phosphine oxide, however, is not readily deoxygenated by **1**, although it does appear to coordinate to the tungsten(II) center.

The reactions shown in Scheme I are a novel type of oxidative addition process. Classical oxidative addition reactions, such as the addition of H_2, involve cleavage of a single bond and formation of two monovalent ligands.[13] In the reactions reported here a formal double bond is cleaved to form a divalent and a neutral ligand. Furthermore, very strong bonds are broken in the reactions: removal of an oxygen atom from CO_2 requires 127 kcal/mol.[14] In the reactions of heterocumulenes, the weaker C=X bond appears to be cleaved, which may reflect the formation of an η^2-cumulene intermediate.[4] Oxidative addition of epoxides may proceed via an oxametallacyclobutane intermediate,[15] as suggested for the reverse reaction, the formation of epoxides from metal oxo complexes.[16] Alternative mechanisms resembling inner-sphere electron-transfer processes[17] can also be imagined, such as direct oxygen atom transfer from an epoxide or from CO_2 to tungsten. These questions will be discussed in detail in a future publication.

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Supplementary Material Available: Spectroscopic data, analytical data, and crystallographic data—tables of atomic coordinates, bond distances and angles, anisotropic temperature factors, and hydrogen atom coordinates (8 pages); table of observed and calculated structure factors (21 pages). Ordering information is given on any current masthead page.

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10-Hydroperoxy-8,12-octadecadienoic Acid: A Diagnostic Probe of Alkoxyl Radical Generation in Metal-Hydroperoxide Reactions

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Alkyl hydroperoxides undergo heterolytic or homolytic cleavage when they react with metals and metalloproteins.[1] Homolytic cleavage generates alkoxyl radicals that oxidize cell constituents when the radicals are formed in plant and animal tissue.[2] One-electron reduction of hydroperoxides in chemical or biochemical systems is difficult to quantitate because alkoxyl radicals possess short half-lives and give rise to a wide variety of products. Recent reports that hydroperoxides contribute to the initiation, promotion, and progression phases of carcinogenesis have focused attention on the possible role of free radicals in these pathological events.[3] The paucity of quantitative information on metal-catalyzed homolysis of hydroperoxides to alkoxyl radicals prompted us to develop chemical probes for this reaction suitable for use in chemical, biochemical, and biological systems. We report here the results of experiments that indicate 10-hydroperoxy-8,12-octadecadienoic acid (**1**) is an ideal molecule for quantitating the reductive pathways available to hydroperoxides.

β-Scission is a well-established reaction of many alkoxyl radicals.[4] The extent to which β-scission occurs is determined by a number of factors, one of which is the stability of the organic radical generated.[5] Reaction of **1**[6] with ferric chloride–cysteine produced in 92% yield 10-oxo-8-decenoic acid (**2**),[7] a β-scission

Scheme I

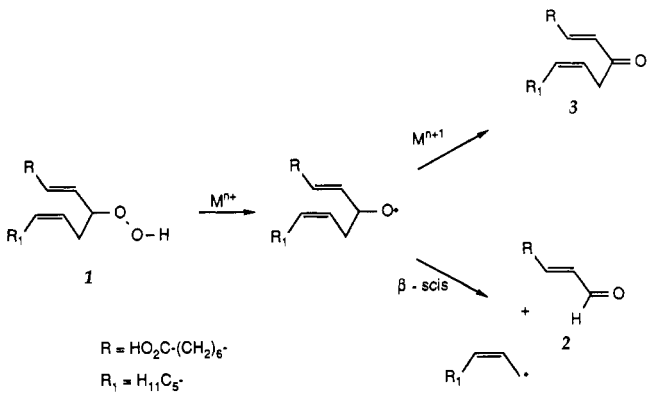

Table I. Metabolism of 10-Hydroperoxy-8,12-octadecadienoic Acid by Metal Complexes

catalyst[a]	**2**,[b] %	**3**, %	**4**, %
$FeSO_4$ (1:1)	84	12	4
$FeCl_3$–cysteine (1:400:100)	92	8	ND[c]
hematin (1:100)	59	35	6
ferrihemoglobin (1:1.3)	65	15	20
PGH synthase (1:100)	4	1	95

