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Reactions of Hydroperoxides with Iron(III) Porphyrins: Heterolytic Cleavage Followed by Hydroperoxide Oxidation

Teddy G. Traylor,*† Cheal Kim,‡ Wen-Pang Fann, and Charles L. Perrin*

Deptartment of Chemistry and Biochemistry, University of California— San Diego
9500 Gilman Dr., La Jolla, CA 92093-0358

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Abstract. Reaction of α,α-dimethylphenethyl hydroperoxide with iron(III) tetramesitylporphyrin in protic solvent gives alkoxy-radical products and little epoxide. Such observations are usually interpreted as evidence for homolysis of the O–O bond in the catalytic process. Yet the same products are now obtained under similar conditions from the reaction of this hydroperoxide with the high-valent oxene (Fe^{+}=O), generated unambiguously. Therefore such products are not necessarily evidence for homolysis but are consistent with heterolysis. Nevertheless, the solvent can affect the nature of O-O cleavage.

INTRODUCTION

The cleavage of an oxygen-oxygen bond in a transition-metal complex is requisite to a wide variety of biological uses of dioxygen and its partially reduced forms.[1] Therefore it is important to establish the mechanisms by which this process occurs, as well as the structural features that drive this reaction in enzymes such as cytochromes P-450[2] and peroxidases.[3] Although many transition-metal systems can be involved in this reaction,[4] the most common systems in mammalian biochemistry utilize heme proteins for oxygen activation. For this reason we have studied iron porphyrins as models for heme-protein oxidases and peroxidases.

There is a general consensus that oxidants XOH that produce stable leaving groups, such as iodosylbenzenes ($ArI(OH)_2$) or hypochlorites, react with iron(III) porphyrins and then undergo heterolytic cleavage of the O-X bond (eq 1).[5-7] Moreover, it was unequivocally established, using perphenylacetic acid, that peracids react by heterolytic cleavage of the O–O bond (eq 2, R = PhCO).[8] It then seemed chemically reasonable that hydrogen peroxide or alkyl hydroperoxides should do so as well (eq 2, R = H or alkyl).[9] Indeed, this is the course taken by peroxidases.[10] Yet the nature of the cleavage, and the structure of the active oxidant, remain unclear, and it has recently been claimed that the complexed peracid, Fe-OOC(O)R, can also be an oxidant.[11]

$$XOH + \overset{|}{Fe^{+}} \underset{H^{+}}{\rightleftharpoons} \overset{|}{FeOX} \longrightarrow \overset{|}{Fe^{+}}{=}O + X^{-} \qquad (1)$$

$$ROOH + \overset{|}{Fe^{+}} \underset{H^{+}}{\rightleftharpoons} \overset{|}{FeOOR} \xrightarrow{BH^{+}} \overset{|}{Fe^{+}}{=}O + ROH \qquad (2)$$

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Early studies using the five-coordinated-iron model, "chelated protohemin", indicated that this mechanism does apply to hydrogen peroxide and alkyl hydroperoxides (eq 2).[8] The kinetics display internal and external general-acid catalyses and other properties that are so similar to those of peracids[8,9,12] that a common heterolytic mechanism was proposed for all of these oxidants (eq 2, R = acyl or alkyl).[8,9]

Yet several reports of reactions of iron(III) porphyrins with alkyl hydroperoxides indicated the production of alkoxy radicals and their decomposition products, especially in those cases where the radical R$^{\cdot}$, derived by fragmentation of $R_3CO^{\cdot}$, is resonance stabilized (eq 3).[13-15] These findings have been taken as evidence for a homolytic cleavage of the O–O bond.

$$R_3COOH + \overset{|}{\underset{|}{Fe^{+}}} \underset{H^{+}}{\rightleftharpoons} \overset{|}{\underset{|}{FeOOCR_3}} \longrightarrow \overset{|}{\underset{|}{Fe\text{-}O}} + R_3CO^{\cdot} \longrightarrow R^{\cdot} + R_2CO \qquad (3)$$

We have been skeptical of suggestions of homolysis in such reactions. Since acyloxy radicals are more stable than alkoxy radicals,[16] homolysis of peresters proceeds faster than homolysis of peroxides. Thus if any reagent is to undergo homolysis it should be peracids. Conversely, if these undergo heterolysis, alkyl hydroperoxides ought to do so too.

