understood by the electronic structure models described by Figures 9-11.

The homologous series presented herein provides a basis for the synthetic design of luminescent multielectron congeners. With the two-electron mixed-valence Rh_2(0,II) complex as a benchmark, the preparation of its multielectron Rh_2(0,0) and Rh_2(II,II) counterparts can be achieved such that a long-lived emissive dσ^* excited state can be preserved. As is explicitly shown in Figures 9 and 10, conversion of the octahedral Rh(II) center of **2** to the trigonal-bipyramidal Rh(0) center of **1** stabilizes a formally highly energetic level that can accommodate the addition of two electrons to the metal core. In this manner, the overall electronic structure necessary for dσ^* luminescence is preserved. Furthermore, two-electron oxidation of the Rh(0) center of **2** does not significantly perturb the σ framework because the formation of an octahedral coordination geometry destabilizes the formally occupied dδ orbital. This strategy should be completely general for several M-M systems contingent upon the successful preparation of the appropriate mixed-valence intermediate. We believe that the torsional flexibility and the electronic properties of the bis(difluorophosphino)alkylamine ligand are crucial to our success in isolating the unusual Rh_2 mixed-valence dimer, and accordingly we are continuing our efforts to assess the capacity of this ligand in stabilizing multielectron mixed-valence forms of other polynuclear metal cores. Because the Rh_2 system offers a foundation for the rational design for four-electron photocatalytic schemes, we are also extending our studies to include the possibility of photochemically interconverting between the Rh_2(0,0), Rh_2(0,II), and Rh_2(II,II) cores.

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Supplementary Material Available: Complete tables of atomic coordinates, bond distances and angles, anisotropic temperature factors, least-squares planes, and torsional angles for **1** and **3** (26 pages); tables of observed and calculated structure factors for **1** and **3** (79 pages). Ordering information is given on any current masthead page.

Suicide Inactivation of Cytochrome P-450 Model Compounds by Terminal Olefins. 1. A Mechanistic Study of Heme N-Alkylation and Epoxidation

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Abstract: Synthetic iron porphyrins are found to be useful models for the suicide inactivation of cytochrome P-450. The epoxidation of 1-alkenes, 1,1-disubstituted alkenes, and styrenes by *meso*-[tetrakis(2,6-dichlorophenyl)porphinatoiron(III) chloride [Fe(OCP)Cl] results in the irreversible formation of *N*-alkylhemins and diminished catalytic activity. The rate of epoxide formation and the rate of N-alkylation are both first order in Fe(OCP)Cl. The efficiency of the inactivation, the number of turnovers of the catalyst per N-alkylation event, i.e., the partition number, can be measured by the ratio of epoxidation and N-alkylation rate constants. Partition numbers are found to be highly sensitive to the structure of the alkenes, somewhat sensitive to the nature of the oxygen atom donor, and relatively insensitive to the nature of the solvent. The conclusions of this study provide insight into the mechanism of the suicide inactivation of P-450 by 1-alkenes.

A wide variety of drugs and xenobiotic agents are known to destroy cytochrome P-450 activity and lead to the accumulation of green pigments in the livers of test animals.[1] Since the family of enzymes called the cytochrome P-450's are important in the degradation of xenobiotics and in the biosynthesis of steroids, the mechanism of their inactivation has been an area of extensive research. Through the work of de Matteis and Ortiz de Montellano and their co-workers, the green pigments were found to be *N*-alkylporphyrins in which a pyrrolic nitrogen of the protoporphyrin IX prosthetic group is covalently modified during substrate metabolism.[2,3]

The many oxidative transformations performed by P-450 on substrates can be classified into four main types: alkane and arene hydroxylation, heteroatom oxidation, dealkylation of heteroatoms, and olefin epoxidation.[4] These heme-containing enzymes bind a dioxygen molecule and convert it into a powerful oxidizing agent, formally an iron(V)-oxo, and release the other oxygen atom as water. Studies of a similar oxidized intermediate (HRP-I) in the enzyme horseradish peroxidase suggest the active oxidant in P-450 may more accurately be described as an oxoiron(IV) porphyrin radical cation, where the porphyrin bears one of the oxidizing equivalents.[5a] Oxygen atom donor molecules like iodosylbenzenes, hydroperoxides, and periodate can directly convert the iron(III) hemin resting state of P-450 to what is believed to be the same iron-oxo intermediate. Model studies with synthetic hemins support the above formulation of the active oxidant.[5b]

Substrate oxidation generally regenerates the iron(III) resting state of the enzyme for another cycle; however, some substrates

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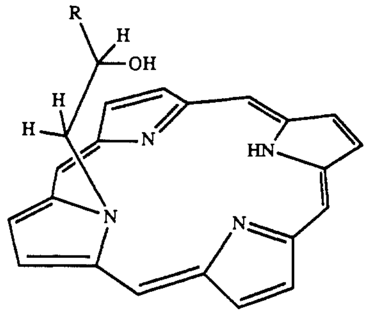

Figure 1. *N*-Alkylporphyrin structure.

lead to loss of P-450 activity through alkylation of a pyrrolic nitrogen of the heme prosthetic group. Allyl barbiturates, dihydropyridines and dihydroquinolines, sydnones, alkyl hydrazines, 1-aminobenzotriazole, and even 1-alkenes and 1-alkynes are all known to inactivate P-450 through the formation of *N*-alkylhemins.[1a] Two of these substrates, 3,5-bis(ethoxycarbonyl)-1,4-dihydrocollidine (DDC) and 2-isopropyl-4-pentenamide (commonly called allylisopropylacetamide or AIA), have received considerable attention. Both drugs are powerful inducers of porphyrin biosynthesis and lead to a loss of P-450 activity. The green pigment from DDC metabolism was characterized[3a] as *N*-methylprotoporphyrin IX and was observed to inhibit ferrochelatase, the enzyme responsible for insertion of iron into protoporphyrin IX.[1] The pigments from AIA, 1-alkenes, and 1-alkynes exhibit no inhibition of ferrochelatase. Ortiz de Montellano determined the structures of these pigments to be *N*-(2-hydroxyalkyl)protoporphyrin IX for AIA and 1-alkenes as in Figure 1 and *N*-(2-oxoalkyl)protoporphyrin IX for 1-alkynes. In each case the adducts resulted from addition of the double or triple bond to the porphyrin ring and the iron–oxo.[1a]

Synthetic metalloporphyrins have been shown to be viable models for cytochrome P-450. With the use of oxygen atom donor molecules, synthetic hemins catalyze amine dealkylation, alkane hydroxylation, and olefin epoxidation and are converted to *N*-alkylhemins during the epoxidation of 1-alkenes.[6-14] We[6] and the research groups of Mansuy[8] and Traylor and Dolphin[7] have characterized several of these *N*-alkylhemins. In contrast to the behavior found with P-450, we have observed that *N*-alkylhemins also form during the epoxidation of 1,1-disubstituted alkenes and styrenes by *meso*-[tetrakis(2,6-dichlorophenyl)porphinato]iron(III) chloride [Fe(OCP)Cl] and pentafluoroiodosylbenzene (PFIB).[6a] We attribute the absence of suicide inhibition of P-450 by these alkenes to their large partition numbers (1000–10 000 turnovers/"suicide" event) and to the greater stability of the model system compared to P-450.[12] For 3-methyl-1-butene and isobutylene we isolated the *N*-alkylhemins and observed them to have the same regiochemistry as Ortiz de Montellano has reported for P-450. Using *cis*- and *trans*-1-deuterio-3-methyl-1-butene, we determined epoxidation and N-alkylation to be stereospecific syn additions to the alkene.[6a] Ortiz de Montellano has reported the same stereochemistry for P-450 N-alkylation using an indirect method.[3d]

In earlier studies we reported what we believed to be evidence for a reversibly formed intermediate in olefin epoxidation in two P-450 model systems.[11] The first-order catalyst dependence, zero-order dependence on alkene concentration at high alkene concentrations, and different rates for different alkenes suggested that decomposition of an alkene–oxo intermediate was the rate-determining step. We suggested that a metallacycle, as first proposed by Sharpless and co-workers for an oxochromium epoxidation catalyst, was the alleged intermediate.[15] Information from this and the following paper and the reports of other research groups[7,12,13,16] force us to reinterpret our evidence for a reversibly formed intermediate in olefin epoxidation.

