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Supplementary Material Available: Experimental details of X-ray study, labeled ORTEP drawing, final positional parameters, and final thermal parameters for **1a** (6 pages); final observed and calculated structure factors for **1a** (21 pages). Supplementary material for **5b** is available elsewhere.[37] Ordering information is given on any current masthead page.

Reevaluation of the Significance of ^{18}O Incorporation in Metal Complex-Catalyzed Oxygenation Reactions Carried Out in the Presence of $H_2{}^{18}O$

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Abstract: We have measured the extent of ^{18}O incorporation into the products of metal complex-catalyzed oxygenations of organic compounds when $H_2{}^{18}O$ is added to the reaction mixture. The oxidants studied were hydrogen peroxide, *tert*-butyl hydroperoxide, *m*-chloroperbenzoic acid (MCPBA), and iodosylbenzene, and the reactions were carried out in organic solvents. In reactions of hydrogen peroxide, *tert*-butyl hydroperoxide, and MCPBA, no or at most a small amount of ^{18}O was incorporated into the products in either olefin epoxidation or alkane hydroxylation reactions catalyzed by (*meso*-tetrakis(2,6-dichlorophenyl)porphinato)iron(III) chloride (Fe(TDCPP)Cl), (*meso*-tetrakis(2,6-dichlorophenyl)porphinato)manganese(III) chloride (Mn(TDCPP)Cl) with imidazole added, iron(II) cyclam (cyclam = 1,4,8,11-tetraazacyclotetradecane), manganese(II) cyclam, and nickel(II) cyclam. Assuming that high-valent metal oxo intermediates are generated in all of the reactions of iron and manganese porphyrin complexes with the oxidants PhIO, H_2O_2, *tert*-butyl hydroperoxide, and MCPBA, we conclude that the high-valent iron oxo and manganese oxo intermediates do not exchange or slowly exchange with labeled $H_2{}^{18}O$ during the course of these catalytic oxygenation reactions under our reaction conditions. Several different iron(III) and manganese(III) porphyrin complexes such as Fe(TDCPP)Cl, (*meso*-tetraphenylporphinato)iron(III) chloride (Fe(TPP)Cl), (*meso*-tetramesitylporphinato)iron(III) chloride (Fe(TMP)Cl), and Mn(TDCPP)Cl were used to catalyze cyclohexene epoxidation by MCPBA at low temperature (−78 °C) in the presence of $H_2{}^{18}O$. The epoxide obtained in the epoxidation of cyclohexene catalyzed by Fe(TDCPP)Cl, Fe(TPP)Cl, Fe(TMP)Cl, and Mn(TDCPP)Cl contained 0%, 4%, 22%, and 0% ^{18}O, respectively. By contrast, in the iodosylbenzene reactions, oxygen from labeled $H_2{}^{18}O$ was fully incorporated into products in aprotic and protic solvents in olefin epoxidation and alkane hydroxylation reactions catalyzed by either iron(III) porphyrin, manganese(III) porphyrin, or metallocyclam (M = Fe, Mn, Ni) complexes. Labeled oxygen from $H_2{}^{18}O$ was also fully incorporated into cyclohexene oxide in the epoxidation of cyclohexene catalyzed by a zinc complex which is not able to form a high-valent zinc oxo species as an intermediate. We conclude from these results that, in the case of iodosylbenzene, the mechanism for oxygen exchange does not involve metal oxo intermediates and that the observation of incorporation of labeled oxygen from $H_2{}^{18}O$ into products does not provide evidence for the intermediacy of metal oxo complexes in iodosylbenzene reactions. In the case of oxidants other than iodosylbenzene, our results also suggest that reactions of high-valent metal oxo complexes with organic substrates in catalytic oxygenation reactions are often comparable in rate to or faster than the reactions with isotopically labeled water that lead to oxygen exchange.

Introduction

Elucidation of the mechanism of oxygen atom-transfer reactions by monooxygenase enzymes has been a major goal of biological and bioinorganic chemistry.[1] Intensive study of cytochrome P-450 and its model compounds such as metalloporphyrins has resulted in a proposed catalytic cycle which involves a high-valent iron oxo species as the oxygenating agent.[1c,d,2] Although high-valent iron oxo species have been widely proposed as the oxygenating intermediates in the catalytic cycle of heme and non-heme iron-containing monooxygenase enzymes and their model compounds, direct evidence for the high-valent iron oxo species has frequently been difficult to obtain.

Several reports have appeared suggesting that high-valent metal oxo complexes exchange oxygen atoms rapidly with $H_2{}^{18}O$ when labeled water is added to such complexes after they have been generated in organic solvents. Thus, it has been found that (1) the oxygen atom in $Cr^{V}(TPP)(O)Cl$ exchanged with the labeled oxygen of $H_2{}^{18}O$,[3a] (2) $(TMP)^{\bullet+}Fe^{IV}(O)Cl$, generated in situ from the reaction of Fe(TMP)Cl and MCPBA at −78 °C, epoxidized norbornene in the presence of $H_2{}^{18}O$, resulting in the formation

Scheme I

$$LM^{n+} + X^{16}O \xrightarrow{-X} [LM^{(n+2)+}{=}^{16}O]$$

$$[LM^{(n+2)+}{=}^{16}O] \xrightarrow[\text{fast}]{H_2{}^{18}O} [LM^{(n+2)+}{=}^{18}O]$$

$$[LM^{(n+2)+}{=}^{18}O] \xrightarrow[S]{} S(^{18}O) + LM^{n+}$$

(S = substrate)