Since the yields of alcohol and ketone are thought to reveal the relative extents of eq 2 and 3, a product analysis has become a standard criterion for distinguishing homolytic cleavage from heterolytic in reactions of alkyl hydroperoxides.[14-15] There are two reasons why this criterion is inconclusive. First, because alkoxy radicals can be trapped by hydrogen transfer (eq 4),[17] the absence of ketone cannot be taken as conclusive evidence against homolysis. Secondly, it is possible that heterolysis (eq 2) occurs, but that alkoxy radicals are produced in the subsequent steps.[18] Eqs 5 and 6, along with eq 4, represent an induced decomposition of hydroperoxides, inititated by the oxene. If these occur, then the formation of products derived from $R_3CO^{\cdot}$ (eq 3) would not constitute conclusive evidence for homolysis. We here investigate whether such false positives can occur.

$$R_3CO^{\cdot} + R_3COOH \longrightarrow R_3COH + R_3COO^{\cdot} \qquad (4)$$

$$\overset{|}{\underset{|}{Fe^{+}\!=\!O}} + R_3COOH \longrightarrow \overset{|}{\underset{|}{Fe\text{-}OH^{+}}} + R_3COO^{\cdot} \qquad (5)$$

$$\overset{|}{\underset{|}{FeOH^{+}}} + R_3COOH \longrightarrow H_2O + \overset{|}{\underset{|}{Fe^{+}}} + R_3COO^{\cdot} \qquad (5')$$

$$2\ R_3COO^{\cdot} \longrightarrow [R_3COOOOCR_3] \longrightarrow O_2 + 2\ R_3CO^{\cdot}\ (\text{or } R_3COOCR_3) \qquad (6)$$

To favor the formation of distinctive products we have used α,α-dimethylphenethyl hydroperoxide (DMPOOH), $PhCH_2C(CH_3)_2OOH$, whose derived alkoxy radical cleaves (eq 7) at least 300 times as fast as *t*-butoxy radical.[20] The decomposition of the DMPO radical leads to acetone (observed but not analyzed), benzyl alcohol, and benzaldehyde (eqs 7 and 8). These are easier to detect than methane and ethane, which were not observed from tBuOOH, even though fragmentation produces $CH_3^{\cdot}$.[15]

$$PhCH_2C(CH_3)_2O^{\cdot} \xrightarrow{\text{fast}} PhCH_2^{\cdot} + (CH_3)_2C{=}O \qquad (7)$$

$$PhCH_2^{\cdot} + O_2 \longrightarrow PhCH_2OO^{\cdot} \longrightarrow PhCHO + PhCH_2OH \qquad (8)$$

We now present a method to test whether ketones can be produced from R_3COOH in the absence of any homolytic O-O cleavage induced by the iron(III) porphyrin catalyst. This test requires conditions where the reaction of eq 3 can be definitely shown not to contribute. We now show that ketones are so produced, and we conclude that this criterion for homolytic O-O cleavage can be misleading.

EXPERIMENTAL

Materials

Iron(III) tetramesitylporphyrin chloride (TMPFeCl) was obtained from previous studies.[19] Pentafluoroiodosylbenzene (PFIB) and *m*-chloroperbenzoic acid (MCPBA) (Aldrich) were prepared or purified as previously described.[20,21] Cyclooctene (Aldrich) was distilled before use. Methylene chloride (Fisher) and methanol (Fisher) were used as received. α,α-Dimethylphenethyl hydroperoxide was synthesized from α,α-dimethylphenethyl alcohol (Aldrich) and 30% hydrogen peroxide (Aldrich) by a published method.[22] The product was recrystallized three times from pentane: mp. 40-42 °C, ^{1}H NMR ($CDCl_3$): δ 7.15-7.35 (5H, multiplet), 7.47 (1H, singlet), 2.89 (2H, singlet), 1.21 (6H, singlet). This NMR spectrum is different from that of its starting alcohol: δ 7.15-7.35 (5H, multiplet), 2.76 (2H, singlet), 1.22 (6H, singlet), 2.1 (1H, v broad).

