoxide rearrangements suggests the possibility of such concerted rearrangements in the biosynthesis of these compounds.[14]

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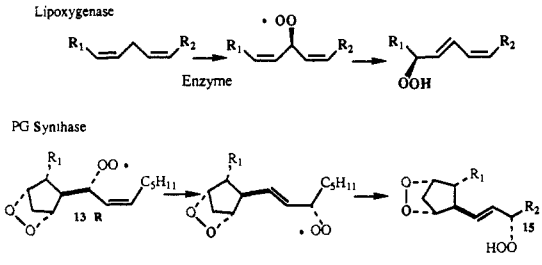
(14) The 3,2 peroxyl rearrangement can be proposed in the biosynthesis of lipoxygenase and prostaglandin products. A lipoxygenase mechanism involving conversion of a nonconjugated hydroperoxide (or peroxyl) to the conjugated diene product would not compromise stereochemistry as is also the case for rearrangement of an intermediate 13-hydroperoxide in the biosynthesis of PGG. In PG biosynthesis, the first oxygen would be delivered to



carbon 13 of the chain and rearrange to the 11-peroxy. Following cyclization of the peroxyl, the second oxygen would also be delivered to carbon 13 and rearrange to the 15-hydroperoxide product. In this mechanism both oxygens are delivered to the same face of the same carbon in the chain.

Metal–Ligand Bond Dissociation Energies in $CpMn(CO)_2L$ Complexes

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The photochemical ligand substitution reactions of $CpMn(CO)_3$ have been well studied and are synthetically very useful routes to substituted $CpMn(CO)_2L$ complexes.[1] In contrast, $CpMn(CO)_3$ is inert toward thermal substitution.[2,3] In an effort to understand the thermodynamic reasons for this reactivity, we have examined Mn–L bond dissociation energies in a number of manganese complexes by time-resolved photoacoustic calorimetry.

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Table I. Enthalpic and Kinetic Data for the Reaction of $CpMn(CO)_3$ with L in Heptane Solution According to Scheme I[a]

ligand	$CpMn(CO)_3$ ΔH_{Mn-CO}, kcal/mol	$CpMn(CO)_2L$ ΔH_2 (-BDE Mn-L), kcal/mol	$k_2 \times 10^{-6}$, L/(mol s)
THF	46.2 ± 1.2	-16.1 ± 1.4	4.4 ± 0.1
acetone	47.8 ± 1.7	-17.4 ± 1.0	3.6 ± 0.4
cis-cyclooctene	47.6 ± 1.4	-24.5 ± 2.3	2.3 ± 0.4
Bu_2S	45.3 ± 1.4	-28.7 ± 2.2	8.2 ± 0.5
$P(OMe)_3$[b]			7.1
PPh_3[b]			11
average	46.7 ± 1.7		

[a] Errors are given as 1 standard deviation of the scatter in the data. [b] See ref 9.

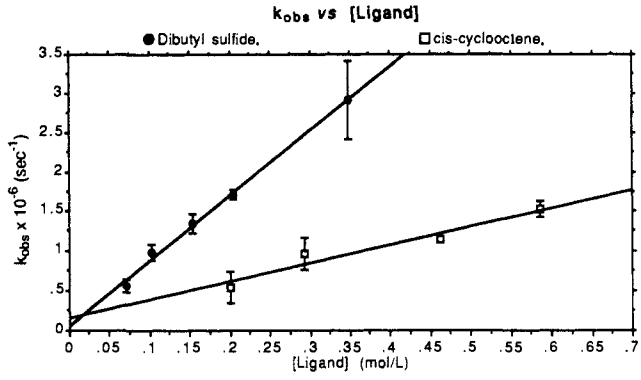

Figure 1. Plot of k_{obsd} vs [ligand] for the reaction of $CpMn(CO)_2S$ with *cis*-cyclooctene and Bu_2S at 25 ± 1 °C in *n*-heptane. For *cis*-cyclooctene, $r^2 = 0.93$; for Bu_2S, $r^2 = 0.996$. Other data is given in Table I. Error bars are the greater of the standard deviation calculated from the scatter in the data and ±10%.

Upon irradiation with light (<~400 nm), $CpMn(CO)_3$ readily dissociates one CO ligand with a quantum yield[4] of 0.65 (Scheme I). In good donor solvents such as THF, the initially formed

Scheme I

$$CpMn(CO)_3 \xrightarrow[\Delta H_{Mn-CO},\ \text{"fast"}]{337.1\ nm} CpMn(CO)_2S \xrightarrow[\Delta H_2,\ k_2,\ \text{"slow"}]{+L} CpMn(CO)_2L$$

$CpMn(CO)_2$ is stabilized as the solvated intermediate $CpMn(CO)_2S$.[1] Substitution of the solvent molecule from this intermediate by "good" ligands such as phosphines and olefins occurs readily, leading to the corresponding $CpMn(CO)_2L$ complexes. This reaction scheme is ideal for examination by photoacoustic calorimetry (PAC), which has been used to examine the energetics and kinetics in a number of organic and inorganic systems.[5] The PAC experiment detects, by way of the resulting thermal expansion, the heat released into solution from reactions initiated by absorption of a short pulse of laser light. From comparison of the amplitude and phase of this signal to a reference signal, both the enthalpy and kinetics of the reactions under study may be obtained. The results of the photoacoustic experiments on $CpMn(CO)_3$ performed in *n*-heptane solution are shown in Table I. The ligand concentrations were varied from ~0.1 to ~0.5 M. Consistent with the mechanism shown in Scheme I, the Mn–CO bond dissociation energies (ΔH_{Mn-CO}) were constant within the concentration range used and were constant between the different ligands. The strength of the Mn–CO bond in $CpMn(CO)_3$ is remarkably high when compared to other known

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