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Table I. Previous Studies of Labeled $H_2{}^{18}O$ Exchange in Monooxygenases and Model Systems

oxidant	catalyst	substrate	^{18}O incorp	ref
OIPh	P-450	cyclohexane	yes	4
	P-450$_{LM_2}$	cyclohexane	yes	5
	P-450$_{cam}$	camphor	yes	6
	Fe bleomycin	*cis*-stilbene	yes	7
	Mn(TPP)Cl	norbornene	yes	3c
	Ni(cyclam)$^{2+}$	norbornene	yes	8a
	Mn(salen)$^+$	norbornene	yes	8b
	Co(salam)	norbornene	yes	8c
	[RuCl(DPPP)$_2$]$^+$	norbornene	yes	10
	Zn(II) bleomycin	stilbene	yes	9a
	Zn$_2$(L)$^{4+}$	cyclohexene	yes	9b
cumene–OOH	P-450	cyclohexane	no	4
	P-450$_{LM_2}$	cyclohexane	no	5
	P-450$_{cam}$	camphor	no	6
	P-450$_{LM_2}$	cyclohexane	8.5%	11
	Fe bleomycin	*cis*-stilbene	no	7a
O_2/NADPH	P-450	cyclohexane	no	4
	P-450$_{LM_2}$	cyclohexane	no	5
O_2/NADH	P-450$_{cam}$	camphor	no	6
O_2/ascorbic acid	Fe bleomycin	*cis*-stilbene	no	7a
O_2	Fe bleomycin	d(CGCGCG)	yes	12
	MMO^a	methane	no	13
	propyl hydroxylase	proline	<7%	14
	DBM^b	dopamine	no	15
	PAH^c	phenylalanine	no	15
MCPBA	P-450$_{cam}$	camphor	no	6
	Fe(ClO$_4$)$_2$	cyclohexanol	9%	16
	Fe(TPA)Cl$_2^+$	cyclohexane	10%	17
	Mn(TMP)Cl	*β*-methylstyrene	40%	18a
	Mn(TMP)Cl^d	*β*-methylstyrene	no	18b
H_2O_2	Fe bleomycin	*cis*-stilbene	no	7a
$NaIO_4$	Fe bleomycin	*cis*-stilbene	no	7a
LiOCl	Mn(TPP)OAc^d	*p*-methoxystyrene	no	19
$KHSO_5$	Mn(TPP)OAc^d	cyclohexene	no	20
Cr^V(TPP)(O)Cl		norbornene	yes	3a
[Fe^{IV}(TMP)$^{\bullet -}$(O)]$^+$		norbornene	yes	3b
[Fe(TPP)(O$_2$)]$^-$		cyclohexane	yes	21
[(L)Mn^V(O)]$^+$			yes	22
[(L$^{\bullet +}$)Fe^{IV}(O)]$^{3+}$			yes	23
Mn^{IV}(TMP)(O)			yes	24
[Fe^{IV}(TMP)$^{\bullet -}$(O)]$^+$			no	25a
Fe^{IV}(O)(HRP compd II)			yes	25b
V(OEP)$^{\bullet -}$(O)			yes	26
Mn^{IV}(O)(HRP compd I)			no	27
Fe^{IV}(O) (cytochrome *c* peroxidase)			yes	28
(SALPN)Mn^V(O)			yes	29

^{a} Methane monooxygenase. ^{b} Dopamine *β*-monooxygenase. ^{c} Phenylalanine hydroxylase. ^{d} Reaction was carried out in the presence of pyridine.

of norbornene oxide with the incorporation of ^{18}O,[3b] and (3) a manganese porphyrin complex prepared by reacting Mn(TPP)Cl with iodosylbenzene in the presence of $H_2{}^{18}O$ epoxidized norbornene to norbornene oxide with 80% incorporation of the ^{18}O label.[3c] On the basis of these and similar experiments, it has often been suggested that the observation of substantial levels of ^{18}O incorporation from labeled $H_2{}^{18}O$ into the oxygenated organic products is sufficient evidence for the intermediacy of high-valent metal oxo complexes (see Scheme I).

As shown in Table I, a large number of experiments of this nature measuring ^{18}O incorporation from $H_2{}^{18}O$ have been reported in the literature. When the oxygenated products were found

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Table II. Percent of Oxygen in Epoxide Incorporated from $H_2{}^{18}O$ in the Epoxidation of Cyclohexene Catalyzed by Various Metal Complexes Using Different Oxidants[a]

catalyst	oxidant	^{18}O (%) in water added[b]	^{18}O (%) in epoxide product[c]	yield (%) of epoxide product[d]
Fe(TDCPP)Cl	PhIO	76	77	60
	H_2O_2	76	≤0.5	21
	t-BuOOH	76	≤0.5	10
	MCPBA	76	2.5	60
Mn(TDCPP)Cl	PhIO	76	75	80
	H_2O_2	76	0	43
$Fe(cyclam)(OTf)_2$	PhIO	76	76	63
	H_2O_2	76	0	30
	MCPBA	97	0	38
$Mn(cyclam)(OTf)_2$	PhIO	76	71	23
	MCPBA	90	0	33
$Ni(cyclam)(NO_3)_2$	PhIO	76	73	18
	MCPBA	90	2.5	18
$Zn_2(L)(OTf)_4$	PhIO	97	90	22

[a] See Experimental Section for detailed experimental procedures. [b] ^{18}O percent of $H_2{}^{18}O$ in the reaction medium. [c] ^{18}O percent in cyclohexene oxide. [d] Based on amounts of oxidants added.

to contain labeled oxygen, it was generally concluded that the oxygenating species was a metal oxo complex. Therefore, the labeled $H_2{}^{18}O$ experiments in iodosylbenzene reactions always led to the conclusion that high-valent metal oxo species were the oxygenating species on the basis of the observation of labeled oxygen incorporation from water into products.

In this paper, we report the results of a study of metal complex-catalyzed oxygenation reactions in which several oxidants, i.e. iodosylbenzene, H_2O_2, *tert*-butyl hydroperoxide, and MCPBA, were reacted with organic substrates to which $H_2{}^{18}O$ had been added. The catalysts used were iron and manganese metalloporphyrin complexes, iron, manganese, and nickel cyclam complexes, and a non-redox zinc complex. The purpose of the study was to gain a more complete understanding of the significance of ^{18}O exchange in catalytic oxygenation reactions. The results of this study indicate (1) that ^{18}O from $H_2{}^{18}O$ exchanged rapidly with ^{16}O derived from $PhI^{16}O$ during metal-catalyzed oxygenation reactions by a mechanism that did not involve high-valent metal oxo intermediates and (2) that, in the case of the metal complexes we examined, exchange of ^{18}O from $H_2{}^{18}O$ with the oxygenation intermediates generated from oxidants other than PhIO (e.g. H_2O_2, ROOH, and MCPBA) was comparable in rate or slow relative to reactions of such intermediates with substrates in catalytic oxygenation reactions.