In this paper we report a detailed study of hemin N-alkylation and olefin epoxidation in the Fe(OCP)Cl/PFIB model system. From computer fitting to experimental data we have obtained partition numbers, a measure of the efficiency of hemin N-alkylation, under a variety of conditions. The partition numbers resemble reported values for P-450.[17] The sensitivity of partition numbers to the nature of the olefin, oxygen atom donor, and reaction conditions provide valuable insight into the mechanisms of olefin epoxidation and hemin N-alkylation.[6a,17] The effect of electronic and steric properties of the hemin catalyst and alkene substrate on partition numbers is reported in Part 2 of this series.[6b]

Results

The polyhalogenated hemins prepared by Traylor, Longo, Chang, and Bruice and their co-workers are very stable as olefin epoxidation catalysts; they undergo many thousands of catalyst turnovers, using iodosylarenes or hypochlorite as oxygen atom donor molecules, without significant hemin loss.[12a,13a,18,19] We reported, however, that during the epoxidation of 1-alkenes, 1,1-disubstituted alkenes, and styrenes, hemins are covalently modified to *N*-alkylhemins and the spectra of reaction aliquots change with time from a Soret at 410–420 nm, typical of the hemins, to a broad, red-shifted Soret at approximately 435 nm.[6a] Traylor and Dolphin, Mansuy, and Miyamoto and their co-workers have observed similar spectral changes during the epoxidation of 1-alkenes and some internal alkenes by synthetic hemins.[7,8,19]

Traylor and Dolphin were the first to characterize an *N*-alkylhemin from the Fe(OCP)Cl/PFIB model system.[7,20] The metal-free covalent adduct of 3,3-dimethyl-1-pentene and Fe(OCP)Cl was isolated by acidic demetalation of the 435-nm pigment

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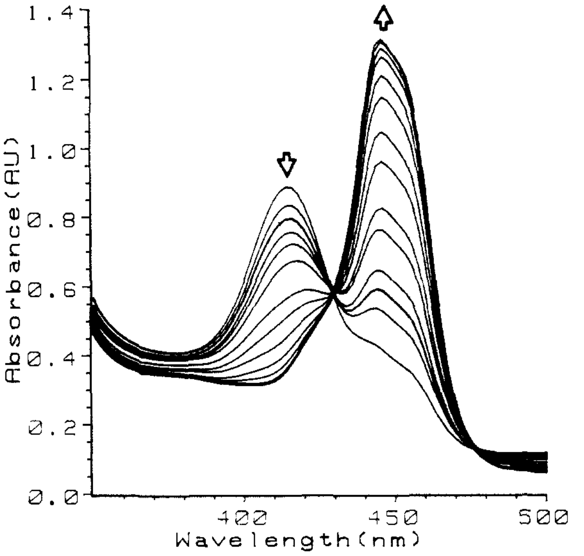


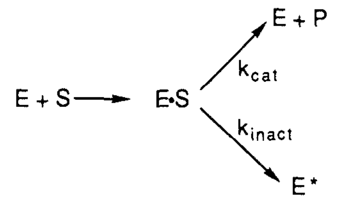
Figure 2. Spectral changes during the epoxidation of vinylcyclohexane by Fe(OCP)Cl and pentafluoroiodosylbenzene.

and identified as 21-(2-hydroxy-4,4-dimethyl-1-pentyl)-5,10,12,20-tetrakis(2,6-dichlorophenyl)-23*H*,23*H*-porphine. The isolated *N*-alkylporphyrin possessed the same regiochemistry as observed for the 1-alkene adducts of P-450 (Figure 1).[3b-d] Metalation of the *N*-alkylporphyrin with $FeCl_2$ yielded the chloroiron(III) *N*-alkylporphyrin with a Soret at 444 nm. When the *N*-alkylhemin was stirred with PFIB, the Soret shifted to 435 nm. They proposed the 435-nm pigment to be a [chloro(pentafluorophenyl)iodoxo]iron(III) *N*-alkylporphyrin with modified PFIB as an axial ligand. The shift from 444 to 435 nm required PFIB since neither *m*-chloroperbenzoic acid (mCPBA) nor *tert*-butyl hydroperoxide caused this transformation. Iodosylbenzene (PhIO) coordination is known for manganese porphyrins, and the resulting adducts still retain oxidizing equivalents.[21]

Although the iodosylbenzene systems are heterogeneous, we have found that the formation of *N*-alkylhemins can be conveniently followed by quenching the sparingly soluble iodosylbenzenes in reaction aliquots with triphenylphosphine. The quenching is rapid even when only a 4–10-fold excess of triphenylphosphine over the amount of PFIB or PhIO in an aliquot is used. No dependence of *N*-alkylhemin spectra on the concentration of added phosphine was observed. In addition to rapidly quenching the excess oxidant and stopping further epoxidation, the phosphine reduces oxidized forms of the Fe(Por)Cl catalyst and the *N*-alkylhemin. The shift in the Soret from 435 to 440–450 nm on treatment with triphenylphosphine probably results from reduction of the oxidized *N*-alkylhemin or iodosylarene–N-alkylhemin adduct to the chloroiron(III) *N*-alkylporphyrin.

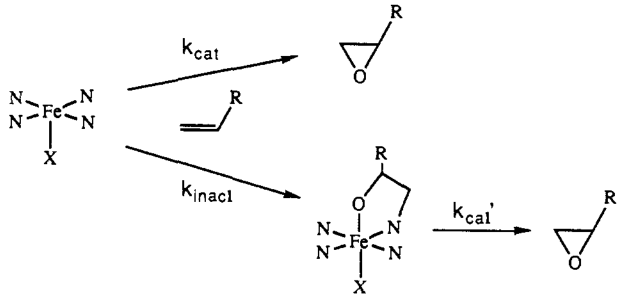
An overlay of spectra of triphenylphosphine-quenched aliquots taken from the epoxidation of vinylcyclohexane (1 M) by Fe(OCP)Cl (8.6 μM) and PFIB in methylene chloride is shown in Figure 2. With time, the 416-nm absorbance of Fe(OCP)Cl diminishes as the 446-nm absorbance of the *N*-alkylhemin increases in intensity. After 5–10 min, the 446-nm absorbance maximizes to a final value (A_∞) and only decreases in intensity slowly (several hours) due to oxidative bleaching of the *N*-alkylhemin. Similar plots were obtained under a variety of reaction conditions and with the other olefins and hemin catalysts[6c] we have studied. The presence of several isosbestic points in all the experiments in this study is consistent with the presence of only two species in the quenched reaction aliquots: the starting hemin catalyst and the *N*-alkylhemin. For 1-decene we previously reported that complete formation of the 446-nm *N*-alkylhemin was followed by the slower formation of a second species with a Soret at 436 nm. This behavior was not observed with the other alkenes we studied. The identity of the 436-nm species is not known, but it may be an *N*-alkylhemin *N'*-oxide or an *N,N'*-dialkylhemin.

Scheme I. Suicide Inactivation Mechanism



$$\text{Partition Number} = \frac{[P]_t}{[E^*]_t} = \frac{k_{cat}}{k_{inact}}$$

Scheme II. Suicide Inactivation of Synthetic Hemins by Terminal Alkenes



Kinetics of Terminal Olefin Epoxidation and Hemin N-Alkylation. In the suicide inhibition mechanism, the substrate branches via two pathways (Scheme I): metabolite formation and enzyme inactivation. The efficiency of inactivation, often called the partition ratio or the partition number, can be measured by the number of turnovers of the enzyme to form metabolite required for inactivation of the enzyme. If both pathways proceed through a common enzyme–substrate complex (E·S), then the partition number can be expressed as the ratio k_{cat}/k_{inact}, where k_{cat} and k_{inact} are the first-order rate constants for metabolite formation and enzyme inactivation, respectively. For P-450 the formation of *N*-alkylhemins inactivates the enzyme; thus, the partition number can be determined by simply measuring the amount of metabolite formed when P-450 activity is lost. This is not trivial since the detection of small amounts of metabolites (200–300 equiv) can be difficult and since the existence of several isozymes of P-450 in microsomal extracts, each with different substrate selectivities and activities, results in an incomplete loss of P-450 activity.

Despite these difficulties both Ortiz de Montellano and Walsh and their co-workers have measured a partition number for allylisopropylacetamide (AIA) of 200–300 turnovers/suicide inactivation event.[17] Ortiz de Montellano and co-workers obtained a value of 230 turnovers/suicide event by titrating both microsomes and a purified isozyme of P-450 with AIA until the spectral changes indicated complete loss of P-450.[17a] They also measured the ratio of the rate of consumption of oxygen compared to the rate of P-450 loss by spectral changes and obtained a more accurate partition number of 290–320 turnovers.[17b] Walsh and co-workers used ^{14}C-labeled AIA and measured the number of turnovers required for loss of P-450 activity, approximately 200 turnovers for rat liver microsomes and 180 turnovers for a purified P-450 isozyme.[17c] The partition number for 2,2,2-trifluoroethyl vinyl ether, an anesthetic agent commonly called fluroxene, was dependent on the source of the P-450 and was determined to be 100–300 turnovers by Ivanetich and co-workers.[17d]

Although the hemin model systems are considerably simpler than the biological system, the suicide inactivation of the model system through *N*-alkylhemin formation does not, except for styrene and substituted styrenes,[6b] result in an inactive catalyst for epoxidation. We and Traylor and co-workers have observed that the *N*-alkylhemins retain diminished catalytic activity in the hemin/iodosylarene heterogeneous system (Scheme II). The

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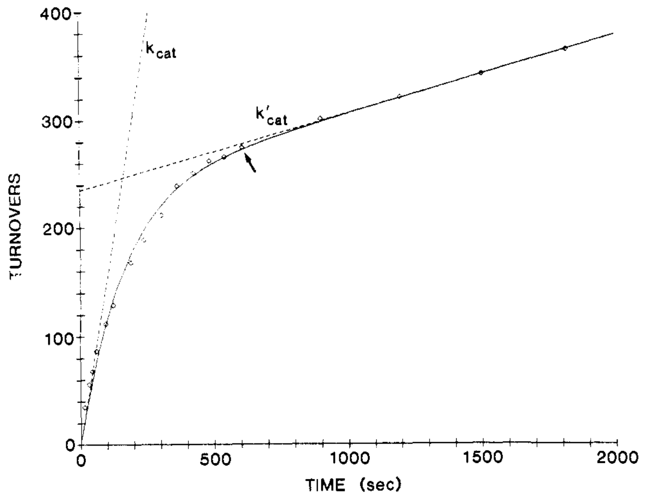

Figure 3. Turnovers as a function of time for the epoxidation of vinylcyclohexane by Fe(OCP)Cl and pentafluoroiodosylbenzene: (◇) experiment, (—) computer fit, (arrow) see text.

residual catalytic activity complicates the determination of a partition number since the number of turnovers of the catalyst (millimoles of epoxide/millimoles of hemin) is sensitive to where the end point for *N*-alkylhemin formation is chosen.

