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

James P. Collman,* Philip D. Hampton, and John I. Brauman

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305-5080. *Received August 11, 1989*

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.

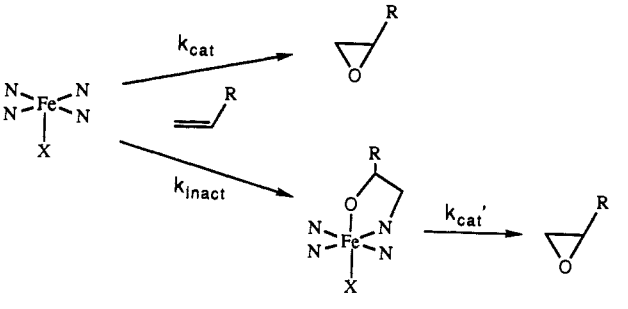
In Part 1 of this study and a previous paper we reported a mechanistic study of the formation of *N*-alkylhemins during the Fe(OCP)Cl/pentafluoroiodosylbenzene (PFIB) catalyzed epoxidation of terminal olefins.[1a-c] We observed *N*-alkylhemin formation for a variety of 1-alkenes (1-decene, 3-methyl-1-butene, 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

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

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

Scheme I. Suicide Inactivation of Synthetic Hemins by Terminal Alkenes



(A_∞) or by the ratio k_{cat}/k_{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.

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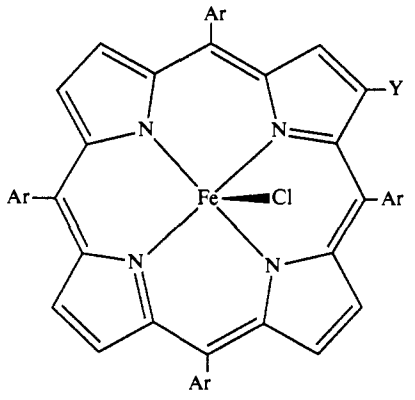

Ar	Y	Fe(Por)Cl
2,6-dibromophenyl	H	Fe(OBP)Cl
2,6-dichlorophenyl	H	Fe(OCP)Cl
2,6-dichlorophenyl	NO_2	Fe(NOCP)Cl
2,6-difluorophenyl	H	Fe(OFP)Cl
pentafluorophenyl	H	Fe(PFP)Cl
p-chlorophenyl	H	Fe(TpClPP)Cl

Figure 1. Synthetic hemins and abbreviations.

The formation of *N*-alkylhemins of P-450 during the metabolism of 2-isopropyl-4-pentenamide (commonly called allylisopropylacetamide or AIA) has been studied by Walsh and Ortiz de Montellano and their co-workers.[2,3] They found the partition number for AIA was approximately 180–300 turnovers/suicide event. The similarity in the binding constants (K_m) for the two reactions of AIA, heme alkylation and metabolism, was consistent with a common enzyme–substrate complex for both pathways. Ortiz de Montellano observed that heme alkylation occurred exclusively on one face of the prochiral double bond of 1-octene but epoxidation occurred without significant facial selectivity.[4] This observation suggested a possible divergence in the mechanism of these two reactions or a different substrate binding site for epoxidation and heme N-alkylation.

Although it would be interesting to know whether different P-450 isozymes have different partition numbers for AIA, the complexity of the natural system and the difficulty of obtaining pure isozymes make such a study difficult. In this paper we report a similar study in a P-450 model system. The effect of steric and electronic properties of synthetic hemins on partition numbers has been determined. The sensitivity of the branching between N-alkylation and epoxidation to steric and electronic effects in the catalyst and alkene has provided information about the mechanisms of olefin epoxidation and hemin N-alkylation. The regiochemistry of *N*-alkylhemin formation for two unhindered catalysts is found to be the same as for Fe(OCP)Cl. Complete experimental details for the stereochemistry of hemin N-alkylation and epoxidation that we previously reported[1b] are also provided. Conclusions from this study provide insight into the mechanism of the suicide inactivation of P-450.