Results

Epoxidation of Cyclohexene by Various Oxidants Catalyzed by (*meso*-Tetrakis(2,6-dichlorophenyl)porphinato)iron(III) Chloride (Fe(TDCPP)Cl) and (*meso*-Tetrakis(2,6-dichlorophenyl)porphinato)manganese(III) Chloride (Mn(TDCPP)Cl) in the Presence of $H_2{}^{18}O$. Epoxidation of cyclohexene was carried out in a CH_2Cl_2/CH_3OH mixture containing 4.8% $H_2{}^{18}O$ and 1.5% $H_2{}^{16}O$ by volume, using conditions similar to those developed by Traylor et al.[30] (see Experimental Section for details). The yields of cyclohexene oxide and the percentage of ^{18}O incorporation into the epoxide product are listed in Table II. In all of the reactions, cyclohexene oxide was the predominant product. The data indicate that labeled oxygen incorporation occurred in the case of the reaction in which iodosylbenzene was the oxidant, but only a trace or small amount of labeled oxygen was incorporated into cyclohexene oxide in the case of the reactions of hydrogen peroxide, *tert*-butyl hydroperoxide, and MCPBA.

Table III. Percent of Oxygen Incorporated into Cyclohexanol from Added $H_2{}^{18}O$ in the Hydroxylation of Cyclohexane Catalyzed by Mn(TDCPP)Cl[a]

oxidant	^{18}O (%) in added water	^{18}O (%) in cyclohexanol product	yield (%) of cyclohexanol product[b]
PhIO	76	77	25
H_2O_2	76	0	28
MCPBA	76	0	42

[a] See Experimental Section for detailed procedures. [b] Based on amounts of oxidants added.

Epoxidation of Cyclohexene by Various Oxidants Catalyzed by $M(cyclam)^{2+}$ (M = Mn, Fe, Ni; cyclam = 1,4,8,11-Tetraazacyclotetradecane) in the Presence of $H_2{}^{18}O$. The epoxidation reactions were carried out in CH_3CN in hydrogen peroxide and iodosylbenzene reactions and in mixtures of CH_3OH and CH_3CN in the case of the MCPBA reaction (see Experimental Section). Cyclohexene oxide was the predominant product with trace amounts of allylic oxidation products in the reactions.[31] As with the iron and manganese porphyrin complex-mediated epoxidation reactions, the labeled oxygen from solvent water was fully incorporated into cyclohexene oxide in the iodosylbenzene reactions catalyzed by iron, manganese, and nickel cyclam complexes but not at all in the hydrogen peroxide and MCPBA reactions catalyzed by iron or manganese cyclam complexes (see Table II). In the cyclohexene epoxidation by $Ni(cyclam)^{2+}$ and MCPBA, a small amount (2.5%) of ^{18}O was found in the cyclohexene oxide product. A control reaction was carried out for the MCPBA reaction at −23 °C in the absence of the metallocyclam complex which showed that only a negligible amount (<4% based on MCPBA added) of epoxide was formed during the time period of the reaction.

Epoxidation of Cyclohexene by $PhI^{16}O$ Catalyzed by the Zinc(II) Complex $Zn_2(m\text{-}XYL(py)_2)(CF_3SO_3)_4$ in the Presence of $H_2{}^{18}O$. The incorporation of oxygen-18 into products from labeled water was examined in the oxygenation of cyclohexene by iodosylbenzene catalyzed by a binuclear zinc complex $Zn_2(m\text{-}XYL(py)_2)(CF_3SO_3)_4$ in acetonitrile solution. Analysis of the cyclohexene oxide product showed that a significant amount of ^{18}O label was incorporated into the product (see Table II).

Control experiments were carried out to ensure that the oxygen of iodosylbenzene was not scrambling with labeled water in aprotic solvents prior to the reaction with the zinc complex. A mixture of solid iodosylbenzene and $H_2{}^{18}O$ was stirred in acetonitrile for 30 min in the presence or absence of the binuclear zinc complex. Unreacted solid iodosylbenzene was isolated from the reaction mixture and dried in vacuo. The infrared spectrum of the iodosylbenzene showed only bands attributable to $PhI^{16}O$ and not to $PhI^{18}O$. Moreover, this solid was reacted with cyclohexene, and the resulting cyclohexene oxide was shown to contain less than 10% ^{18}O. Cyclohexene oxide, which was stirred in the presence of the zinc complex and $H_2{}^{18}O$ for 1.5 h in acetonitrile, was also found not to exchange with $H_2{}^{18}O$.

Hydroxylation of Cyclohexane by PhIO, H_2O_2, or MCPBA Catalyzed by Mn(TDCPP)Cl in the Presence of $H_2{}^{18}O$. Cyclohexanol was the major product in the hydroxylation of cyclohexane by various oxidants such as hydrogen peroxide, iodosylbenzene, and MCPBA catalyzed by the Mn(III) porphyrin complex in the presence of 35 equiv of 4-methylimidazole in a solvent mixture of CH_2Cl_2 and CH_3OH. Only a small amount (less than 10%) of cyclohexanone was formed. The data in Table III indicate that ^{18}O from labeled water was incorporated into the cyclohexanol product in the case of the iodosylbenzene reaction but not in either the hydrogen peroxide or the MCPBA reaction.

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Table IV. Cyclohexene Epoxidation by MCPBA and Metalloporphyrin (M = Fe, Mn) Complexes in the Presence of $H_2^{18}O$ at −78 °C[a]

metalloporphyrins	^{18}O (%) in epoxide product[b]	yield (%) of epoxide product[c]
Fe(TDCPP)Cl	<1	50
Fe(TPP)Cl	4	31
Fe(TMP)Cl	22	36
Mn(TDCPP)Cl	<1	30

[a] See Experimental Section for detailed procedures. [b] ^{18}O percent in cyclohexene oxide. [c] Based on amount of MCPBA added.