In our previous study[6a] partition numbers were measured in the Fe(OCP)Cl/PFIB model system[7] by determining the amount of epoxide formed when hemin N-alkylation was observed to be essentially complete, that is, the point where the absorbance is maximized (A_∞) at the *N*-alkylhemin Soret (440–450 nm). GC analysis of the triphenylphosphine-quenched aliquots from reaction mixtures provides a profile of the epoxide formed as a function of time. Figure 3 shows a plot of the number of turnovers of vinylcyclohexane oxide versus time for the same experiment whose spectra are shown in Figure 2. The smooth curve is a computer fit to the data (see below). The arrow in this figure indicates the point where the absorbance at 446 nm stops changing, the last spectrum in Figure 2. This point corresponds to roughly 270 turnovers of the catalyst. Although the slope of the curve (k_{cat}') at this point is at least 10-fold smaller than the initial rate (k_{cat}), the activity of the *N*-alkylhemin results in an error bar of about 20% for partition numbers. This method relies on the stability of the *N*-alkylhemin toward oxidative bleaching and on the ability to obtain good absorbance data.

As we previously reported, the conversion of the hemin [Fe(Por)Cl] to *N*-alkylhemin [Fe(*N*-alkyl)Cl] is first order in Fe(Por)Cl as determined from the spectral changes in the Soret region. The rate constant (k_{inact}) for *N*-alkylhemin formation can be obtained from plots of ln ($A_\infty - A$) versus time, where A is the absorbance of the aliquot at a particular wavelength and A_∞ is the average absorbance value when spectral changes are complete. In general, the wavelength chosen was the Soret of the *N*-alkylhemin (λ_{max} 440–450 nm) although absorbance changes at the Fe(Por)Cl Soret region yielded similar rate constants. From the ratio of the initial rate of epoxidation to the rate of *N*-alkylhemin formation, we obtained partition numbers close to those determined from the A_∞ method above. Due to the rapid reaction it was difficult to obtain early data points; as a result, the k_{cat} values and, thus, the partition numbers from the ratio k_{cat}/k_{inact} had large error bars in our earlier study.[6a] Doubling the amount of epoxide formed at 1 half-life of the reaction ($0.693/k_{inact}$) also provided partition numbers similar to those measured by the other methods.

Computer Fitting. Computer fitting to epoxidation data provides us with more accurate partition numbers, especially in cases where the *N*-alkylhemin exhibits rapid bleaching under catalytic conditions or when solvent evaporation or other factors make the absorbance data poor. Since both inactivation and epoxidation are first order in catalyst, apparent rate constants k_{cat} and k_{inact} can be assigned to these processes as in Scheme II and eqs 1 and 2. The catalytic activity of the *N*-alkylhemin (eq 3) has also been assigned a first-order rate constant, k_{cat}'.

$$\mathrm{Fe(Por)Cl} \xrightarrow{k_{cat}} \text{epoxide} \tag{1}$$

$$\mathrm{Fe(Por)Cl} \xrightarrow{k_{inact}} \mathrm{Fe(\mathit{N}\text{-alkyl})Cl} \tag{2}$$

$$\mathrm{Fe(\mathit{N}\text{-alkyl})Cl} \xrightarrow{k_{cat}'} \text{epoxide} \tag{3}$$

From the rate constants in these equations, expressions for the rates of formation of epoxide and *N*-alkylhemin can be obtained as in eqs 4 and 5. In these equations $[\mathrm{Fe(Por)Cl}]_t$ and $[\mathrm{Fe(\mathit{N}\text{-alkyl})Cl}]_t$ are the concentrations of hemin and *N*-alkylhemin, respectively, at a given time. Integration and substitution for the amount of added catalyst $[\mathrm{Fe(Por)Cl}]_0$ yields an equation for epoxide formation or catalyst turnovers as a function of time (eq 6).

$$\frac{d[\text{epoxide}]}{dt} = k_{cat}[\mathrm{Fe(Por)Cl}]_t + k_{cat}'[\mathrm{Fe(\mathit{N}\text{-alkyl})Cl}]_t \tag{4}$$

$$\frac{d[\mathrm{Fe(\mathit{N}\text{-alkyl})Cl}]}{dt} = k_{inact}[\mathrm{Fe(Por)Cl}]_t \tag{5}$$

$$\frac{[\text{epoxide}]_t}{[\mathrm{Fe(Por)Cl}]_0} = k_{cat}'t + \frac{k_{cat} - k_{cat}'}{k_{inact}}[1 - e^{-k_{inact}t}] \tag{6}$$

Nonlinear least-squares analysis of epoxidation data using eq 6 consistently provided fits with excellent correlation coefficients ($R^2 = 0.99$–0.999); see Figure 3. Estimates for the rate constants, the initial and final rates of epoxide formation, and the spectral value for k_{inact} were used as initial values for the computer fit. When the initial estimates were changed by 1 order of magnitude, the rate constants from the fit were unchanged; thus, no other fit to the data was possible. In some cases, for example with the styrenes, no catalysis by the *N*-alkylhemin could be detected ($k_{cat}' = 0$); computer fits to these data converged only when the first term in eq 6 was omitted.

The values of k_{inact} obtained from fits to the epoxidation data and from ln ($A_\infty - A$) versus time are very similar. Thus, the loss of catalytic activity is due to the formation of the *N*-alkylhemins. The significance of these rate constants will be considered in the Discussion. With computer fitting, the partition number for a given olefin can be determined from the epoxide present when spectral changes are complete, the A_∞ method, or by the ratio of fit rate constants, the k_{cat}/k_{inact} method.

The data in Figure 3, fit to eq 6, give the smooth curve with values for k_{cat}, k_{cat}', and k_{inact} of 1.5, 0.071, and 0.0062 s^{-1}, respectively. The spectrally determined k_{inact} from the absorbance changes in Figure 2 is 0.0056 s^{-1}, very similar to that determined from the fit to epoxide data. The partition number as determined by the ratio of rate constants is 250 turnovers, which is very close to the A_∞ value of 270 turnovers determined above. Similar agreement between the two methods of determining partition numbers has been observed for the other olefins and the other hemin catalysts.[6b]

Partition Number Dependence on the Olefin. Previously we reported that partition numbers in the Fe(OCP)Cl/PFIB system are very sensitive to the nature of the olefin: 130 turnovers/suicide for 1-decene, 830 for methylenecyclohexane, and 12 000 for styrene. In addition to these olefins we now report a partition number of 230 turnovers for vinylcyclohexane using the same epoxidation system. Each of these partition numbers represents the average of at least five experiments.

Table I lists the partition numbers and apparent rate constants for the epoxidation of 1-decene by Fe(OCP)Cl/PFIB in individual experiments. The partition numbers obtained by either the A_∞ method or the ratio k_{cat}/k_{inact} are in good agreement. In these experiments, the catalyst concentration was held constant and the concentration of olefin was varied; no dependence of the partition numbers on the olefin concentration was observed. The average value of the partition number is 120 turnovers (±10%) from these experiments, which is very close to the value of 130 turnovers that we previously reported. Experiments performed at higher catalyst concentrations provided partition numbers similar to those in Table I.

Table I. Partition Number and Rate Constant Data for the Epoxidation of 1-Decene by Fe(OCP)Cl and Pentafluoriodosylbenzene

expt no.^{a}	[1-decene] (M)	partition no. (turnovers)		fit			vis $k_{inact} \times 10^3$ (s^{-1})
		A_∞	k_{cat}/k_{inact}	k_{cat} (s^{-1})	k_{cat}' (s^{-1})	$k_{inact} \times 10^3$ (s^{-1})	
1	2	130	120	0.36	0.0086	3.1	4.3
2	1	130	130	0.47	0.034	3.7	4.8
3	1	120	120	0.57	0.022	4.8	4.7
4	1	140	110	0.60	0.039	5.3	4.5
5	1^{b}	120	110	1.23	0.019	12	8.3
6	0.1	110	100	0.63	0.085	6.2	11
7	0.1	120	89	0.70	0.090	7.8	6.6

^{a}All reactions were performed with 6.2 mM Fe(OCP)Cl and PFIB in methylene chloride. ^{b}Reaction was 0.1 M in 1-epoxyhexane.