[a] Conditions for each experiment were as follow: 3.2 mM $FeSO_4$, 3.2 mM **1** in methanol/water 4/1; 0.05 mM $FeCl_3$, 12.8 mM cysteine, 3.2 mM **1** in methanol/water 4/1; 0.5 μM hematin, 50 μM **1** in 0.1 M $NaPO_4$ (pH 7.8), 200 μM Tween 20; 300 μM ferrihemoglobin (1.2 mM heme), 1.6 mM **1** in 0.1 M $NaPO_4$ (pH 7.8), 200 μM Tween 20; 1 μM PGH synthase, 500 μM phenol, 100 μM **1** in 0.1 M $NaPO_4$ (pH 7.8), 200 μM Tween 20. [b] Values are reported as percent conversion based on recovered **1**. The percentages of **1** recovered were 2, 0, 44, 6, and 6, respectively, in the five experiments. [c] ND: not detected.

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(6) [1-^{14}C]-**1** (21.2 μCi/mmol) was prepared by photosensitized oxygenation of [1-^{14}C]linoleic acid (90 mM, 23.6 μCi) in the presence of methylene blue (0.4 mM) in methanol. The solution was cooled to 0 °C and exposed to a 1000-W high-pressure sodium lamp, filtered to remove UV light. The solution was bubbled with oxygen during irradiation. Monohydroperoxides were purified on a silicilic acid column and then applied to a Whatman Magnum 9 10-μm silica column. Elution was performed with hexane/2-propanol/acetic acid (988/12/1 v/v) at a flow rate of 3.5 mL/min. The identity of **1** was verified by GC-MS of the methyl ester–trimethylsilyl ether of the alcohol reduction product (**4**).

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product of a putative alkoxyl radical (Scheme I). 10-Oxo-8,12-octadecadienoic acid (**3**) was produced in 8% yield but 10-hydroxy-8,12-octadecadienoic acid (**4**) was not detected. Reaction of 10-hydroperoxy-8-octadecenoic acid under similar conditions produced **2** in 20% yield, illustrating the importance of the allylic double bond on β-scission. 10-Oxo-8-octadecenoic acid and 10-hydroxy-8-octadecenoic acid were formed from 10-hydroperoxy-8-octadecenoic acid in 79% and 1%, respectively. Support for the intermediacy of an alkoxyl radical in the formation of **2** was provided by detection of the β-scission products octenal and 2-octenol in a total yield of 10% relative to **2** following reaction of **1** with ferric chloride–cysteine. Reaction of **1** with $FeSO_4$, hematin, or ferrihemoglobin produced **2**, **3**, and **4** in yields that are summarized in Table I. In all cases, **2** was the major product. In contrast to the reaction of **2** with iron protoporphyin IX, zinc protoporphyrin IX did not produce any aldehyde, suggesting that acid catalysis is not responsible for metalloporphyrin-catalyzed β-scission of **2**.

The data in Table I indicate that hematin and ferrihemoglobin catalyze *homolytic* cleavage of the O–O bond of **1**. Literature precedents indicate that hemeperoxidases catalyze *heterolytic* cleavage of the O–O bond of hydroperoxides.[1d-f] We, therefore, reacted prostaglandin H synthase, a heme-containing peroxidase, with **1** in the presence of phenol. Under these conditions, the alcohol **4** was produced in 95% yield.[8] The dramatic difference in product profiles between ferrihemoglobin and PGH synthase is consistent with homolytic vs. heterolytic hydroperoxide reduction and demonstrates the ability of **1** to differentiate one- and two-electron reduction pathways. This experiment also illustrates the importance of the protein component in determining the mechanism of hydroperoxide reduction by hemeproteins.

10-Hydroperoxy-8,12-octadecadienoic acid offers several advantages as a diagnostic probe for alkoxyl radical formation during the reaction of hydroperoxides with metals or metalloproteins. It is soluble in organic solvents or aqueous buffers, which makes it useful for investigating a variety of catalytic systems. A single major product (**2**) results from its conversion to alkoxyl radicals, which is easily separated by HPLC. The hydroperoxide is readily synthesized by photooxygenation of linoleic acid, and radioactively labeled material of high specific activity can be prepared from commercially available [^{14}C]- or [^{3}H]linoleic acid. This greatly facilitates quantitation of reaction products at virtually any starting concentration of **1**. Finally, **1** is an analogue of naturally occurring fatty acid hydroperoxides and should be able to probe the redox environment of the membrane phase of cells, the site at which most cellular hydroperoxide biosynthesis occurs.[9] We are currently employing **1** to determine the fate of hydroperoxides in chemical, biochemical, and biological systems.