Instruments

Product analysis was performed on a Varian 3700 gas chromatograph equipped with a 10% Carbowax 20M on 80/100 Supelcoport column and a flame ionization detector. Response factors for all products were determined, relative to cyclohexanol or dodecane, as previously described.[20]

Oxidation Procedures

Epoxidation of cyclooctene by oxidants (DMPOOH, MCPBA, or PFIB) alone. Cyclooctene ($1\text{-}5\times10^{-2}$ mmol) was dissolved in the proper solvent mixture (25/75 CH_2Cl_2/CH_3OH for MCPBA and DMPOOH and 25/75/0.1 $CH_2Cl_2/CH_3OH/H_2O$ for PFIB), and the oxidant (10^{-3} mmol) was added from a standard solution in the same solvent (total volume 0.1 ml). The solution was stirred vigorously for about 20 seconds, and aliquots were removed at subsequent times and analyzed by gas chromatography. For DMPOOH epoxidations each aliquot was quenched with an equal volume of 0.2 M Ph_3P before analysis.

Epoxidation of cyclooctene by oxidants (DMPOOH, MCPBA, or PFIB) with catalytic TMPFeCl. TMPFeCl, an internal standard (cyclohexanol or dodecane), and cyclooctene were combined in one of the two solvent mixtures above, and the oxidant was added from a standard solution in the same solvent to start the reaction (total volume 0.1 ml). The mixture was stirred vigorously for about 20 seconds, and aliquots of the solution were withdrawn subsequently and analyzed by gas chromatography. For DMPOOH epoxidations each aliquot was quenched with Ph_3P as described above.

Competition between ROOH and cyclooctene for the high-valent intermediate generated by reaction of oxidant (MCPBA or PFIB) with TMPFeCl. TMPFeCl, an internal standard, and cyclooctene were mixed in one of the above solvent systems. DMPOOH was added from a standard solution in the same solvent, and the reaction solution was shaken for 2-3 seconds. A solution of the oxidant (MCPBA or PFIB) was then added to the reaction mixture to give a total volume of 0.1 ml. An aliquot was withdrawn and analyzed by gas chromatography. At the same time the remainder of the solution was quenched as described above and then analyzed by gas chromatography.

Kinetics of reaction of DMPOOH with triphenylphosphine. Solutions of 10^{-3} M DMPOOH and 1.5×10^{-4} M Ph_3P in 25/75 methanol/dichloromethane were made up quickly at 25 °C and the disappearance of the phosphine was followed by the exponential decrease of absorbance at 260 nm. The pseudo-first-order rate constant was divided by the concentration of DMPOOH to afford a second-order rate constant.

RESULTS

Independent Generation of Oxene

Our objective is to test whether the reactions of eq 2 followed by eqs 5 and 6 can produce the same radical-derived products as those obtained from the known homolytic decomposition of alkyl hydroperoxides. To do so we require a way to create the heterolysis intermediate, $Fe^{+}=O$ (the oxene), in the presence of the alkyl hydroperoxide and under the usual conditions for catalyzed decomposition of the hydroperoxide. This is possible because some oxidants react with the catalyst much faster than do hydroperoxides, as shown in eqs 9-11.[18a] It follows that at $5x10^{-4}$ M catalyst the half-lives of the reactions of eqs 9, 10, and 11 are 0.14, 0.7, and 140 s, respectively. Therefore if equal concentrations of hydroperoxide DMPOOH and either MCPBA or PFIB are used and if the reaction is quenched after 20 sec, the faster oxidants will have reacted completely to produce oxene, while the reaction of the catalyst with the hydroperoxide will have proceeded to the extent of only about 10%.

