groups make C somewhat more electrophilic than S. Electron donors enhance the greater electrophilicity of C that is already present in thioformaldehyde. Furthermore, the selectivity of the more reactive Danishefsky diene is greater than for 2-alkoxybutadiene, in accord with greater frontier orbital control for the diene which has the higher energy HOMO.[10]

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Hematin-Catalyzed Rearrangement of Hydroperoxylinoleic Acid to Epoxy Alcohols via an Oxygen Rebound

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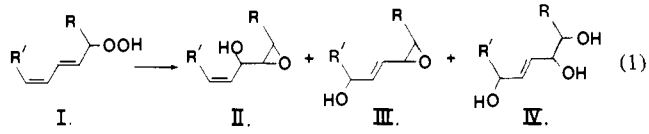
Fatty acid hydroperoxides arise in mammalian tissue by lipid peroxidation and by the action of lipoxygenases on unsaturated fatty acids.[1] Cleavage of the hydroperoxide group concomitant with cyclization to an adjacent double bond generates several different epoxide-derived products including leukotrienes, epoxy alcohols, and trihydroxy fatty acids.[2] The pathways of leukotriene biosynthesis are well understood because of the importance of leukotrienes as mediators of inflammatory and hypersensitivity reactions.[3] Less information is available on the synthesis of epoxy alcohols (eq 1). Pace-Asciak et al. have recently demonstrated

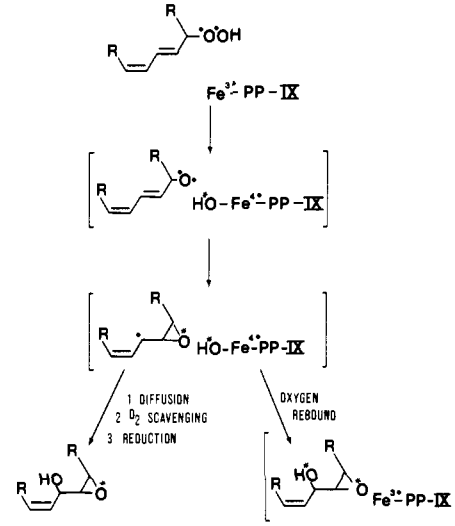


(1)

$R = C_5H_{11}$, $R' = (CH_2)_7COOH$

that both hydroperoxide oxygens are retained in the conversion of 12-hydroperoxy-5,8,10,14-eicosatetraenoic acid to epoxy alcohols and triols by subcellular fractions of rat lung.[4] This observation raises the intriguing question of how the terminal peroxide oxygen is transferred to carbons four and six atoms removed from the peroxide group. We have been studying the reaction of fatty acid hydroperoxides with hematin [hydroxo(porphyrinato)iron(III)], the prosthetic group of several hydroperoxide-metabolizing enzymes.[5] We wish to report that hematin catalyzes the rearrangement of I to isomeric 9- and 11-hydroxy-12,13-epoxyoctadecenoic acids in which both the hydroxyl and epoxide oxygens derive from the hydroperoxide group. The most likely mechanism for this transformation is a unique example of an oxygen rebound in which the metal complex reduces the hydroperoxide group to an alkoxyl radical and transfers the hydroperoxy oxygen to intermediate carbon-centered radicals generated by alkoxyl radical cyclization.

Scheme I. Proposed Mechanism for the Hematin-Catalyzed Conversion of Hydroperoxy Fatty Acids to Epoxy Alcohols[a]



[a] For simplicity, hydroxylation is only considered at the allylic terminus proximal to the epoxide.

Hematin (5×10^{-7} M) and I[6] (5×10^{-5} M) were stirred at 25 °C in 0.1 M sodium phosphate (pH 7.8) containing 2×10^{-4} M Tween 20. After 10 min, the solution was acidified to pH 3.5 and products extracted into ethyl acetate. Solvent was removed in vacuo, the residue was methylated with diazomethane, and the products were isolated and purified by a combination of reversed- and normal-phase HPLC. The purified product zones were silylated and analyzed by gas chromatography–mass spectrometry (GC-MS).[7] Five products were identified; the two major ones were 11-hydroxy-12,13-epoxy-9-octadecenoic acid (II) and 9,12,13-trihydroxy-10-octadecenoic acid (IV). Together, they account for 66% of the identified products.[8] Triol IV is presumed to arise via hydrolysis of the unstable allylic epoxy alcohol III and, in fact, a trace of III is detected.