Results

The porphyrins used in this study are shown in Figure 1. Because of wide variations[5] in the nomenclature of tetraarylporphyrins we have chosen the brief, descriptive abbreviations listed in Figure 1. The halogenated porphyrins, except for Fe(NOCP)Cl, have been previously prepared by Traylor, Longo, and Bruice and their co-workers.[6,7]

Table I. *cis*-Olefin/*trans*-Olefin Selectivity Dependence on Porphyrin Ligand

Fe(Por)Cl	oxidant	cis/trans[a]
Fe(OBP)Cl	PFIB	12
Fe(OCP)Cl	PFIB	13
Fe(OCP)Cl	PhIO	12
Fe(OFP)Cl	PFIB	3.0
Fe(TpClPP)Cl	PFIB	4.0
	mCPBA[b]	2.7

[a] *cis*-Cyclooctene oxide/*trans*-2-decene oxide ratio. [b] No Fe(Por)Cl catalyst, *m*-chloroperoxybenzoic acid.

Table II. Oxidation Potentials for Zn(Por) and Fe(Por)Cl

Por[a]	$Zn(Por)^+$	$Zn(Por)^{2+}$	$Fe(Por)Cl^+$	$Fe(Por)Cl^{2+}$
TPP			+0.96	+1.28
TMP			+0.93	+1.34
TpClPP	+0.67	+0.96	+1.05	+1.34
OBP	+0.84	+1.08	+1.14	+1.44
OFP	+0.87	+1.12	+1.22	+1.47
PFP	+1.04	+1.28	+1.43	+1.62
OCP	+0.85	+1.09	+1.16	+1.45
NOCP	+0.98	+1.25	+1.31	+1.54

[a] $E_{1/2}$ vs SCE in 0.2 M tetrabutylammonium perchlorate (TBAP)/CH_2Cl_2, referenced to ferrocene. $E_{1/2}$ values standardized to SCE with a value of 0.307 V for ferrocene in 0.2 M $LiClO_4/CH_3CN$.[12]

Substitution at the 2- and 6-positions of the aryl rings of a tetraarylporphyrin can be used to change the steric properties of a porphyrin. The ability to form μ-oxo dimers is one measure of the steric encumbrance around the metal center. For Fe(OCP)OH and Fe(TMP)OH, the bulky 2,6-substituents prevent the formation of a μ-oxo dimer whereas "Fe(TPP)OH" exists only as the dimer. Both steric and electronic properties affect dimer formation, however, since Fe(OFP)OH exists as a monomer and the essentially isosteric Fe(PFP)OH exists as both a monomer and dimer.[7a,8]

A quantitative measure of the steric properties of a porphyrin is the *cis*- versus *trans*-olefin selectivity. Table I shows the ratio of cyclooctene oxide to *trans*-2-decene oxide, formed during the epoxidation of a 1:1 mixture of cyclooctene and *trans*-2-decene, for a series of catalysts possessing differing steric requirements. The sterically bulky chlorine and bromine atoms (van der Waals radii 1.77 and 1.92 Å, respectively)[9] in the catalysts Fe(OBP)Cl and Fe(OCP)Cl cause *cis*-olefins to be epoxidized preferentially over *trans*-olefins. Much lower cis selectivity is exhibited for the less sterically bulky Fe(OFP)Cl. Since the van der Waals radius[9] for fluorine is relatively small (1.47 vs 1.20 Å for hydrogen), it is not surprising that Fe(TpClPP)Cl has a selectivity similar to that of Fe(OFP)Cl. The selectivities of these less encumbered porphyrins resemble that of *m*-chloroperoxybenzoic acid (mCPBA).