Table II. Partition Number and Rate Constant Data for the Epoxidation of Vinylcyclohexane by Fe(OCP)Cl and Pentafluoroiodosylbenzene

expt no.	[Fe(OCP)Cl] (mM)	[VCy]^{a} (M)	partition no. (turnovers)		fit			vis $k_{inact} \times 10^3$ (s^{-1})
			A_∞	k_{cat}/k_{inact}	k_{cat} (s^{-1})	k_{cat}' (s^{-1})	$k_{inact} \times 10^3$ (s^{-1})	
1	11.6	1.0	210	200	1.54	0.078	7.8	7.7
2	10.4	1.0	220	220	1.69	0.057	7.6	11.2
3	10.4	1.0	220	200	1.31	0.073	6.4	8.7
4	10.1	1.0	230	230	0.63	0.041	2.8	3.5
5	9.0	1.0	250	250	3.41	0.081	13.4	13.2
6	8.6	1.0	270	240	1.55	0.073	6.4	5.6
7	5.2	1.0	230	200	1.89	0.084	9.6	11.0
8	5.2	1.0	200	170	2.70	0.12	15.6	21.4
9	5.2	1.0	220	190	3.10	0.13	15.9	18.5
10	2.7	1.0	230	180	3.10	0.14	17.0	24.0
11	9.8	0.5	250	300	0.53	0^{b}	1.8	2.5
12	8.6	0.2	240	220	1.62	0.11	7.2	9.3

^{a}[VCy] = concentration of vinylcyclohexane. All experiments in methylene chloride with PFIB. ^{b}Fit converged only when k_{cat}' was set to zero.

Table III. Partition Number and Rate Constant Data for the Epoxidation of Styrene by Fe(OCP)Cl and Pentafluoroiodosylbenzene

expt. no.	[Fe(OCP)Cl]^{a} (mM)	partition no. (turnover)		fit			vis $k_{inact} \times 10^3$ (s^{-1})
		A_∞	k_{cat}/k_{inact}	k_{cat} (s^{-1})	k_{cat}' (s^{-1})	$k_{inact} \times 10^3$ (s^{-1})	
1	3.52	12000	13000	6.3	0^{b}	0.49	0.59
2	3.24	11000	13000	5.4	0^{b}	0.40	0.68
3	3.24	13000	15000	5.2	0^{b}	0.35	0.51
4	2.69	12000	12000	15.1	0^{b}	1.29	1.73
5	2.69	11000	11000	17.7	0^{b}	1.58	1.58

^{a}Styrene (1 M) with PFIB in methylene chloride. ^{b}Fit converged only when k_{cat}' was set to zero.

Since epoxides are reactive alkylating agents, 1-epoxyhexane was added (experiment 5) to a standard 1-decene reaction. The 0.1 M concentration of added epoxide is greater than the amount of epoxide ever formed in a partition number determination. The rate constants for 1-decene epoxidation in this experiment were slightly larger, yet the partition number remained constant. The lack of any effect of added epoxide on the partition number confirms that active turnover of the olefin and not accumulation of the product epoxide leads to N-alkylation of the catalyst. Our report of syn stereochemistry for the formation of the *N*-alkylhemins is also inconsistent with alkylation of the catalyst by an epoxide.[3d,6a]

Tables II and III list the partition numbers and rate constants for the epoxidation of the olefins vinylcyclohexane and styrene by Fe(OCP)Cl/PFIB in individual experiments. The partition numbers in both tables show good agreement even though the catalyst and olefin concentrations were varied and different Fe(OCP)Cl and PFIB batches were used. The average partition numbers for vinylcyclohexane are 230 (±10%) from A_∞ and 220 (±20%) from k_{cat}/k_{inact}. The partition numbers for styrene epoxidation by Fe(OCP)Cl and PFIB in Table III are all very similar and in good agreement by the two methods of determination: average values 12000 (±10%) from A_∞ and 13000 (±15%) from k_{cat}/k_{inact}. The catalytic activity of the *N*-alkylhemin from styrene is negligible in these experiments.

In contrast to the reproducibility of the partition numbers, the rate constants in Tables I–III exhibit a wide variability. In Table I the k_{cat} and k_{inact}(fit) values range over a factor of 2 (omitting line 5) even though the same batch of PFIB and the same Fe(OCP)Cl solution were used in these experiments. This variability is also observed in the epoxidation of vinylcyclohexane (Table II) and styrene (Table III). In Table II, k_{cat} values vary by a factor of 6 and k_{inact}(fit) values vary by almost 1 order of magnitude, and in Table III there is a factor of 3 range of the rate constants. For comparison of experiments performed under identical reaction conditions, entries with the same Fe(OCP)Cl concentration used both the same catalyst batch and the same PFIB batch. We feel that the variability in the rate constants is probably due to the heterogeneity of the reaction conditions.

Table IV. Maximum Turnover Numbers for Fe(Por)Cl-Catalyzed Epoxidation of Cyclooctene with Several Oxidants

catalyst^{a}	oxidant	max turnovers^{b}
Fe(OCP)Cl	PFIB	>100000^{c}
Fe(OCP)Cl	LiOCl/BAC^{d}	>15000^{c}
Fe(TMP)Cl	PFIB	600
Fe(TMP)Cl	PhIO	2000
Fe(TpClPP)Cl	PFIB	200
Fe(TpClPP)Cl	PhIO	400

^{a}Cyclooctene to Fe(Por)Cl ratio was 400000 for Fe(OCP)Cl, 20000 for Fe(TMP)Cl, and 90000 for Fe(TpClPP)Cl. Cyclooctene (1 M) in methylene chloride. For full porphyrin names see ref 20. ^{b}Millimoles of cyclooctene oxide/millimoles of Fe(Por)Cl. ^{c}Catalyst was still not completely bleached. ^{d}BAC = benzyldimethyltetradecylammonium chloride.

The ability to determine partition numbers as large as 12000 for Fe(OCP)Cl and styrene is due to the stability of Fe(OCP)Cl. Traylor reported that this hemin can catalyze 10000 turnovers of norbornene with the oxygen atom donor PFIB without noticeable hemin loss.[12a] Table IV shows the stability of several catalysts in the epoxidation of *cis*-cyclooctene by a variety of oxygen atom donors. In agreement with Traylor, we find Fe(OCP)Cl to be extremely stable; at least 50% of the catalyst was still present after 100 000 turnovers of *cis*-cyclooctene with PFIB. Although its longevity with lithium hypochlorite as an oxygen atom donor is lower, Fe(OCP)Cl is significantly more stable than either Fe(TMP)Cl or Fe(TpClPP)Cl.[20]

Stability of the *N*-Alkylhemins. Traylor and co-workers have reported that *N*-alkylhemins are reversibly formed during the epoxidation of norbornene, cyclohexene, and a cofacial diene[22] and can revert to the starting hemins under appropriate conditions.[7b,c] They proposed that a reversible N-alkylation could explain our observation of different rates of epoxidation for different olefins in our mechanistic study of the Fe(PFP)Cl/PFIB system.[11b] They also argued that the very slow rate of epoxidation of norbornene that we observed and the competitive inhibition of cyclooctene epoxidation by norbornene are due to the formation of the less active *N*-alkylhemins under reaction conditions.

In contrast to the behavior of the putative *N*-alkylhemins from internal alkenes, we find no evidence for *N*-alkylhemin reversibility with the adducts of 1-alkenes, 1,1-disubstituted alkenes, and the styrenes[6b] under either catalytic or quenched conditions. The quenched aliquots from experiments showed no detectable loss of absorbance at the Soret of the *N*-alkylhemin (λ 440–450 nm) even when 12 h or more had passed since quenching with triphenylphosphine. The similarity of the extinction coefficients calculated for the *N*-alkylhemins under a variety of conditions and even with different olefins, approximately 1.5 × 10^5 M^{-1} cm^{-1} (±20%), suggests the N-alkylation is quantitative for all the olefins studied.[6c]

The stability of the *N*-alkylhemins under active turnover of an internal olefin was also investigated. The *N*-alkylhemin from 1-hexene was formed by stirring a solution of Fe(OCP)Cl (6.2 μM) and 1-hexene (1 M) in methylene chloride with 100 mg of PFIB. After 15 min an aliquot showed N-alkylation was essentially complete. The solvent, alkene, and epoxide were removed at reduced pressure, and a 1 M solution of *cis*-cyclooctene in methylene chloride was added. After 800 turnovers of *cis*-cyclooctene, quenched reaction aliquots showed no significant loss of absorbance at the *N*-alkylhemin Soret (446 nm); thus, the N-alkylation by 1-hexene is not reversible under these conditions.