Epoxidation of Cyclohexene by MCPBA Catalyzed by Iron(III) Porphyrin and Manganese(III) Porphyrin Complexes in the Presence of $H_2^{18}O$ at −78 °C. The epoxidation of cyclohexene by MCPBA and metalloporphyrin complexes such as Fe(TDCPP)Cl, Fe(TMP)Cl, Fe(TPP)Cl, and Mn(TDCPP)Cl was studied at −78 °C in a solvent mixture of CH_2Cl_2 and CH_3OH in the presence of $H_2^{18}O$. The results listed in Table IV demonstrate that the percentage of ^{18}O in the epoxide formed depended on the nature of the porphyrin ligand bound to iron. In the case of Mn(TDCPP)Cl as a catalyst, the epoxide product did not contain ^{18}O. A control reaction in which cyclohexene was stirred with MCPBA in the absence of metalloporphyrins at −78 °C showed that only a small amount (less than 5%) of cyclohexene oxide was produced.

Discussion

The oxidation of cyclohexene and cyclohexane by iodosylbenzene, hydrogen peroxide, *tert*-butyl hydroperoxide, and MCPBA catalyzed by either Fe(TDCPP)Cl, Fe(TPP)Cl, Fe(TMP)Cl, Mn(TDCPP)Cl, $Fe(cyclam)^{2+}$, $Mn(cyclam)^{2+}$, $Ni(cyclam)^{2+}$, or a binuclear zinc complex was studied in the presence of labeled $H_2^{18}O$. Tables II and III unambiguously show that labeled oxygen incorporation into the oxygenated products occurred whenever iodosylbenzene was used as an oxidant in the alkene epoxidation and alkane hydroxylation reactions but only infrequently when the other oxidants, i.e. H_2O_2, *t*-BuOOH, and MCPBA, were used.

$$\text{substrate} + PhI^{16}O + H_2^{18}O \xrightarrow{\text{catalyst}} \text{product}(^{18}O) \quad (1)$$

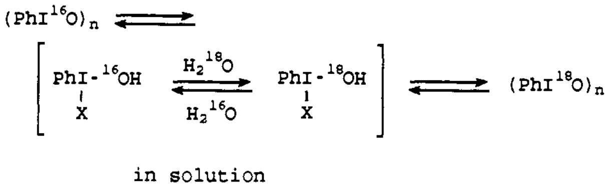
$$\text{substrate} + RO^{16}OH + H_2^{18}O \xrightarrow{\text{catalyst}} \text{product}(^{16}O) \quad (2)$$

^{18}O Incorporation in Iodosylbenzene Reactions. There has not been general agreement in the literature concerning the nature of oxygen exchange of iodosylbenzene with labeled water in cytochrome P-450 or metal complex-mediated oxygenation reactions of organic substrates. Some of the experiments reported are as follows: (1) The oxygen atom in iodosylbenzene was reported not to exchange in water in the absence of metal catalysts.[6] (2) Iodosylbenzene was reported not to undergo prior isotopic exchange with labeled water in the presence or absence of metal catalysts in aprotic solvent.[8] (3) In contrast to (2), iodosylbenzene was reported to exchange rapidly with labeled water in acetonitrile in the absence of metal catalysts.[32] This conclusion was reached on the basis of a study of the oxidation of CH_3SCH_3 by $PhI^{16}O$ in the presence of $H_2^{18}O$ at 60 °C in CH_3CN. (4) Iodosylbenzene was reported to exchange rapidly with labeled water in a solvent mixture of methanol and water in the absence of metal ions.[7,33] (5) The oxygen atom derived from iodosylbenzene was found to exchange with labeled water prior to oxygen transfer to the substrate in the cytochrome P-450 system.[4] This oxygen exchange was reported to be the result of the formation of a high-valent iron oxo intermediate which exchanged its oxygen with water. (6) The oxygen of iodosylbenzene was reported to exchange with the oxygen of labeled water coordinated to the cytochrome P-450 prior to the formation of iron oxo species.[34] These apparently contradictory results can now be resolved on the basis of the results we describe in this paper.

Our control experiments, in which solid iodosylbenzene was stirred with labeled water in acetonitrile in the presence or absence of a catalyst and then reisolated and analyzed, demonstrated that the *solid* iodosylbenzene polymer itself did not exchange oxygen atoms with labeled water in the absence or presence of the catalyst in aprotic solvent. Iodosylbenzene is an insoluble polymer which apparently dissociates irreversibly when it reacts with the metal complex catalyst. The reisolated iodosylbenzene was the intact polymer iodosylbenzene, and its oxygen atoms had not been scrambled by exposure to labeled water in our experiments. This observation is consistent with results 1 and 2 above, which showed that the oxygen of solid iodosylbenzene polymer does not exchange with the oxygen of water in the absence or presence of metal catalyst (see eq 3).

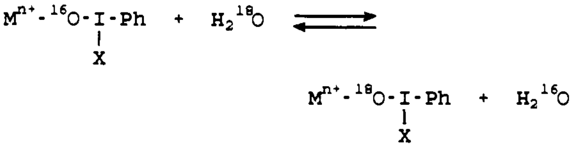
$$(PhI^{16}O)_n + H_2^{18}O \;\cancel{\rightleftharpoons}\; (PhI^{18}O)_n + H_2^{16}O \quad (3)$$

In a methanolic solution, iodosylbenzene and its derivatives were reported to exchange with solvent water (point 4 above).[35] In this case, the iodosylbenzene dissolves in the methanolic solution, unlike the situation described above where the virtually insoluble iodosylbenzene polymer was stirred in water. Under these conditions, iodosylbenzene is believed to react with methanol to give $PhI(OMe)_2$, PhI(OMe)(OH), or related species.[33] Thus, oxygen exchange of PhIO may occur readily under such conditions by a mechanism involving methanolysis followed by hydrolysis. This is in fact the method used to prepare ^{18}O-labeled iodosylbenzene.[33] Other evidence for the hydrolysis of hypervalent iodine compounds in an aqueous methanolic solution is obtained from the reaction of the tosylimine analogue of iodosylbenzene, $MeC_6H_5SO_2N{=}IC_6H_5$, and cytochrome P-450.[5,36] The product in the reaction with cyclohexane is cyclohexanol, not the amide, and this result is rationalized by the hydrolysis of the tosylimine analogue of iodosylbenzene in the methanolic solution. This explanation is consistent with points 3 and 4 above, from which it can be concluded that monomerized products formed when iodosylbenzene goes into solution can readily exchange with labeled water (eq 4).