The electronic properties of porphyrins can be determined conveniently by electrochemistry. The oxidation and reduction potentials of metalloporphyrins are very sensitive to substitution at the meso and β-pyrrolic positions of the porphyrin.[10] For zinc porphyrins oxidations and reductions occur on the porphyrin ring since the d^{10} metal is not electroactive. The position of the one- and two-electron porphyrin ring oxidations for zinc porphyrins is a useful indication of how electron rich the porphyrin ligand is. For iron porphyrins both the metal and the porphyrin can be

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(3) (a) Ortiz de Montellano, P. A.; Mico, B. A. *Arch. Biochem. Biophys.* **1981**, *206*, 43. (b) Ortiz de Montellano, P. R.; Mico, B. A.; Mathews, J. M.; Kunze, K. L.; Miwa, G. T.; Lu, A. Y. H. *Arch. Biochem. Biophys.* **1981**, *210*, 717.

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(5) Examples follow. *meso*-Tetrakis(2,6-dichlorophenyl)porphine dianion: Cl_8TPP, TDCPP, and (2,6-Cl)PP. *meso*-Tetrakis(pentafluorophenyl)porphine dianion: F_{20}TPP and TFPP. 2,3,7,8,12,13,17,18-Octabromo-*meso*-tetrakis-(2,6-dichlorophenylporphine) dianion: (88TPP)Cl and β-Br_8-OCP.

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Table III. Partition Number Dependence on Porphyrin Substitution

	vinylcyclohexane		methylenecyclohexane		styrene	
Fe(Por)Cl	A_∞	k_{cat}/k_{inact}	A_∞	k_{cat}/k_{inact}	A_∞	k_{cat}/k_{inact}
Fe(OFP)Cl	160	140	590	660	4700	5000
Fe(OCP)Cl	230	210	820	840	12000	13000
Fe(OBP)Cl	220	200	900	1000	12000	14000
Fe(PFP)Cl	140	130	1100	1200	4600	5000
Fe(NOCP)Cl	140	150	*a*	*a*	7200	7800

[a] Not determined.

oxidized; thus the site of oxidation is more ambiguous.[11]

The potentials for the one- and two-electron oxidations of a variety of Zn(Por) and Fe(Por)Cl are listed in Table II. The oxidation potentials in this table are all internally consistent since each metalloporphyrin was referenced to the ferrocene couple. The reported potential for ferrocene relative to SCE (+0.307 V, 0.2 M $LiClO_4$ in acetonitrile)[12] was used to correct the ferrocene-referenced potentials to approximate SCE values.

The three porphyrins OBP, OCP, and OFP all have very similar oxidation potentials. The first and second oxidation potentials for Zn(OFP) are only 20–30 mV positive of the potentials for Zn(OCP) and Zn(OBP). A slightly greater difference is seen in the hemins where Fe(OFP)Cl is more difficult to oxidize by about 60–80 mV. These three porphyrins are substantially different from TPP, TMP, and TpClPP, which are easier to oxidize by about 100–200 mV.

The porphyrins PFP and NOCP are considerably harder to oxidize than their isosteric counterparts OFP and OCP. For Zn(PFP) and Fe(PFP)Cl the one-electron oxidation potentials are 170 and 210 mV positive of Zn(OFP) and Fe(OFP)Cl, respectively. The oxidation potentials for Zn(NOCP) and Fe(NOCP)Cl are shifted 130–150 mV positive of the OCP complexes.

Effect of Porphyrin Substitution on Partition Numbers. Both epoxidation and N-alkylation are first order in Fe(Por)Cl for all of the catalysts studied. From computer fitting to epoxidation data, values for the apparent rate constants k_{cat}, k_{cat}', and k_{inact} can be obtained. Partition numbers can be determined by either the ratio k_{cat}/k_{inact} or the A_∞ method.[1a] Average partition numbers for the epoxidation of vinylcyclohexane, methylenecyclohexane, and styrene by the hemin catalysts shown in Figure 1 and PFIB are listed in Table III. Each entry represents the average of at least two experiments. Supplementary tables 1S–3S list the actual partition numbers for individual experiments with the five catalysts and the three olefins. Although the apparent rate constants for the hemin-catalyzed epoxidations exhibit considerable variation between different runs under comparable reaction conditions, the partition numbers are in good agreement (10–20%). In the previous paper we attributed the variability in the rate constants to the heterogeneity of the system.