Epoxidation of α-methylstyrene with PFIB and Fe(OCP)Cl or Fe(PFP)Cl exhibited an anomalous behavior, unlike the other olefins. After 20 000 turnovers of α-methylstyrene, only approximately 90% of the Fe(OCP)Cl was converted to *N*-alkylhemin, on the basis of spectral changes, and a significant absorbance of the Fe(OCP)Cl catalyst was still present. The triphenylphosphine-quenched aliquots of an α-methylstyrene reaction were stable to any absorbance change in the λ 440–450 nm region. Removal of the oxidant from an aliquot by filtration and quenching after 15–20 min led to a greater absorbance in the Fe(Por)Cl region (410–420 nm) and a lower 440–450-nm absorbance than when a similar aliquot was quenched immediately. The regeneration of Fe(Por)Cl was only partial (~20%) regardless of the time allowed before quenching. When the solid PFIB was consumed in the α-methylstyrene reaction, quenched aliquots showed an increase in the absorbance of Fe(OCP)Cl and a decrease in the *N*-alkylhemin absorbance. This behavior was not observed for any of the other olefins. The apparent regeneration of the Fe(Por)Cl catalyst may be due to the formation of reactive byproducts during α-methylstyrene epoxidation, which are quenched by phosphines but can dealkylate the *N*-alkylhemin under unquenched conditions. As a result of this dealkylation the formation of the *N*-alkylhemin was never complete as indicated by a low extinction coefficient for the *N*-alkylhemin and a high k_{cat}'.

A conjugated diene, 2,3-dimethyl-1,3-butadiene, was also investigated as a potential suicide substrate. After over 100 000 equiv of the monoepoxide had been produced, only a slight increase in the 440–450-nm region was observed; the increase was insignificant and could have been due to the high conversion (10%) of the olefin and the monoepoxide acting as a suicide substrate. Although this suggests 2,3-dimethyl-1,3-butadiene does not N-alkylate Fe(OCP)Cl, the *N*-alkylhemin may have formed but it was too unstable to detect.[7b,c]

Table V. Oxidant Dependence of the Partition Numbers for the Epoxidation of Vinylcyclohexane and Styrene by Fe(OCP)Cl

olefin[a]	[Fe(OCP)Cl] (mM)	oxidant	partition no.	
			A_∞	k_{cat}/k_{inact}
VCY	2.7–11.6	PFIB[b]	230	220
VCY	9.8–10.1	PhIO	370	350
VCY	9.8–10.1	LiOCl[c]	570	650
STY	2.7–3.5	PFIB[b]	12000	13000
STY	2.4	PhIO	28000	28000

[a] VCY = vinylcyclohexane (1 M) and STY = styrene (1 M) in methylene chloride. [b] Average values of partition numbers in Tables II and III. [c] In CH_2Cl_2/water biphase with 10 mM benzyldimethyltetradecylammonium chloride (BAC).

Although *N*-alkylhemins are known to be light sensitive, we found no evidence for a partition number dependence on ambient light levels. Epoxidation of styrene under bright light led to a bleaching of the *N*-alkylhemin as it was formed. However, this photobleaching did not affect the partition number.

Epoxidation by PhIO and OCl^-. Iodosylbenzene (PhIO), like PFIB, is a sparingly soluble, polymeric oxidant, and studies have suggested that it generates the same active oxidant as PFIB with hemin catalysts.[11c] Miyamoto and co-workers have reported NaOCl-supported epoxidation of olefins under biphasic conditions using the phase-transfer agent benzyldimethyltetradecylammonium chloride (BAC) with Fe(OCP)Cl and other hemins as catalysts.[19] Since there have only been a few studies of epoxidation supported by hypochlorite and iron porphyrins, little is known about the active oxidant in this system. Partition number data for iodosylbenzene and lithium hypochlorite/BAC supported epoxidation of vinylcyclohexane and styrene by Fe(OCP)Cl are listed in Table V. The partition numbers in this table reflect the averages of at least two experiments.

In the heterogeneous Fe(OCP)Cl/PhIO system both the rates of epoxide formation and N-alkylation are first order in Fe(OCP)Cl and partition numbers can be determined with either the A_∞ or the k_{cat}/k_{inact} method. The partition numbers for the iodosylbenzene-supported oxidations are larger than those with PFIB as the oxidant; although the increases are relatively small, they are definitely outside of the range for PFIB experiments. The rate constants from fits to epoxidation data for vinylcyclohexane are comparable to experiments with PFIB (Table II)—k_{cat} ranges from 1.3 to 3.1 s^{-1}, k_{cat}' is from 0.03 to 0.06 s^{-1}, and k_{inact} is from 0.004 to 0.009 s^{-1}. The rate constants for styrene epoxidation are also comparable to those with PFIB (Table III)—24–28 s^{-1} for k_{cat} and 0.0079–0.011 s^{-1} for k_{inact}. Iodosylbenzene is as efficient as PFIB in olefin epoxidation on the basis of the above k_{cat} values. This is in contrast to other reports of slower epoxidation with PhIO.[12a]

The instability of the relatively electron-rich Fe(TMP)Cl in the PFIB system (Table IV) prevented the measurement of its partition numbers with 1-alkenes; however, in the iodosylbenzene system the catalyst shows good stability in the epoxidation of cyclooctene (2000 maximum turnovers). Since Fe(TMP)Cl should have similar steric properties as Fe(OCP)Cl but is much more electron-rich, determining partition numbers for Fe(TMP)Cl could provide information about the sensitivity of partition numbers to the electronic properties of the catalyst. The epoxidation of vinylcyclohexane by Fe(TMP)Cl/PhIO resulted in rapid bleaching of the catalyst with no increase in the absorbance in the 440–450-nm region, and about 200 equiv of vinylcyclohexane oxide was detected when the hemin was completely bleached and epoxidation ceased. The value of 200 turnovers resembles the partition number we measured for Fe(OCP)Cl (230 turnovers), although the absence of a λ 440–450 nm band, possibly due to oxidative bleaching of the *N*-alkylhemin, prevents us from definitely claiming this is a partition number for Fe(TMP)Cl.

As observed with the iodosylbenzenes, both epoxidation and N-alkylation are first order in Fe(OCP)Cl for the biphasic

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[22] 1,4,4a,5,8,8a-Hexahydro-1,4,5,8-*endo,endo*-dimethanonaphthalene.[7c]

Table VI. Solvent Dependence of the Partition Number for Vinylcyclohexane Epoxidation by Fe(OCP)Cl and Pentafluoroiodosylbenzene

		partition no.	
[Fe(OCP)Cl][a] (mM)	solvent	A_∞	k_{cat}/k_{inact}
2.7–11.6[b]	CH_2Cl_2	230	220
5.8	CH_3CN	210	180
8.6–9.0	benzene	360	350

[a] Benzene and acetonitrile solvents at 1 M vinylcyclohexane. [b] Average of partition numbers in Table II.

LiOCl/BAC (10 mM) system with vinylcyclohexane as the substrate. Rapid bleaching of the *N*-alkylhemin in the hypochlorite system complicates the determination of partition numbers with the A_∞ method, but the partition numbers are in reasonable agreement with the k_{cat}/k_{inact} ratios from computer fitting. The partition number for vinylcyclohexane is almost 3-fold larger with hypochlorite compared to PFIB. Apparent rate constants in the hypochlorite system (k_{cat} ~ 0.5 s^{-1} and k_{inact} ~ 0.001 s^{-1}) are somewhat smaller than in the iodosylarene systems. No attempt was made to determine the reproducibility of these rate constants.

During the epoxidation of styrene by hypochlorite and Fe(OCP)Cl no increase in the 440–450-nm region was observed as the Fe(OCP)Cl Soret gradually diminished. The formation of epoxide was not first order in Fe(OCP)Cl. When the bleaching was complete, approximately 4000 equiv of styrene oxide per starting Fe(OCP)Cl was detected. Although this turnover number is less than the 15 000 maximum turnovers of cyclooctene by this system (Table IV), there are insufficient data to determine if this is a true partition number for styrene.

The dependence of the partition numbers on the oxidant concentration cannot be determined in the iodosylarene systems since the iodosylbenzenes are only sparingly soluble in methylene chloride. Their concentration can, however, be varied in the homogeneous alcohol/methylene chloride/water solvent system of Traylor. In this system, the rates of epoxidation are dramatically accelerated and the hemins and *N*-alkylhemins have comparable catalytic activities.[12b] The rapid reactions require fast kinetics to monitor and, thus, are not amenable to GC analysis during the reaction.

Unlike the iodosylarenes, the concentration of hypochlorite can be conveniently varied in the methylene chloride layer by changing the concentration of the phase-transfer agent (BAC). At higher BAC concentrations (>10 mM) the methylene chloride and aqueous layers separated only with great difficulty, and no attempt was made to follow the kinetics of these emulsions. When the BAC was decreased from 10 to 2.2 mM, the rate of vinylcyclohexane epoxidation slowed considerably and the kinetics were no longer first order in Fe(OCP)Cl. The change in the reaction order may be due to rate-limiting transfer of the hypochlorite into the organic layer at the low BAC concentrations. Although a fit to the data was not possible, 600–700 turnovers of vinylcyclohexane oxide were detected when the *N*-alkylhemin was completely formed. Since 600–700 turnovers is close to the measured partition numbers at 10 mM BAC, it appears that there is no oxidant concentration dependence of heme N-alkylation in the hypochlorite system.