$$(PhI^{16}O)_n \rightleftharpoons \left[\underset{\text{X}}{\underset{|}{PhI}}{-}^{16}OH \underset{H_2^{16}O}{\overset{H_2^{18}O}{\rightleftharpoons}} \underset{\text{X}}{\underset{|}{PhI}}{-}^{18}OH\right]_{\text{in solution}} \rightleftharpoons (PhI^{18}O)_n \quad (4)$$

In the case of the observed oxygen atom exchange between iodosylbenzene and water in the presence of metal catalysts, the most likely explanation is that oxygen exchange occurs after iodosylbenzene is dissolved and is coordinated to a metal complex but before the oxygen atom is transferred to the substrate. In support of this hypothesis is the observation by Hill and his coworker of oxygen atom exchange between a manganese porphyrin iodosylbenzene complex dissolved in acetone and labeled water added to the solution.[37] This result indicates that the iodosylbenzene coordinated to a metal complex can readily exchange with labeled water (eq 5).



$$M^{n+}{-}^{16}O{-}\underset{\text{X}}{\underset{|}{I}}{-}Ph + H_2^{18}O \rightleftharpoons M^{n+}{-}^{18}O{-}\underset{\text{X}}{\underset{|}{I}}{-}Ph + H_2^{16}O \quad (5)$$

We found from our experiments that a small amount of labeled $H_2^{18}O$ present in the reaction medium caused significant ^{18}O

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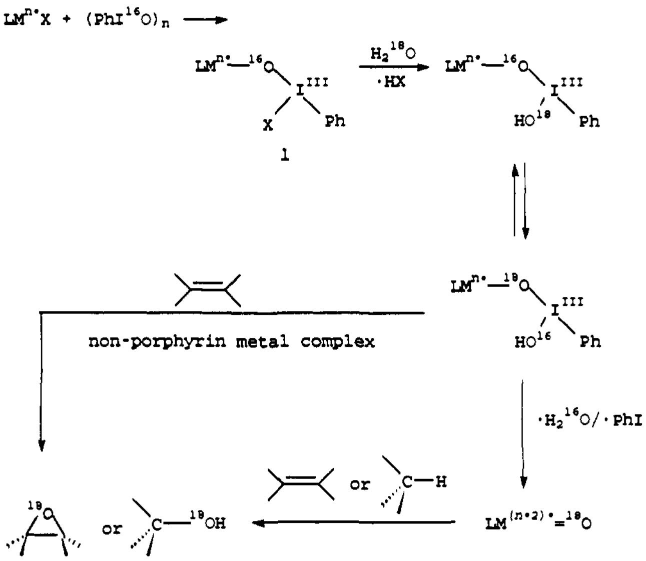
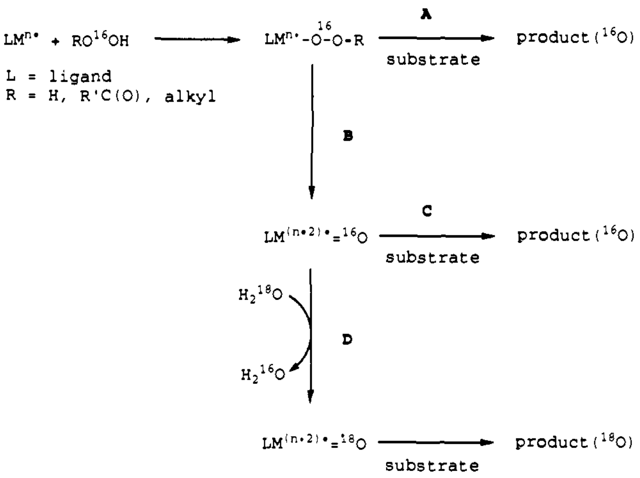
Scheme II



Scheme III



incorporation into products in aprotic or protic solvents in all of the iodosylbenzene reactions regardless of which catalyst was present. Even when the catalyst was a non-redox-active zinc complex, which cannot form high-valent metal oxo intermediates, a high percentage of ^{18}O was incorporated into the epoxide product. These results clearly demonstrate that the incorporation of labeled oxygen from $H_2{}^{18}O$ into products is not occurring via high-valent metal oxo intermediates in the iodosylbenzene reactions. On the basis of these observations, we propose a mechanism for the labeled oxygen incorporation into products in the iodosylbenzene reactions (see Scheme II). In this mechanism, the metal complex and iodosylbenzene polymer react to form a metal–iodosylbenzene complex, LM^{n+}–OI(Ph)(X) (**1**). This species has been isolated in a manganese porphyrin reaction[37] and also proposed in a Lewis acidic metal-catalyzed epoxidation reaction.[38] We propose that oxygen exchange occurs between this complex and labeled water. This species then directly transfers an oxygen atom to a substrate in the case of a non-porphyrin metal complex, as described in Yang et al.,[38] or forms a high-valent metal oxo complex.

^{18}O Study in Metal Complex-Catalyzed Oxygenations by H_2O_2, *t*-BuOOH, and MCPBA. It has been known for a long time that the origin of the oxygen in oxygenated products in monooxygenase enzyme systems is dioxygen, not solvent water. In iron bleomycin-mediated *cis*-stilbene epoxidation reactions, Hecht and coworkers reported a detailed labeling study designed to ascertain if the oxygen in the epoxide product was similarly derived directly from the oxidant or whether it was scrambled when the reaction was carried out in the presence of labeled water.[7] Using hydrogen peroxide, cumene hydroperoxide, ascorbic acid/O_2, iodosylbenzene, and $NaIO_4$ as oxidants, they found that the epoxide oxygen was derived from the oxidant in the hydrogen peroxide, cumene hydroperoxide, and ascorbic acid/O_2 reactions but that the source of oxygen in the iodosylbenzene and $NaIO_4$ reactions was the labeled water. They proposed that the labeled oxygen in *cis*-stilbene oxide obtained from the iodosylbenzene and $NaIO_4$ reactions was due to preequilibration of the oxidant with labeled water prior to the oxygen atom transfer to iron bleomycin. In support of this conclusion, they showed that iodosylbenzene and $NaIO_4$ gave exchange with labeled water in the absence of iron bleomycin under their reaction conditions. They concluded from their study that a high-valent iron oxo species was the epoxidizing agent in the case of all of the oxidants. They attributed the lack of exchange in the case of the hydrogen peroxide, cumene hydroperoxide, and ascorbic acid/O_2 reactions to a mechanism whereby a high-valent iron oxo intermediate transferred its oxygen directly to *cis*-stilbene at a rate faster than that of oxygen exchange with labeled water.