Experiments were performed in which [$^{18}O_2$]-I[6] was reacted with hematin under an $^{16}O_2$ atmosphere. The 11-hydroxyl of II retained 93% ^{18}O and the 9-hydroxyl of IV retained 66%. When [$^{16}O_2$]-I was reacted with hematin under an $^{18}O_2$ atmosphere, the 11-hydroxyl of II contained 18% ^{18}O, and the 9-hydroxyl of IV contained 32% ^{18}O. The results of these experiments indicate that the 11-hydroxyl oxygen of II and the 9-hydroxyl oxygen of IV are derived predominantly from the hydroperoxide.[9] A percentage of the hydroxyl oxygens in II and IV is derived from O_2. The incorporation of hydroperoxide oxygen is higher at carbon 11 than at carbon 9 in both II and III.

The possibility of an intermolecular hydroperoxide oxygen transfer was evaluated by reacting hematin with an equal mixture of [$^{18}O_2$]-I and [$^{16}O_2$]-I followed by determination of the isotopic composition of epoxyol II. Intermolecular transfer would yield II containing one atom of ^{18}O and one atom of ^{16}O whereas intramolecular transfer would produce II with two atoms of either isotope but not one of each. The relative intensities of the mo-

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(7) The details of product identification will be the subject of a separate publication. Epoxy alcohol II was identical chromatographically and spectroscopically with an authentic standard provided by Dr. H. W. Gardner.

(8) The other products were 13-keto-9,11-octadecadienoic acid and 13-hydroxy-9,11-octadecadienoic acid. In addition, 18% of hydroperoxide I was recovered.

(9) The epoxide oxygen of II and the 13-hydroxyl oxygen of IV are derived quantitatively from the hydroperoxide, as expected.

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lecular ions measured experimentally were M (43), M +2 (6), and M + 4 (51). Considering that a portion of the 11-hydroxyl group is derived from dioxygen, this result clearly indicates that the transfer of the hydroperoxy oxygen to carbon 11 of II is intramolecular.

These findings indicate that hematin catalyzes the cyclization of the internal peroxide oxygen to the 11,12-double bond and the transfer of the terminal peroxide oxygen to carbons 9 or 11. A mechanistic hypothesis consistent with the experimental observations is outlined in Scheme I. Hematin reduces the hydroperoxide by one electron generating a fatty acid alkoxyl radical and a ferryl-hydroxo complex.[10] The alkoxyl radical cyclizes to an epoxide-containing allylic radical.[11] The epoxy allylic radical can couple at either of the allylic termini with the hydroxyl radical coordinated to hematin or to dioxygen following diffusion from the solvent cage. The reciprocal relationship between the incorporation of hydroperoxide or molecular oxygen at carbons 9 or 11 suggests that the ferryl-hydroxo complex and dioxygen compete for the trapping of the same intermediate, the epoxy allylic radical.[12] The higher percentage of peroxy oxygen trapping at carbon 11 is most likely due to the proximity of this allylic terminus to the ferryl-hydroxo complex.

Oxygen rebounds have been observed in the peroxide-dependent and iodosylbenzene-dependent hydroxylations of alkanes catalyzed by ferrous ion and metalloporphyrins, respectively.[13] In both cases, the metal center reduces the oxidizing agent by two electrons and forms an oxo complex that transfers oxygen to the alkane. Oxygen rebounds have not been observed in peroxide-dependent oxidations catalyzed by iron porphyrins presumably because of the propensity of the catalyst to reduce peroxide by one electron in the initial step of oxidation.[14] Our finding that hematin catalyzes the rearrangement of I to epoxy alcohols via an oxygen rebound derives from the fact that the initial peroxide reduction product, an alkoxyl radical, can cyclize to generate a carbon-centered radical capable of coupling to the hydroxyl radical coordinated to iron. The 11,12-double bond of I thus serves as an intramolecular trap that transforms the initial peroxide reduction product into a derivative capable of participating in an oxygen rebound. The coupling reaction may be aided by the fact that the radical pair is generated in a solvent cage provided by detergent micelles.[15] Recent work has shown that micelles limit the diffusion of geminate radicals to an extent that suggests the microenvironment of a radical pair in a micelle acts as a "supercage" relative to that in homogeneous solution.[16] This can result in the prolongation of the lifetime of the solvent cage by factors of up to 10^4.[16a] This would not only enhance the probability that the epoxy allylic radical would couple to the hydroxyl group but also increase the cyclization of the initial alkoxyl radical to the epoxy allylic radical prior to diffusive separation of the initial radical pair.

This report demonstrates that simple heme complexes, in the absence of protein, can catalyze the rearrangement of unsaturated fatty acid hydroperoxides to epoxy alcohols in a reaction that appears mechanistically related to that observed in mammalian tissues. Since the activity in rat lung cytosol that catalyzes this reaction is not abolished by heating and does not chromatograph in a discrete zone, it has been suggested that it is not due to an enzyme.[4] Our results suggest that free heme present in lung extracts may play a role in epoxy alcohol formation in such in vitro experiments.