Solvent Effects on Partition Numbers. The epoxidation of vinylcyclohexane by Fe(OCP)Cl and PFIB exhibits only a modest sensitivity to the reaction solvent as seen in Table VI. In acetonitrile both k_{cat} (~12 s^{-1}) and k_{inact} (~0.067 s^{-1}) are accelerated by about 1 order of magnitude, yet their ratio of 200 turnovers is close to the partition number for vinylcyclohexane in methylene chloride (230 turnovers). The partition number in benzene is somewhat increased compared to that in acetonitrile and methylene chloride. The value of 350 turnovers in benzene is outside of the error for the partition number in methylene chloride. The apparent rate constants in benzene k_{cat} (0.6–0.7 s^{-1}) and k_{inact} (0.0018–0.0019 s^{-1}) are slightly lower than those in methylene chloride (Table II).

The differences in the apparent rate constants in the three solvents are likely due to the heterogeneity of the reaction. The rates of epoxidation and N-alkylation in acetonitrile increased when the reaction stir rate was increased; under these conditions the reaction was too fast to obtain good data for a fit. By visual inspection, the rate of reaction of triphenylphosphine with solid PFIB is much faster in acetonitrile and slightly slower in benzene than it is in methylene chloride. These data suggest that the solubility of the oxidant in the three solvents may differ considerably and may affect the apparent rate constants.

Table VII. Effect of Additives on the Partition Number for Vinylcyclohexane Epoxidation by Fe(OCP)Cl and Pentafluoroiodosylbenzene

		partition no.	
[Fe(OCP)Cl[a] (mM)	additive (concn, mM)	A_∞	k_{cat}/k_{inact}
2.7–11.6[b]		230	220
10.1	$PhCH_2CHO$ (21)	240	240
5.8	PhI (10)	280	290

[a] At 1 M vinylcyclohexane with PFIB in CH_2Cl_2. [b] Average of partition numbers in Table II.

Effect of Additives on Partition Numbers. The effect of added phenylacetaldehyde and iodobenzene on the partition number for vinylcyclohexane is shown in Table VII. The two additives were investigated since aldehydes are known to accelerate metalloporphyrin epoxidations and since the partition number for PhIO was larger than for PFIB. As Table VII indicates, the partition numbers are relatively unaffected by the presence of either additive.

Addition of phenylacetaldehyde to the standard conditions for vinylcyclohexane epoxidation by Fe(OCP)Cl/PFIB increases with both k_{cat} (2.5 s^{-1}) and k_{inact} (0.01 s^{-1}) by a factor of 4, yet the ratio k_{cat}/k_{inact} remains constant (compare line 4 of Table II for an experiment with the same catalyst concentration and PFIB batch and no added aldehyde). The amount of added phenylacetaldehyde (21 mM) is greater than the amount that could possibly form during the epoxidation of styrene.

The acceleration of olefin epoxidation by the presence of aldehydes in a manganese(III) porphyrin/hypochlorite system has been proposed by Nolte and co-workers to be due to the formation of either carbonyl oxides or dioxiranes.[16] Both are known to epoxidize alkenes.[23] Since carbonyl oxides or dioxiranes could directly epoxidize alkenes without forming an iron–oxo intermediate in the Fe(OCP)Cl/PFIB system, they could increase the rate of epoxide formation (k_{cat}) without affecting the rate of hemin N-alkylation (k_{inact}) and could lead to a larger apparent catalytic activity for the *N*-alkylhemin (k_{cat}'). The partition number is unaffected by the addition of aldehyde; thus, neither oxidant, if they are present, contributes significantly to the epoxidation reaction in the iron system.

It does not appear that the increased partition numbers with PhIO (Table V) are due to the presence of iodobenzene, the product of oxygen atom transfer, since the partition number for vinylcyclohexane was relatively unaffected (Table VII) by added iodobenzene. No PhIO was detected in the unreacted solid PFIB isolated from this reaction.

Discussion

Synthetic hemins have been reported to model most of the reactions performed by P-450, and in this study we have shown they are also viable models for the suicide inactivation of the enzyme by allyl barbiturates and 1-alkenes. Unlike P-450 where only 1-alkenes lead to *N*-alkylhemin formation, we have observed that the inactivation in the hemin/PFIB model system also occurs with 1,1-disubstituted alkenes and styrenes. In addition to structurally characterizing several of these adducts, we have reported the stereochemistry of hemin N-alkylation to be a syn addition of the pyrrolic nitrogen and iron–oxo to the 1-alkene. As initially reported by Traylor and co-workers,[7a] we also have observed only the *N*-alkylhemin regiochemistry where the terminal

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[23] (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670. (c) Groves, J. T.; Stern, M. K. *J. Am. Chem. Soc.* **1988**, *110*, 8628.

carbon is attached to the pyrrolic nitrogen (Figure 1). This regio- and stereospecificity is the same as has been reported for P-450. A complete discussion of both the stereochemistry and regiochemistry of N-alkylation will be presented in Part 2 of this series.[6b] The formation of *N*-alkylhemins occurs during the epoxidation of terminal alkenes, is irreversible for all the alkenes we have studied, and results in a less active catalyst for olefin epoxidation. All of these observations are consistent with a mechanism-based inactivation; in biological systems such a process is called suicide inactivation. The efficiency of inactivation by a suicide substrate, the relative branching between metabolite formation and enzyme inactivation (Scheme I), is referred to as the partition number for a substrate. In this paper we describe in full the determination of partition numbers for epoxidation/N-alkylation, which we reported in a preliminary paper. The partition numbers we have measured in the Fe(OCP)Cl/PFIB system with 1-decene or vinylcyclohexane as substrates are very similar to values that have been reported for P-450. From these studies we believe that the synthetic hemin/iodosylarene systems are viable models for the suicide inactivation of P-450.

Traylor and co-workers have observed what appears to be a *reversible* formation of *N*-alkylhemins during the epoxidation of norbornene and a cofacial diene[22] by synthetic hemins and iodosylbenzenes.[7b,c] None of the *N*-alkylhemins of the terminal alkenes we have studied exhibit a reversible formation. Although α-methylstyrene does exhibit a *pseudo*reversiblity under catalytic conditions, this reversibility does not occur with the other terminal olefins, is not quantitative, and probably results from dealkylation of the *N*-alkylhemin by reactive byproducts in the reaction mixture.

We have observed that olefin epoxidation and *N*-alkylhemin formation are first order in the hemin catalyst, and from computer fitting to epoxidation data we have succeeded in measuring partition numbers for a variety of alkenes and catalysts. Apparent rate constants (Scheme II) for epoxidation by the Fe(Por)Cl catalyst (k_{cat}) and the *N*-alkylhemin (k_{cat}') and for N-alkylation of the catalyst (k_{inact}) can be obtained from computer fits to epoxidation data. The values of k_{inact} from these fits are in good agreement with values obtained from the time-dependent visible spectral changes (Figure 2). The partition number, the number of successful catalyst turnovers per N-alkylation event, have been determined either by measurement of the amount of epoxide present when spectral changes are essentially complete by visible spectra (A_∞) or, alternatively, by the ratio of epoxidation and N-alkylation rate constants (k_{cat}/k_{inact}).

The partition numbers for a given olefin were highly reproducible and independent of the concentration of olefin and Fe(OCP)Cl catalyst and the presence of a competing olefin substrate. In Tables I and II the concentration of olefin was varied over a factor of 5 without any effect on the partition numbers for 1-decene and vinylcyclohexane. The concentration of catalyst was also varied over a factor of 5 without any effect on the partition number for vinylcyclohexane. We have reported that the partition number for 1-decene is unaffected by the addition of cyclooctene as a competing olefin substrate.[6a] The branching of the substrate between the pathways of olefin epoxidation and hemin N-alkylation is affected in the same way by changes in the concentrations of catalyst and olefin and the presence of cyclooctene. In our previous paper we suggested that these observations are consistent with, but do not require, a common intermediate in olefin epoxidation and hemin N-alkylation. Branching of the two reaction pathways from either the starting catalyst Fe(OCP)Cl or a common iron–oxo intermediate would also explain our observations.