Another example of a system in which high-valent metal oxo species did not exchange rapidly with labeled water was reported by Meunier and his co-workers, who studied catalytic epoxidations of *p*-methoxystyrene and cyclohexene by LiOCl and $KHSO_5$ catalyzed by the Mn(TPP)OAc complex in the presence of nitrogen base.[19,20] They showed that oxygen atom transfer from the oxidizing intermediate to olefin was faster than the oxygen exchange between the oxidizing intermediate and labeled water. By contrast, Groves and his co-worker showed that the oxygen of a high-valent manganese oxo species was exchangeable with $H_2{}^{18}O$ in the β-methylstyrene epoxidation by MCPBA and Mn(TMP)Cl in the absence of pyridine but there was no ^{18}O incorporation into the product in the presence of pyridine.[18]

By utilizing well-studied Fe and Mn porphyrin systems in which high-valent metal oxo complexes are generally accepted to be the active oxygen atom-transfer reagents,[30,39] we have been able to assay the extent of oxygen exchange between some high-valent metal oxo complexes and labeled water in catalytic oxygenation reactions. As shown in Table II for the cyclohexene epoxidations by H_2O_2, *t*-BuOOH, or MCPBA catalyzed by Fe(TDCPP)Cl or Mn(TDCPP)Cl complexes and in Table III for the cyclohexane hydroxylations by H_2O_2 or MCPBA catalyzed by the Mn(TDCPP)Cl complex, we find that no or at most a small amount of ^{18}O was incorporated into the products from labeled water under our reaction conditions. The active oxidants in these reactions have been suggested to be $[(Porph)^{\bullet+}Fe^{IV}(O)]^+$ and $[(Porph)Mn^{V}(O)]^+$ formed via the heterolytic cleavage of the O–O bond in MOOR (R = H, CR'_3, C(O)R′).[30,39] If the intermediates are high-valent metal oxo species as suggested, then we can conclude that oxygen exchange between the high-valent metal oxo species and labeled water (Scheme III, pathway D) is slower than oxygen transfer from the high-valent metal oxo intermediate to organic substrates (Scheme III, pathway C) under our reaction conditions. Another possible explanation for the absence of ^{18}O incorporation from $H_2{}^{18}O$ into products is that the substrate may in some cases react directly with the MOOR species, which is generally presumed to be the precursor to the high-valent metal oxo complexes. This is the case when pathway A is faster than pathway B in Scheme III. In such a case, we also would not observe oxygen exchange with labeled water. Although we have suggested the possibility of an iron–hydroperoxide species as an intermediate in the iron cyclam complex-catalyzed epoxidation reaction,[31] there is no direct evidence for such a mechanism in the metalloporphyrin systems nor in the non-porphyrin metal systems at present. Another possibility is that the oxidizing species formed from the reaction is an alkyl radical ($ROO^\bullet$), as suggested by Bruice and co-workers

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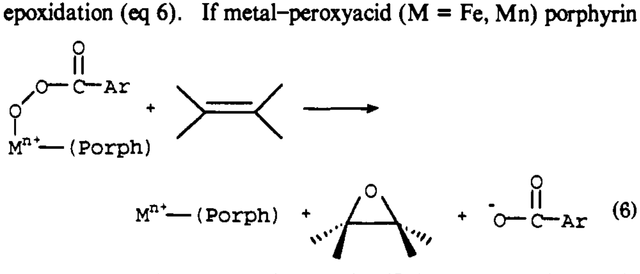
in the case of the Fe(TDCPP)Cl plus *t*-BuOOH reaction.[40] If this species is generated under our reaction conditions, we also would not observe any labeled oxygen incorporation into the products.

In the case of the catalytic oxygenation reactions by Mn(TDCPP)Cl, the axial position opposite the oxo group of metal oxo species is believed to be coordinated by an imidazole ligand, which may prevent labeled water from binding to manganese. Thus, blocking of the axial position may contribute to the observed lack of oxygen exchange in manganese porphyrin complex-catalyzed oxygenations of organic substrates in the presence of nitrogen bases.[18-20] In the reaction of the manganese cyclam complex and MCPBA, once again no oxygen incorporation into the cyclohexene oxide product is observed. It has been suggested by Groves and Stern that oxomanganese(IV) porphyrin complexes fail to exchange with added $H_2{}^{18}O$,[18] and the same is apparently true for oxomanganese(IV) cyclam complexes, if such species are indeed formed.[31b] In the case of the nickel cyclam and MCPBA reaction, a small amount of labeled oxygen is found in the epoxide product, indicating that a reactive species formed in the reaction exchanges its oxygen with labeled water. This species may be the nickel oxo complex which has been suggested by Koola et al.[8a] and Kinneary et al.[32] to be an intermediate in the iodosylbenzene reactions.

Oxygen exchange between $H_2{}^{18}O$ and high-valent iron oxo complexes prepared at low temperature in solution has been shown both by Groves et al.[3b] and by Khenkin and Shteinman.[21] The former reported the generation of $(TMP)^{\bullet-}Fe^{IV}(O)Cl$ in the reaction of Fe(TMP)Cl and MCPBA in the solvent mixture of CH_2Cl_2 and CH_3OH containing $H_2{}^{18}O$ at −78 °C. When norbornene was added to the reaction mixture, norbornene oxide containing ^{18}O was produced.[3b] They concluded from this result that the green species generated from the reaction was exchanging its oxygen atom with labeled water. However, Hashimoto et al.[25a] reported that the oxygen exchange of the green species with water did not occur on the basis of the Raman spectrum of the ^{16}O-derived green complex in the presence of labeled $H_2{}^{18}O$, indicating that the oxygen atom of the $[(TMP)^{\bullet-}Fe^{IV}(O)]^+$ complex was not easily exchangeable with the oxygen of water. Another reaction reported by Khenkin and Shteinman,[21] in which $[Fe(TPP)(O_2)]^-$ was reacted with Ac_2O in CH_2Cl_2–CH_3OH–C_6H_{12} in the presence of $H_2{}^{18}O$ at −50 °C, showed ^{18}O incorporation in the cyclohexanol product. They concluded that the hydroxylating species was a high-valent iron oxo species on the basis of the observation of oxygen exchange with labeled water.