$$C_6F_5IO + \overset{|}{\underset{|}{Fe^{+}}} \xrightarrow[CH_2Cl_2/MeOH/H_2O]{10^4\ M^{-1}s^{-1}} C_6F_5I + \overset{|}{\underset{|}{Fe^{+}=O}} \quad (9)$$

$$ArC(=O)OOH + \overset{|}{\underset{|}{Fe^{+}}} \xrightarrow[CH_2Cl_2/MeOH]{2x10^3\ M^{-1}s^{-1}} ArC(=O)OH + \overset{|}{\underset{|}{Fe^{+}=O}} \quad (10)$$

$$t\text{-}BuOOH + \overset{|}{\underset{|}{Fe^{+}}} \xrightarrow[CH_2Cl_2/MeOH]{\sim 10\ M^{-1}s^{-1}} \text{products} \quad (11)$$

It is also necessary to prevent appreciable product formation via direct reaction of hydroperoxide with catalyst (eq 11). Kinetic studies at spectrophotometric concentrations provide a rate constant of $2.0 \pm 0.1\ M^{-1}s^{-1}$ for reaction of DMPOOH with triphenylphosphine. Thus rapid quenching of unreacted alkyl hydroperoxide can be accomplished simply by adding excess triphenylphosphine. Table 1 shows the gas chromatographic analyses of DMPOOH both alone and about 2 minutes after addition of excess triphenylphosphine. The hydroperoxide decomposes in the inlet to produce benzaldehyde and benzyl alcohol along with α,α-dimethylphenethyl alcohol (DMPOH). Because no benzaldehyde is observed after the quenching procedure, this quenching must be complete in a few seconds. Indeed, the above rate constant corresponds to a half-life of 3 sec under these conditions.

Table 1. Yields of products from decomposition of 0.01 M DMPOOH in the gas chromatograph.

%PhCHO	%DMPOH	$\%PhCH_2OH$
9.0	17.7	22
0.0[a]	85[a]	0.5[a]

[a]Quenched with triphenylphosphine.

Product Studies

Table 2 shows the reaction of 0.01 M DMPOOH with 0.1 M cyclooctene in the presence of $5x10^{-4}$ M iron(III) tetramesitylporphyrin chloride. Little epoxide is formed. Instead increasing amounts of benzaldehyde and benzyl alcohol are formed, even after immediate quenching. These are exactly the results that were observed previously and that are usually taken as evidence for homolysis in the first step.[14-15] In fact this would seem to

be the cleanest evidence for homolysis, inasmuch as the conversion to alkoxy radical-derived products is almost 100%.

Table 2. Products[a] from epoxidation of cyclooctene by DMPOOH with TMPFeCl in 25/75 CH_2Cl_2/MeOH.

Time, s	%PhCHO	%DMPOH	%$PhCH_2OH$	%epoxide
50[b]	6.4	70	2.0	0
120[b]	13.5	62	2.1	0
1800[b]	~56	20	6	~2

[a]Based on hydroperoxide. [b]Quenched with triphenylphosphine.

Some control experiments are required to demonstrate pairwise unreactivity at short times. Table 2 also shows that little reaction between hemin and alkyl hydroperoxide takes place in 50 seconds. Table 3 shows that under our usual conditions (0.1 M cyclooctene) little uncatalyzed epoxidation by 0.01 M MCPBA alone occurs

Table 3. Epoxidation of cyclooctene by MCPBA, DMPOOH, or PFIB alone in 25/75 CH_2Cl_2/MeOH.

oxidant	time, s	[cyclooctene], M	%epoxide[a]
MCPBA	40	0.1	4.8
MCPBA	42	0.5	26
DMPOOH	40[b]	0.1	0.4
DMPOOH	40[b]	0.5	0.4
PFIB	40	0.1	2

[a]Based on oxidant. [b]Quenched with triphenylphosphine.

in the first 40 sec and even less by DMPOOH or PFIB. Table 4 shows that PFIB reacts directly with the hydroperoxide but only to the extent of a few percent in 25 sec. Thus there is no rapid reaction, either homolytic or heterolytic, between hydroperoxide and iron(III) porphyrin. The only reaction that proceeds appreciably in the first 30 sec is the known reaction[18a] of the catalyst with PFIB or MCPBA (eqs 9,10). Therefore we are able to create the oxene (Fe^{+}=O) in the presence of the hydroperoxide without appreciable reaction of the catalyst with the hydroperoxide.