The partition numbers show a strong dependence on the nature of the terminal alkene. In this and the previous study we have obtained partition numbers for a variety of olefins with Fe(OCP)Cl: 1-decene (130 turnovers), vinylcyclohexane (230 turnovers), methylene cyclohexane (830 turnovers), and styrene (12000 turnovers). The partition numbers for vinylcyclohexane and 1-decene are very close to those reported for AIA (200–300 turnovers) and fluroxene (100–300 turnovers).[17] Both steric and electronic effects are probably responsible for the almost 100-fold difference in the partition numbers for 1-decene and styrene. In the following paper the effect of electronic and steric properties of the hemin and substituted styrenes on partition numbers is examined.[6b]

A modest sensitivity of the partition numbers to the nature of the oxygen atom donor is observed. The partition numbers for vinylcyclohexane and styrene have been investigated with Fe(OCP)Cl and with pentafluoroiodosylbenzene (PFIB), iodosylbenzene (PhIO), or hypochlorite as the oxygen atom donor. Although the difference between the iodosylarenes is small for vinylcyclohexane, 360 turnovers (PhIO) and 230 turnovers (PFIB), there is over a factor of 2 difference in the partition numbers for styrene, 28000 (PhIO) and 12000 (PFIB). Since both oxidants are believed to generate the same hemin oxidant, it is surprising that the partition numbers are so different. In Part 2 of this study we present evidence that the electronic and steric properties of the active oxidants derived from PhIO and PFIB are similar. The larger partition number for PhIO is not due to the presence of iodobenzene in the reaction since the partition number for vinylcyclohexane with Fe(OCP)Cl and PFIB is unaffected by the addition of iodobenzene. Iodosylbenzene coordination to the iron–oxo may influence the partition numbers by altering the position of the iron atom with respect to the porphyrin ring; such coordination should be less favorable for the electron-poor PFIB. The much larger partition number for vinylcyclohexane with hypochlorite (610 turnovers) compared to PFIB (230 turnovers) is consistent with the different character of the iron–oxo, which we have observed from competitions of substituted styrenes.[6b] The sensitivity to the oxygen atom donor will be discussed in more detail in the following paper.

Partition numbers are relatively insensitive to the nature of the solvent. Only a modest increase in the partition number for vinylcyclohexane is observed in benzene, and no effect is seen in the coordinating solvent acetonitrile even though the apparent rate of epoxidation is increased by a factor of 10. The insensitivity of the partition numbers to the nature of the solvent, the concentrations of olefin and catalyst, and the presence of cyclooctene suggests that heme N-alkylation and epoxidation may proceed by a similar mechanism. Possible mechanisms for these reactions will be considered in Part 2.

Apparent Rate Constants and the Nature of the Rate-Determining Step. Although the partition numbers, as measured by either A_∞ or the ratio k_{cat}/k_{inact}, were highly reproducible in each of the above experiments, the apparent rate constants k_{cat} and k_{inact} were not reproducible and exhibited a wide variation between experiments conducted under identical reaction conditions. Because of this variability we now question our evidence that breakdown of an oxo–olefin intermediate is the rate-determining step in the PFIB/Fe(PFP)Cl heterogeneous system.[11b,c,20] We now believe that oxo formation may be the rate-limiting step and that the heterogeneity of the system is responsible for the irreproducibility of the rate constants.

Traylor and co-workers have shown that oxo formation is the rate-determining step in a homogeneous hemin/iodosylarene system. Soon after we reported the kinetics of olefin epoxidation in the heterogeneous Fe(PFP)Cl/PFIB system,[11b] Traylor published a kinetic study of a mixed-solvent system that solubilized the iodosylarenes.[12b] They found the rate of oxidant disappearance by UV spectroscopy to be first order in oxidant and in Fe(Por)Cl and proposed oxo formation to be the rate-determining step in this system. The rates of reaction were several orders of magnitude faster than those we observed. Oxo formation in the heterogeneous system involves either reaction of the Fe(Por)Cl catalyst with the low concentrations of soluble PFIB or reaction of the catalyst with the solid oxidant. Since the rate of reaction of PFIB with triphenylphosphine is affected by the nature of the solvent in the same manner as the k_{cat} values we have measured, it is possible that the rate of oxo formation could be very sensitive to reaction conditions, including the nature of the added olefin.

Traylor has also observed the apparent reversible accumulation of *N*-alkylhemins during the epoxidation of norbornene and some other internal olefins.[7c] Since the *N*-alkylhemins have lower catalytic activity, the slow rate of epoxidation of norbornene in our previous study[11b] (0.1 s^{-1}; compared to the value of cyclooctene of 10 s^{-1}) is probably due to the formation of an *N*-alkylhemin, as proposed by Traylor. If we eliminate this olefin from the data in our previous paper, then the rate constants we observed only differ by factor of 4 (31 s^{-1} for *trans*-β-methylstyrene and 7.9 s^{-1} for *cis*-cyclododecene).[11b] It is not clear whether *N*-alkylhemins can also form with the other internal alkenes in our previous study. As Traylor has suggested, the formation of a less active catalyst through *N*-alkylhemin formation would also explain the apparent competitive inhibition of cyclooctene epoxidation by added norbornene.[7b,c]

The range of rate constants k_{cat} and k_{inact} (Tables I–III) for individual olefins is large, over a factor of 5 for k_{cat} and 10 for k_{inact}. Rate constants only showed good agreement when the same oxidant and catalyst batch were used. In our previous study of the kinetics of the Fe(PFP)Cl/PFIB system we only used a small number of different oxidant batches; thus, a dependence of the rate constants on oxidant batches would have gone undetected. We did report a modest catalyst batch dependence of the rates.[11c]

The average epoxidation rate constants for olefins with Fe(OCP)Cl in this and the following paper are somewhat different: 1-decene, ~0.7 s^{-1}; vinylcyclohexane, ~2 s^{-1}; methylenecyclohexane, ~2 s^{-1}; styrene, ~10 s^{-1}; 2,6-dimethylstyrene, ~6 s^{-1}; *p*-(trifluoromethyl)styrene, ~8 s^{-1}; *p*-chlorostyrene, ~9 s^{-1}; *p*-methylstyrene, ~20 s^{-1}. Because of the variability of the rate constants, the factor of 30 difference in the rates is probably not significant and can be explained without invoking an olefin–oxo intermediate. The rate differences could be due to the formation of a less active catalyst, for example, an *N*-alkylhemin, a hemin *N*-oxide, or an iron(IV) complex. Groves has observed porphyrin *N*-oxides in the reaction of $Fe(TMP)^+$ with mCPBA;[24a] such a species might have a diminished catalytic activity like the *N*-alkylhemins. Electron transfer between a formal iron(V)–oxo and the iron(III) catalyst could yield iron(IV) species. The formation of iron(IV) complexes has been reported by Sawyer and Gold during the reaction of Fe(OCP)Cl with either PFIB or *m*-chloroperoxybenzoic acid (mCPBA);[24b,c] Groves and Balch and their co-workers have reported that iron(IV) complexes are less potent oxygenating agents than the formal iron(V)–oxo.[24d,e]

The faster rates of the styrenes compared to the aliphatic alkenes could be due to aldehyde formation, since the presence of phenylacetaldehyde (21 mM) increased the apparent rate of vinylcyclohexane epoxidation by a factor of 4. Only small amounts (~2 mM) of aldehydes, however, are formed during the epoxidation of the styrenes (5–10%). We do not believe that the rate acceleration in this system is due to the formation of carbonyl oxides or dioxiranes as proposed by Nolte for a manganese porphyrin/hypochlorite system.[16] The mechanism of the aldehyde rate enhancement is not clear, but it may be due to the formation of small amounts of phenylacetic acid, to a greater reactivity of metalloporphyrin intermediates, or to a greater solubility or reactivity of the PFIB. The latter has been observed with alcohols in the soluble PhIO or PFIB system of Traylor and co-workers.[12b]

If oxo formation is the rate-determining step in the hemin/iodosylarenes system, then the reduced catalytic activity of the *N*-alkylhemins could be due to a slower rate of iron–oxo formation for the *N*-alkylhemins. The electrochemistry of *N*-alkylhemins shows that they are much more difficult to oxidize than the corresponding hemins.[25] This resistance to oxidation might slow the rate of iron–oxo formation. The observation of the 435-nm pigment, an apparent PFIB/*N*-alkylhemin coordination complex, suggests that oxygen atom transfer is less facile since no coordination complexes of this type are known for the hemins.

Although the rate constants exhibit variability in this system, the partition numbers are highly reproducible and dependent on the nature of the olefin. The similarity of our partition numbers for 1-decene (130 turnovers) and vinylcyclohexane (230 turnovers) to the partition numbers measured for P-450 (100–300 turnovers) suggests the mechanisms for the model system and for P-450 are similar. In the following paper, the effects of steric and electronic properties of the olefin and catalyst on the partition numbers are reported and the possible mechanisms for olefin epoxidation and heme N-alkylation are discussed. These studies are the first attempts to use simple iron porphyrins to probe the mechanism of the suicide inactivation of P-450 by terminal olefins.

Experimental Section

Materials. All solvents and other chemicals were used as received unless noted otherwise. All olefins were passed through neutral alumina prior to use. Styrene was distilled, purified on neutral alumina, and used immediately. The porphyrins[20] H_2TMP, $H_2(TpClPP)$, and $H_2(OCP)$ were prepared by the methods of either Traylor or Lindsey and their co-workers.[12a,26] Epoxide standards were prepared by *m*-chloroperoxybenzoic acid (mCPBA) oxidation of the alkenes.