Our results provide a possible explanation for some of these apparently contradictory results. In the present study of iron porphyrin-catalyzed epoxidation of cyclohexene by MCPBA at low temperature in the presence of $H_2{}^{18}O$, we have found that the extent of the ^{18}O enrichment in the product epoxide depends on the nature of the iron(III) porphyrin complexes. The percentages of ^{18}O in cyclohexene oxide formed in reactions of Fe(TMP)Cl, Fe(TPP)Cl, and Fe(TDCPP)Cl were 22%, 4%, and 0%, respectively, under our reaction conditions. The general trend appears to be that the presence of electron-donating groups on the porphyrin such as methyl results in high ^{18}O incorporation, whereas electron-withdrawing groups such as chloride give no ^{18}O enrichment in the product. Two possible explanations may be considered, i.e. either that the rate of oxygen exchange with water is decreased when electron-withdrawing substituents are present on the porphyrin ligand (Scheme III, pathway D) or that the rate of reaction with olefin increases when electron-withdrawing groups are present on the porphyrin ligand (Scheme III, pathway C). We favor the latter explanation on the basis of the results of Traylor and Miksztal[41] indicating that the intermediate generated from the electronegatively substituted iron porphyrin complex and iodosylbenzene showed great reactivity toward epoxidation.

Another possible explanation of these results is that metal–peroxyacid species are the active oxygenating agents in these systems, as mentioned before. It has been shown by Groves et al.[42] and Watanabe et al.[43] that addition of olefins to solutions of Mn–peroxyacid and Fe–peroxyacid porphyrin complexes gives epoxidation (eq 6). If metal-peroxyacid (M = Fe, Mn) porphyrin complexes are the oxygenating species (Scheme III, pathway A), no oxygen incorporation from water into products is expected.



(6)

In summary, we have shown (1) that the incorporation of labeled oxygen into products obtained from metal complex-catalyzed oxygenation of organic substrates by iodosylbenzene is not sufficient evidence that high-valent metal oxo intermediates are involved in the mechanism since the oxygen of the iodosylbenzene is exchanged with the oxygen of water prior to the formation of reactive oxidants and (2) that the assumption that high-valent metal oxo species invariably exchange with labeled water at high rates is incorrect. We conclude that care should be used in viewing the results of labeled water experiments as indirect evidence for the formation of high-valent metal oxo intermediates since the rates of oxygen exchange between the high-valent metal oxo species and water may depend on reaction conditions and the reactivity of the particular metal complex.

Experimental Section

Materials. Acetonitrile, methanol, and dichloromethane were refluxed over CaH_2 and distilled under argon. Acetonitrile was further dried by passing through a column of Woelm activity grade Super I alumina in a drybox. Cyclohexene, cyclohexene oxide, cyclohexane, cyclohexanol, cyclohexanone, *n*-decane, $Zn(CF_3SO_3)_2$, and cyclam (1,4,8,11-tetraazacyclotetradecane) were purchased from Aldrich Chemical Co. and used without further purification. $H_2{}^{18}O$ (97% ^{18}O enrichment), H_2O_2 (30%), and *tert*-butyl hydroperoxide (90%) were purchased from Aldrich. MCPBA was prepared by a literature method.[44] $Fe(CF_3SO_3)_2$ was prepared by a literature method.[45] Iodosylbenzene was prepared from iodobenzene diacetate by a literature method.[46] Fe(TDCPP)Cl, Fe(TMP)Cl, Fe(TPP)Cl, and Mn(TDCPP)Cl were obtained from Midcentury Chemicals. $Fe(cyclam)(CF_3SO_3)_2$, $Mn(cyclam)(CF_3SO_3)_2$, and $Ni(cyclam)(NO_3)_2$ were prepared by mixing equimolar amounts of $Fe(CF_3SO_3)_2$, $Mn(CF_3SO_3)_2$, and $Ni(NO_3)_2$ and cyclam ligand in anhydrous CH_3CN.[47] The binuclear zinc complex $Zn_2(m\text{-XYL}(py)_2)(CF_3SO_3)_4$ was prepared by reacting 2 equiv of $Zn(CF_3SO_3)_2$ with the ligand *m*-XYL(py)$_2$ (*m*-XYL(py)$_2$ = *N,N,N′,N′*-tetrakis[2-(2-pyridyl)ethyl]-*α,α′*-diamino-*m*-xylene) in CH_3CN.[48]

Instrumentation. Product analyses were performed on a Hewlett Packard 5890A gas chromatograph coupled with Hewlett Packard Model 5970B mass selective detector (MSD).

Reaction Conditions. All reactions were carried out at ambient temperatures under argon unless otherwise indicated.

Epoxidation of Cyclohexene by Iodosylbenzene, H_2O_2, *tert*-Butyl Hydroperoxide, or MCPBA Catalyzed by Fe(TDCPP)Cl or Mn(TDCPP)Cl in the Presence of Labeled $H_2{}^{18}O$. These reactions were carried out in an inert-atmosphere drybox or argon atmosphere. The iron or manganese porphyrin complex (2×10^{-3} mmol) was dissolved in a mixture of CH_2Cl_2 (1.2 mL) and CH_3OH (0.8 mL) containing cyclohexene (2 mmol), $H_2{}^{18}O$ (106 μL, 97% ^{18}O enrichment), and $H_2{}^{16}O$ (28.6 μL for iodosylbenzene, *tert*-butyl hydroperoxide, and MCPBA reactions and 0 μL for the H_2O_2 reaction). 4-Methylimidazole (7×10^{-2} mmol) was added to the Mn(TDCPP)Cl-catalyzed reaction. Iodosylbenzene (0.4 mmol) and MCPBA (0.4 mmol) were added all at once to the reaction mixture. All

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the iodosylbenzene disappeared within 2 min. H_2O_2 (0.4 mmol) and *tert*-butyl hydroperoxide (0.4 mmol) were slowly added to the reaction mixture over 1 min. After the reaction solution was stirred for 10 min for the Fe(TDCPP)Cl reaction and for 1 h for the Mn(TDCPP)Cl reaction, the solution was analyzed by GC/MS. ^{16}O and ^{18}O compositions in cyclohexene oxide were determined by the relative abundances of mass peaks at m/z = 83 and 97 for ^{16}O and m/z = 85 and 99 for ^{18}O.