Table 4. Reaction of 0.01 M PFIB with 0.01 M DMPOOH in 25/75/0.1 CH_2Cl_2/MeOH/H_2O without catalyst.

Time, s	%PhCHO	%DMPOH	%$PhCH_2OH$
25[a]	7.6	81	2.2
60[a]	13.7	74	8.5

[a]Quenched with triphenylphosphine.

We next ask whether the products attributed to homolysis are obtained in the absence of homolytic cleavage. Table 5 shows the products of the reaction of 0.01 M PFIB, DMPOOH, and $5x10^{-4}$ M catalyst at short reaction times in 25/75/0.1 CH_2Cl_2/MeOH/H_2O. Cyclooctene (0.1 M) was included in order to observe the competition between epoxidation and reaction of the oxene with DMPOOH and also to prevent hemin destruction. Without DMPOOH a good yield of epoxide is observed, as expected. In the presence of DMPOOH the yield of epoxide after one minute is markedly reduced. Moreover, the yield of DMPOH is not increased by

quenching, in contrast to the results in Table 1, indicating that essentially all of the DMPOOH has decomposed in a short time. This also contrasts with Table 2, in which very little DMPOOH decomposition occurs during this time in the absence of PFIB.

Table 5. Competition between DMPOOH and cyclooctene for the oxene formed from PFIB and TMPFeCl.

[DMPOOH], M	time, s	%PhCHO[a]	%DMPOH[a]	%$PhCH_2OH$[a]	%epoxide[b]
0	60[c]				55
0.01[d]	35[c]	46	24	5.8	1.3
0.01	60	47	22	6.3	4.9
0.01	60[c]	46	21	7.3	4.7
0.01[d]	65[c]	47	23	5.7	1.5

[a]Based on DMPOOH. [b]Based upon PFIB. [c]Quenched with triphenylphosphine. [d]Mixed thoroughly.

It is interesting to compare the yields of the two alcohols and benzaldehyde in Tables 5 and 2. After 1 minute in the presence of PFIB these yields are nearly the same as in the absence of PFIB after 30 minutes, the time required for complete reaction of DMPOOH. These products are characteristic of the alkoxy radical, and the similarity indicates that the same amount of radical is produced in the absence of direct reaction of DMPOOH as in the direct reaction.

Table 6 displays a similar study using 0.01 M MCPBA to prepare the oxene in 25/75 CH_2Cl_2/MeOH. Clearly the results are very similar to those obtained with PFIB except that the reaction is slower. The extensive production of radical-derived products remains, and yields are close to those of Tables 2 and 5. In this case, as with PFIB, the oxene is formed but the alkyl hydroperoxide is converted to the alkoxy radical. These results are further evidence that the hydroperoxide reacts not with the hemin itself (eq 3) but with the oxene (eq 5).

Table 6. Competition between DMPOOH and cyclooctene for the oxene formed from MCPBA and TMPFeCl.

[DMPOOH], M	time, s	%PhCHO[a]	%DMPOH[a]	%$PhCH_2OH$[a]	%epoxide[b]
0	40				18
0	1200				18
0.01	50[c]	41	34	7.4	8.3
0.01	60	47	17	15	9.1
0.01	60[c]	46	25	8.6	9.1
0.001[d]	30[c]	47	48	7.0	<1
0.001[d]	60[c]	52	41	7.7	<1

[a]Based on DMPOOH. [b]Based on MCPBA. [c]Quenched with triphenylphosphine. [d]0.01M cyclooctene, 0.001 M MCPBA.

DISCUSSION

Radical-Derived Products from Oxene

Several kinds of observations have been interpreted as evidence for homolytic cleavage of hydrogen peroxide and alkyl hydroperoxides by iron(III) porphyrins[14-15,23] as well as by other kinds of iron(III) complexes (eq 3).[24] We address here one of the most commonly used criteria for homolysis, namely, the formation of products derivable from an alkoxy-radical intermediate.