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(7) Products of the reaction of **1** with different metal complexes were separated by HPLC by using the conditions described above and quantitated by using a radioactive flow detector. The purified products were methylated with diazomethane and analyzed by GC-MS. Methoximes were formed from carbonyl-containing compounds by treatment of the products (100 μg) with methoxyamine hydrochloride (5 mg) in pyridine (0.5 mL) for 15 h at 25 °C. Silyl ether derivatives of hydroxy compounds were prepared by treatment of dry samples with an excess of bis(trimethylsilyl)trifluoroacetamide. The proposed structure of **2** was confirmed by ^{1}H NMR [($CDCl_3$) δ 9.5 (d, J = 8 Hz, 1 H), 6.8 (dt, J = 15.5, 6.8 Hz, 1 H), 6.1 (ddt, J = 15.5, 8, 1.3 Hz, 1 H)] and by IR (2740, 1710, 1690 cm^{-1}).

(8) Prostaglandin H synthase was purified from ram seminal vesicles. The enzyme exhibits heme-dependent cyclooxygenase and peroxidase activities. Recent studies indicate that hydroperoxides oxidize the heme by two electrons to a ferryl–oxo complex that undergoes stepwise one–electron reduction to resting enzyme if a reducing substrate is present. Lambeir, A.-M.; Markey, C. M.; Dunford, H. B.; Marnett, L. J. *J. Biol. Chem.* **1985**, *260*, 14894–14896. Phenol was included to support catalytic turnover of the higher oxidation states of the peroxidase. Phenol has no effect on the products of reaction of **1** with ferrihemoglobin. The small amount of **2** formed in the experiments with PGH synthase (4%) is due to free heme in the enzyme preparation.

(9) Hydroperoxyoctadecadienoic acids partition into the membrane phase of cells but do not appear to be incorporated into phospholipids by esterification into the glycerol component. Funk, C. D.; Powell, W. S. *J. Biol. Chem.* **1985**, *260*, 7481–7488.

Vinyl Radical Cyclizations Mediated by the Addition of Stannyl Radicals to Triple Bonds

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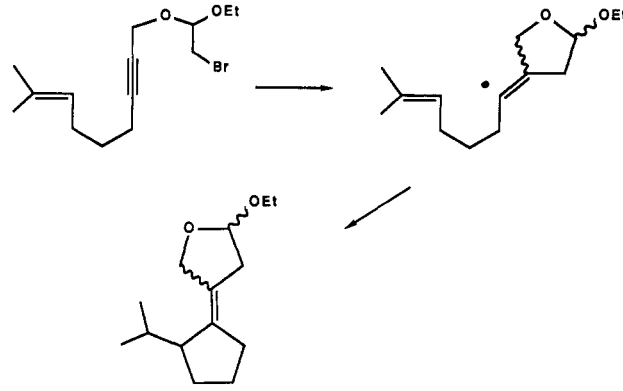
In our original report[1] of the vinyl radical cyclization, the vinyl radical was produced by the reaction of a vinyl bromide with a stannyl radical. We now describe an alternative.

It occurred to us that an attractive route would be opened if one could direct the addition of a radical species selectively to the triple bond of a suitable enyne. We have described elsewhere a rather special solution to this problem, in which the desired regioselectivity was achieved by tethering the initiating radical so as to enforce its addition to the triple bond.[2]



We now illustrate the more general process shown in Scheme I, in which the external radical A is a stannyl radical.[3] For example, refluxing a 0.02 M benzene solution of enyne **1** containing tributylstannane (1.1 equiv) and AIBN (0.04 equiv) for 3–4 h led to 85% yield of the tin-substituted methylenecyclopentane **2**. It is of particular interest, of course, that the tin substituent can readily be removed without effecting other structural changes: simple stirring with dry silica in methylene chloride caused protiodestannylation[4] to **3**. Even on a 20-g scale,[5] the cyclization of **1** can be run, without isolation of the intermediate[2,6,7] to produce pure **3**, bp 80–85 °C (0.2 mm), in 90%

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(6) The vinylstannane **2** may be isolated by flash chromatography. ^{1}H NMR δ 5.62 (br s, 1 H) with satellites, 3.73 (s, 3 H), 3.71 (s, 3 H).

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