Epoxidation of Cyclohexene by H_2O_2, Iodosylbenzene, or MCPBA Catalyzed by Fe(cyclam)$^{2+}$, Mn(cyclam)$^{2+}$, or Ni(cyclam)$^{2+}$ in the Presence of Labeled $H_2{}^{18}O$. The hydrogen peroxide and MCPBA reactions were carried out in an inert atmosphere of dry argon, and the iodosylbenzene reaction was carried out in a drybox. The metallocyclam complex (2×10^{-2} mmol) was dissolved in 5 mL of acetonitrile containing cyclohexene (1 mmol), $H_2{}^{18}O$ (106 μL, 97% ^{18}O enrichment), and $H_2{}^{16}O$ (0 μL for the hydrogen peroxide reaction and 28.6 μL for the iodosylbenzene reaction). H_2O_2 (0.4 mmol) was slowly added to the reaction mixture over 1 min, whereas iodosylbenzene (0.4 mmol) was added all at once to the reaction solution. After the reaction solution was stirred for 30 min, the reaction mixture was analyzed by GC/MS. The MCPBA reaction was done in a reaction solution containing the metallocyclam complex (2×10^{-2} mmol), cyclohexene (3 mmol), and $H_2{}^{18}O$ (106 μL, 97% ^{18}O or 90% ^{18}O enrichment) in a solvent mixture of CH_3OH (3 mL) and CH_3CN (2 mL) at −23 °C. After 30 min of stirring for the Mn– and Ni–cyclam reactions and 60 min for the Fe–cyclam reaction, the reaction was quenched with saturated aqueous Na_2SO_3. A control reaction for the MCPBA reaction was carried out in the absence of the metal–cyclam complex at −23 °C by stirring the solution of cyclohexene and MCPBA for 60 min.

Epoxidation of Cyclohexene by PhI^{16}O Catalyzed by a Binuclear Zinc Complex in the Presence of Labeled $H_2{}^{18}O$. The binuclear zinc complex $Zn_2(L)(OTf)_4$ (1×10^{-2} mmol) was dissolved in 2 mL of CH_3CN containing cyclohexene (1 mmol) and $H_2{}^{18}O$ (36.1 μL, 97% ^{18}O enrichment, 1.9 mmol of ^{18}O). PhI^{16}O (0.4 mmol) was added all at once to the reaction mixture. The reaction mixture was stirred for 2 h and analyzed by GC/MS.

Control Experiments for Oxygen Exchange between PhI^{16}O and $H_2{}^{18}O$ in Aprotic Solvent. (a) For the case in which the binuclear zinc complex was absent, iodosylbenzene (100 mg, 0.45 mmol) was stirred in CH_3CN (3 mL) in the presence of $H_2{}^{18}O$ (125 μL, 97% ^{18}O enrichment) for 30 min. Iodosylbenzene was then isolated and dried in vacuo (88 mg recovered). An infrared spectrum of the isolated iodosylbenzene was recorded. The isolated iodosylbenzene was assayed in the epoxidation of cyclohexene catalyzed by the binuclear zinc complex. The epoxide formed was analyzed by GC/MS for ^{18}O content. (b) For the case in which the binuclear zinc complex was present, iodosylbenzene (140 mg, 0.64 mmol) was stirred in CH_3CN (3 mL) containing the binuclear zinc complex (0.01 mmol) and $H_2{}^{18}O$ (125 μL, 97% ^{18}O enrichment) for 20 min. The unreacted iodosylbenzene was then isolated and dried in vacuo. The isolated iodosylbenzene was assayed in the epoxidation of cyclohexene catalyzed by the binuclear zinc complex. (c) In order to test the stability of cyclohexene oxide under the reaction conditions, cyclohexene oxide (12.1 μL, 0.12 mmol) was stirred in CH_3CN (3 mL) containing the binuclear zinc complex (0.01 mmol) and $H_2{}^{18}O$ (36 μL, 97% ^{18}O enrichment) for 1.5 h. The reaction solution was analyzed for the cyclohexene oxide by GC/MS.

Hydroxylation of Cyclohexane by H_2O_2, MCPBA, and PhIO Catalyzed by Mn(TDCPP)Cl in the Presence of Labeled $H_2{}^{18}O$. The manganese porphyrin complex (2×10^{-3} mmol) was dissolved in a mixture of CH_2Cl_2 (1.2 mL) and CH_3OH (0.8 mL) containing cyclohexane (4 mmol), 4-methylimidazole (7×10^{-2} mmol), $H_2{}^{18}O$ (106 μL, 97% ^{18}O enrichment) and $H_2{}^{16}O$ (28.6 μL for PhIO and MCPBA reactions and 0 μL for the H_2O_2 reaction). Oxidants (0.4 mmol) were added to the reaction mixture. After the mixture was stirred for 1 h, the ^{16}O:^{18}O ratio in cyclohexanol was determined by the relative abundances of mass peaks at m/z = 57 and 82 for ^{16}O and m/z = 59 and 84 for ^{18}O.

Epoxidation of Cyclohexene by MCPBA Catalyzed by Several Different Iron(III) Porphyrin Complexes and the Manganese(III) Porphyrin Complex at −78 °C. The metalloporphyrin complex (6.1×10^{-3} mmol) was dissolved in a solvent mixture of CH_2Cl_2 (5 mL) and CH_3OH (1 mL) containing cyclohexene (3 mmol) and $H_2{}^{18}O$ (50 μL, 97% ^{18}O enrichment). The solution was cooled to −78 °C. A solution of MCPBA (6.0×10^{-2} mmol) in 0.7 mL of CH_3OH was added to the reaction solution, and the mixture was stirred for 1.5 h, after which time saturated aqueous Na_2SO_3 was added. The CH_2Cl_2 layer was directly analyzed by GC/MS.

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