Table 2 shows that the reaction of DMPOOH with iron(III) tetramesitylporphyrin affords little epoxidation and high yields of products derived from the alkoxy radical. Formation of these products is usually taken as evidence for homolysis of the O-O bond.

An alternative possibility involves heterolysis (eq 2, R = $PhCH_2C(CH_3)_2$) followed by reaction of the oxene with additional alkyl hydroperoxide to give peroxy radicals (eq 5) and then alkoxy radicals (eq 6). This mechanism requires the production of some $PhCH_2(CH_3)_2COH$ (DMPOH) from eq 2. However, this is the initiation step for a radical-chain decomposition of the hydroperoxide (eqs 5-8). If the chain length is long, this alcohol can be a minor product.[25] Therefore it is not necessary that it be a major one, despite an assertion that it must be formed in 50% yield if the mechanism involves heterolytic cleavage of the hydroperoxide O-O bond.[26]

The experimental results in Table 5 and 6 show that this sequence is indeed a viable process for the production of alkoxy radicals. In these cases the time is too short for reaction between DMPOOH and hemin catalyst, whether by heterolysis (eq 2) or by homolysis (eq 3), and only eq 9 or 10 proceeds. Yet products from alkoxy radical are formed. Thus we have succeeded in converting the alkyl hydroperoxide to an alkoxy radical without its undergoing a homolytic cleavage.

Yet the product distributions found for the reaction of DMPOOH with PFIB or MCPBA are remarkably similar to those in Table 2 from DMPOOH plus hemin catalyst. Although this similarity does not provide definitive evidence for heterolysis of the O-O bond followed by oxidation of alkyl hydroperoxide, it shows that this product distribution does not, despite frequent claims,[14-15,23,26] provide evidence against heterolysis. It is especially noteworthy that oxene-induced hydroperoxide decomposition is observed even at low concentrations (0.001 M) of oxidants (Table 6). We therefore assert that alkoxy-radical production does not necessarily require homolysis of FeOOR.

Evidence for heterolysis of hydrogen peroxide and alkyl hydroperoxides by some iron(III) porphyrins has been well documented.[18,27] The oxene has been inferred as an intermediate in reactions with hydroperoxides. Several iron(III) porphyrins react with *t*-butyl hydroperoxide or hydrogen peroxide to give high-yield (75-100%) epoxidation of alkenes. The products from norbornene have the same stereoselectivity (exo/endo=23) as from genuine oxene reactions of iron(III) porphyrin + PFIB. In addition, structure-reactivity studies show evidence for continual changes in transition-state structure rather than any change of mechanism from heterolysis with peracids to homolysis with hydroperoxides.[28] The observation of ^{18}O incorporation from $H_2{}^{18}O$ is further evidence for oxene as the reactive intermediate in epoxidations by H_2O_2 and tBuOOH.[29] The present results and those presented elsewhere show that the evidence for homolysis by any iron(III) porphyrin is far from convincing but can be quite consistent with heterolysis.

Mechanism

Our results show only that all our products are derived from the oxene. We cannot disprove the proposal[15a,30] that heterolysis consists of homolysis followed by cage electron transfer (eq 12). However, this is simply a more circuitous mechanism for accomplishing what can be reached more directly and more simply by heterolysis. Besides, this proposal is made less plausible by the fact that electron-deficient hemins give more epoxide products.[27] Such hemes should be more resistant to oxidation, remain radicals, and afford less epoxide.

$$\text{FeOOR} \longrightarrow \overline{\text{FeO}\cdot\text{OR}} \longrightarrow \overline{\text{Fe}^{+}\text{=O}^{-}\text{OR}} \qquad (12)$$

Of course we cannot conclude that all reactions of hydroperoxides with hemins are heterolytic. Marnett and coworkers have found convincing evidence for homolysis under some conditions.[31] They found that reaction of long-chain allylic hydroperoxides with hematin in aqueous detergent produces products derivable from alkoxy radicals. They could show that these do not arise from heterolysis to an oxene, followed by a subsequent reaction of oxene with hydroperoxide, since added phenols, which would intercept the oxene, do not

reduce the proportion of those radical products.[32] Similar behavior is seen with ferric bleomycin in water or methanol.[33] With TPPFeCl there are simultaneous homolytic and heterolytic O-O bond cleavages, depending on solvent and on the spin state of the iron.[34] Likewise, there are competitive heterolytic and homolytic O–O bond cleavages by sperm-whale myoglobin and its mutants.[35] According to an isotopic-labeling experiment with 2,6-di-*t*-butyl-4-hydroperoxy-4-methyl-2,5-cyclohexadienone, 92% of the radical products arise by peroxide homolysis and 8% via the hydroperoxy radical (eqs 5 and 6).