Acknowledgment. We are grateful to John Groves for helpful discussions. Harold Gardner kindly provided a sample of epoxy alcohol II for chromatographic comparison. Mass spectra were obtained at the Michigan State University Regional Mass Spectrometry Facility with the aid of Betty Baltzer. This work was supported by a research grant from the National Institutes of Health (GM 23642). L.J.M. is a recipient of an American Cancer Society Faculty Research Award (FRA 243).

(10) The interaction of hydroperoxides with hematin is complex. Investigators have proposed that hematin reduces hydroperoxides by one electron or two electrons or oxidizes them by one electron: (a) Portsmouth, D.; Beal, E. A. *Eur. J. Biochem.* **1971**, *19*, 479-487. (b) Jones, P.; Mantle, D.; Davies, D. M.; Kelley, H. C. *Biochemistry* **1977**, *16*, 3974-3978. (c) Kalyanaraman, B.; Mottley, C.; Mason, R. P. *J. Biol. Chem.* **1983**, *258*, 3855-3858. Our data strongly suggest that under the conditions described hematin reduces fatty acid hydroperoxides by one electron.

(11) (a) Gardner, H. W. *J. Agric. Food Chem.* **1975**, *23*, 129-136. (b) Gardner, H. W.; Weisleder, D. W.; Kleiman, R. *Lipids* **1978**, *13*, 246-252. (c) Gardner, H. W.; Kleiman, R. *Biochim. Biophys. Acta* **1981**, *665*, 113-125.

(12) If the epoxyols that incorporate O_2 at carbons 9 and 11 arise via a separate intermediate than those that retain both peroxide oxygens, the incorporation of O_2 at both carbons should be equivalent.

(13) (a) Groves, J. T.; McClusky, G. A. *J. Am. Chem. Soc.* **1976**, *98*, 859-861. (b) Groves, J. T.; Nemo, T. E.; Myers, R. S. *Ibid.* **1979**, *101*, 1032-1033. (c) Chang, C. K.; Kuo, M.-S. *Ibid.* **1979**, *101*, 3413-3415.

(14) (a) Groves, J. T. In "Metal Ion Activation of Dioxygen"; Spiro, T. G., Ed.; Wiley-Interscience: New York, 1980; p 125-162. (b) Oxygen rebound has been reported in the enzymatic decarboxylation of peroxyphenylacetic acid to benzyl alcohol catalyzed by cytochrome P-450. White, R. E.; Sligar, S. G.; Coon, M. J. *J. Biol. Chem.* **1980**, *255*, 11108-11111. One-electron reduction of the peroxide was proposed as the first step in the reaction.

(15) The reaction undoubtedly occurs in detergent micelles. Hematin exists in buffered aqueous solution as a dimer that possesses very low peroxidase activity: (a) Brown S. B.; Dean, T. C.; Jones, P. *Biochem. J.* **1970**, *117*, 733-739. (b) Jones, P.; Robson, T.; Brown, S. *Ibid.* **1973**, *135*, 353-359. Addition of Tween 20 at the concentrations indicated induces a dramatic bathochromic shift of the Soret band from the broad, poorly defined structural absorption of the dimer to the sharp much more intense absorption of the monomer dissolved in an organic solvent. The system can, therefore, be considered to contain hematin in equilibrium between aqueous and micellar compartments. Only hematin dissolved in the micellar compartment is catalytically active.

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Integrated Chemical Systems: Photocatalysis at Semiconductors Incorporated into Polymer (Nafion)/Mediator Systems

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The utilization of semiconductors for photoelectrochemical and photocatalytic processes in which light is used to drive chemical reactions often requires the construction of integrated chemical systems.[1] These are designed heterogeneous systems consisting of several components acting in a synergistic way to carry out a particular process. For example, the photogeneration of hydrogen on p-type semiconductor electrodes (e.g., GaAs and Si) is enhanced by the addition to its surface of a viologen-bearing polymer layer containing platinum.[2] A number of studies on the utilization of semiconductor particles (e.g., TiO_2, CdS), frequently treated with appropriate catalysts to carry out photocatalytic and photosynthetic processes, have been described.[3] In these systems irradiation of suspensions or colloidal dispersions of the semiconductors in solutions of suitable redox couples (relays) and other reagents produces electron/hole pairs which drive oxidations and reductions

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(3) See, for example: (a) Frank, S. N.; Bard, A. J. *J. Phys. Chem.* **1977**, *81*, 1484. (b) Kraeutler, B.; Bard, A. J. *J. Am. Chem. Soc.* **1978**, *100*, 5985. (c) Kalyanasundaram, K.; Borgarello, E.; Gratzel, M. *Helv. Chim. Acta* **1981**, *64*, 362. (d) Thewissen, D. H. M. W.; Tinnemans, A. H. A.; Eeuwhorst-Reinten, M.; Timmer, K.; Mackor, A. *Nouv. J. Chim.* **1983**, *7*, 191.

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