Preparation of PhIO and PFIB. Iodosylbenzene (PhIO) was prepared from iodosylbenzene diacetate according to the literature procedure[27] and dried at 20 °C (0.05 mmHg) for 3 h. Pentafluoroiodosylbenzene (PFIB) was prepared according to a modified literature procedure.[28] *Caution*: an explosive![29] Instead of removing the trifluoroacetic anhydride and nitric acid under vacuum, the reaction mixture was stirred at room temperature with a slow stream of nitrogen passing over the solution. When the brown nitric oxide gas had subsided and the bulk of the solution had solidified, the solid was rapidly filtered, placed in a round-bottom flask, and dried at 40 °C (in vacuo) for 2 h.

The yellow-white solid was sublimed as in the literature preparation and immediately hydrolyzed in saturated $NaHCO_3$ at room temperature. During the hydrolysis, vigorous stirring was essential to completely hydrolyze the intermediate. The solid that collected on the sides of the round-bottom flask was periodically washed back down with saturated $NaHCO_3$. After about 5 h of stirring, the solid was filtered, washed extensively with water, and dried in vacuo, just until the drying flask warmed to room temperature. The solid was stored at -20 °C without evidence of decomposition. Only batches that yielded 95–100% yields of cyclooctene oxide from cyclooctene (1 M) with Fe(OCP)Cl (10 μM) as a catalyst in CH_2Cl_2 were used in the kinetic studies. Experiments using batches with lower epoxide yields (60–80%), however, yielded identical partition numbers.

Methods. Visible spectra were recorded either on a Cary 219 spectrophotometer or on a Hewlett-Packard 8450A diode array spectrophotometer (2-nm resolution). Reaction samples were analyzed for epoxides with a Hewlett-Packard HP-5880A gas chromatograph equipped with nitrogen carrier gas and a FID detector. Either a 10% OV-101 on Chromosorb W-HP 80/100 or a 10% PEG-20M on Supelcoport 80/100 packed column, each 6 ft in length, was used for separation of reaction mixtures.

Procedure for Kinetics Measurements. (A) Iodosylarenes as Oxidants. Solid pentafluoroiodosylbenzene (PFIB) or iodosylbenzene (PhIO) [500–40 000 equiv/Fe(OCP)Cl], olefin (0.2–1 M), internal standard (dodecane or tetradecane), and solvent (CH_2Cl_2, benzene, or acetonitrile) were combined in a vial and thermostated to 15 °C with a constant-temperature bath. A solution of the catalyst Fe(OCP)Cl in methylene chloride (0.2–0.6 mM) was added to the vial for a total volume of 20 mL and a catalyst concentration of 1–10 μM. The catalyst concentration range was limited by the weak visible absorbances at low concentrations and by the large amounts of PFIB and PhIO required at high concentrations.

At convenient time intervals 0.8-mL aliquots were removed from the heterogeneous mixture and quenched into 100 μL of a triphenylphosphine solution (1–3 M) containing enough PPh_3 to rapidly consume the solid oxidant. After all the solid oxidant had disappeared, the samples were analyzed by visible spectroscopy (λ 350–700 nm). Gas chromatographic analysis of the aliquots was completed within 24 h of the experiment. Changes in absorbance at the Soret region (λ 440–450 nm) of the *N*-alkylhemin were fit to a first-order equation; the plots were generally linear to at least 2 half-lives. Epoxide formation versus time data was

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fit to eq 6 (vide supra) with a Digital VAX Station II/GPX and RS1 software.

(B) LiOCl Oxidant/Phase-Transfer System. To a well-stirred solution of olefin (1 M), phase-transfer agent (10 mM), benzyldimethyltetradecylammonium chloride (BAC; Fluka), internal standard, and Fe(OCP)Cl (1-10 mM) in methylene chloride (total volume 20 mL) was added 1-5 mL of a ca. 0.3 M aqueous LiOCl solution prepared by dissolving solid LiOCl (30% by weight, Fluka) in water. Periodically the stirring was stopped, the aqueous and methylene chloride layers were allowed to settle, and a 0.8-mL aliquot of the organic layer was removed. The aliquot was immediately quenched into 100 μL of a PPh_3 solution as above, and ca. 100 mg of $MgSO_4$ was added to remove residual water. During the removal of an aliquot, the stirring was stopped for approximately 20 s. The aliquots were then filtered through glass wool and analyzed by visible spectroscopy. GC analysis and computer fitting were performed as above.

Maximum Turnover Numbers. The data in Table IV were obtained by stirring a 1 M solution (2-mL volume) of cyclooctene, dodecane standard, and Fe(Por)Cl catalyst in methylene chloride with the oxidant (PhIO, PFIB, or aqueous LiOCl/BAC) until the catalyst solution was decolorized [Fe(TMP)Cl and Fe(TpClPP)Cl] or when the oxidant was consumed [Fe(OCP)Cl]. The amount of epoxide formed was analyzed by GC, and the remaining catalyst was determined by visible spectra of reaction aliquots.

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Registry No. Fe(OCP)Cl, 91042-27-2; cytochrome P-450, 9035-51-2; 1-decene, 872-05-9; vinylcyclohexane, 695-12-5; styrene, 100-42-5; cyclooctene, 931-88-4.

Suicide Inactivation of Cytochrome P-450 Model Compounds by Terminal Olefins. 2. Steric and Electronic Effects in Heme N-Alkylation and Epoxidation

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Abstract: This paper reports a continuation of our study of synthetic hemins as models for the suicide inactivation of P-450 by 1-alkenes. The branching between epoxidation and heme N-alkylation, as measured by the partition number, has been studied as a function of the steric and electronic properties of substituted styrenes and of several chloro(tetraarylporphyrin)iron catalysts. Partition numbers exhibit only a modest sensitivity to steric properties of the catalyst and are relatively insensitive to the electronic properties of both the catalyst and the olefin. *N*-Alkylporphyrins isolated from the epoxidation of terminal alkenes by three of these hemins show the same regiochemistry as the *N*-alkylporphyrins reported for P-450. On the basis of the stereochemistry of epoxidation and N-alkylation, the insensitivity of the partition numbers to electronic effects, and the relative reactivities of terminal alkenes, we discuss various possibilities for the mechanism of epoxide and *N*-alkylhemin formation.

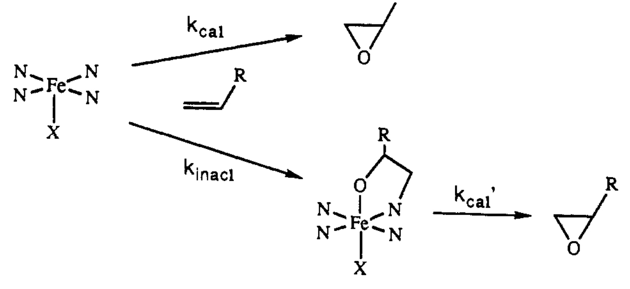
In Part 1 of this study and a previous paper we reported a mechanistic study of the formation of *N*-alkylhemins during the Fe(OCP)Cl/pentafluoroiodosylbenzene (PFIB) catalyzed epoxidation of terminal olefins.[1a-c] We observed *N*-alkylhemin formation for a variety of 1-alkenes (1-decene, 3-methyl-1-butene, vinylcyclohexane), 1,1-disubstituted alkenes (methylenecyclohexane, isobutylene), and styrenes. The efficiency of the hemin N-alkylation, the partition number, was determined for several of these olefin substrates. The formation of *N*-alkylhemins in this system is a viable model for the suicide inactivation of P-450 by 1-alkenes.

Epoxide and *N*-alkylhemin formation were found to be first order in Fe(OCP)Cl as shown in Scheme I. Computer fitting of the time dependence of epoxide formation to eq 1 allowed us

$$\frac{[\text{epoxide}]_t}{[\text{Fe(Por)Cl}]_0} = k_{\text{cat}}'t + \frac{k_{\text{cat}} - k_{\text{cat}}'}{k_{\text{inact}}}[1 - e^{-k_{\text{inact}}t}] \qquad (1)$$

to obtain apparent rate constants for epoxidation by the hemin (k_{cat}) and *N*-alkylhemin (k_{cat}') and for heme N-alkylation (k_{inact}). Partition numbers could be obtained either from the amount of epoxide formed when spectral changes were essentially complete (A_∞) or by the ratio $k_{\text{cat}}/k_{\text{inact}}$ with the rate constants from computer fitting. Although the rate constants exhibited variability between experiments, the partition numbers were highly reproducible. Partition numbers were found to be sensitive to the nature of the olefin (1-decene, 130; vinylcyclohexane, 230; methylenecyclohexane, 830; styrene, 12000), but insensitive to the concentrations of olefin and hemin catalyst Fe(OCP)Cl and the presence of a competing olefin substrate (cyclooctene).[1b] Hemin N-alkylation only occurs during the processing of terminal alkene and not after epoxide is formed since added epoxide had no effect on the partition number.

Scheme I. Suicide Inactivation of Synthetic Hemins by Terminal Alkenes



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