We cannot definitively rule out homolysis in all cases. All we can conclude is that heterolysis of hydrogen peroxide and alkyl hydroperoxides by some iron(III) porphyrins (including some that were claimed to undergo homolysis)[23] is definitely demonstrated by high epoxide yields, structure-reactivity studies,[28] and by ^{18}O labeling and stereospecific epoxidation.[29] By contrast most of the evidence for homolysis which we have subjected to the critical scrutiny described here is quite consistent with heterolysis followed by oxene-induced radical processes. These include alkoxy-radical formation,[14-15] loss of epoxidation stereospecificity,[23b] low epoxide yields,[23,36] and kinetic evidence.[23c] Nevertheless the major evidence for homolysis has been the formation of products derived from alkoxy radicals, and we have here shown that these can instead be produced by reaction of the alkyl hydroperoxide with the oxene.

We do not address the decomposition of hemin-OOR in aprotic solvents, which has been proposed to occur by homolysis.[37] Our method is obviously not applicable to that system nor is there reason to propose heterolysis to an alkoxide ion in the absence of a proton source.

Indeed, it is likely that the solvent plays a key role in determining the nature of O-O cleavage. A nonpolar aprotic solvent favors homolytic cleavage of an uncharged FeOOR intermediate. However, a polar, protic solvent facilitates the proton transfers that permit heterolytic cleavage of ROH as leaving group.

The understanding of these processes has led to some practical applications. We have found that the oxene derived from electron-rich iron(III) porphyrins reacts 10^2-fold as fast with alkyl hydroperoxides as with alkenes whereas with electron-deficient porphyrins this preference is very slight.[27] This means that the low yield of epoxidation (~10%) with tetramesitylhemin can be increased to 75% by using iron(III) tetrakis(2,6-dichlorophenyl)porphyrin and to 100% with iron(III) perfluorotetraphenylporphyrin. Similar differences in selectivity have been seen with iron(III) porphyrin peroxo compexes.[38] These considerations also clarify the repeated reports of nonstereospecific low-yield epoxidations.[23,36] In those studies electron-rich hemins were almost invariably used. The resulting high-valent oxene does not produce epoxide but instead oxidizes the alkyl hydroperoxide to produce a peroxy radical (eq 5). Then that radical epoxidizes with loss of stereospecificity, or leads to alkoxy radical, which cleaves to ketone (eq 3).[15,26] By using electron-deficient hemins, the oxidation of hydroperoxide and the subsequent side reactions are avoided. In this way hydrogen peroxide can serve as a very efficient epoxidizing reagent.

CONCLUSIONS

Reactions in hydroxylic solvents of an alkyl hydroperoxide with iron(III) tetramesitylporphyrin and with its high-valent oxene species, generated independently, give the same mixture of products, including ketone that is usually considered to arise from fragmentation of the alkoxy radical. Therefore we conclude that the observation of ketone does not necessarily provide evidence for homolysis of the O-O bond in order to account for the alkoxy radical. Instead these products can arise indirectly, by reaction of hydroperoxide with oxene. Moreover, we conclude that reaction of hydrogen peroxide or alkyl hydroperoxides with iron(III) porphyrins proceeds by heterolysis of the O–O bond, especially in protic solvents. Nevertheless, it is recognized that the solvent can play a key role in determining the nature of O-O cleavage.

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† Deceased, June 14, 1993.

‡ Present address: Dept. of Fine Chemicals, Seoul National Polytechnic University, 172 Kongnung 2-Dong, Nowon-Gu, Seoul, Korea.

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