The data in Table III show that the partition numbers are only moderately sensitive to the steric and electronic properties of the catalyst. The partition numbers for Fe(OBP)Cl and Fe(OCP)Cl are similar for all three olefins; only a slightly larger partition number was observed for Fe(OBP)Cl with the more sterically encumbered methylenecyclohexane. The similarity of partition numbers for Fe(OBP)Cl and Fe(OCP)Cl is consistent with the similar cis/trans selectivity for the two catalysts. The modest variation in the partition numbers (Tables 1S and 3S) for Fe(OBP)Cl experiments (30%) is probably due to the insolubility of Fe(OBP)Cl, which made the preparation of catalyst solutions difficult. The partition numbers for Fe(OFP)Cl are all only a little smaller than for Fe(OBP)Cl and Fe(OCP)Cl.

The catalyst pairs Fe(PFP)Cl/Fe(OFP)Cl and Fe(NOCP)Cl/Fe(OCP)Cl exhibit similar partition numbers despite the significantly different electronic properties of the catalysts in each pair. Except for methylenecyclohexane, Fe(PFP)Cl and Fe(OFP)Cl have identical partition numbers. A comparison of the partition numbers for Fe(NOCP)Cl and Fe(OCP)Cl shows that the more electron-poor porphyrin actually undergoes a slightly more facile N-alkylation. The *N*-alkylhemins of Fe(OBP)Cl, Fe(OCP)Cl, Fe(OFP)Cl, and Fe(PFP)Cl all exhibit Soret bands at 442–446 nm whereas the *N*-alkylhemin from the Fe(NOCP)Cl exhibits a diminished and red-shifted Soret at 456 nm. The 10-nm shift in the *N*-alkylhemin parallels the shift in the Soret of Fe(NOCP)Cl (428 nm) compared to Fe(OCP)Cl (418 nm). The conversion of each catalyst to *N*-alkylhemin showed isosbestic behavior by UV–vis spectroscopy.

Table IV. Dependence of Styrene Oxide/Phenylacetaldehyde Ratio on the Nature of the Catalyst and Oxidant

catalyst	oxidant	epoxide/aldehyde
Fe(OBP)Cl	PFIB	14
Fe(OCP)Cl	PFIB	22
Fe(OCP)Cl	PhIO	17
Fe(NOCP)Cl	PFIB	16
Fe(OFP)Cl	PFIB	11
Fe(PFP)Cl	PFIB	14[a]
$Fe(OCP)BF_4$	PFIB	22

[a] From ref 13.

Table V. Partition Number Data for the Epoxidation of Substituted Styrenes by Fe(OCP)Cl and PFIB

substituted styrene[a]	[Fe(OCP)Cl] (mM)	partition no. A_∞	partition no. k_{cat}/k_{inact}
p-CH_3	2.7	14000	14000
	2.7	14000	14000
p-Cl	2.9	14000	15000
	2.6	14000	17000
	2.7	11000	14000
p-CF_3	2.6[b]	6600	6900
	2.6[c]	6900	7200
2,6-dimethyl	2.9[d]	3600	3000
	4.8[d]	2800	2400

[a] Substituted styrene concentration 1 M unless noted otherwise. [b] 0.5 M *p*-(trifluoromethyl)styrene. [c] 0.3 M *p*-(trifluoromethyl)styrene. [d] 0.5 M 2,6-dimethylstyrene.

Due to difficulty in routinely separating styrene oxide and phenylacetaldehyde by GC analysis, the partition numbers for the epoxidation of styrene reported in Table III and VI include both aldehyde and epoxide. The contribution of phenylacetaldehyde to the partition numbers is minor since less than 10% of the oxidized product is aldehyde and since the GC response factors of epoxide and aldehyde are essentially the same. Table IV lists the epoxide/aldehyde ratios as a function of the Fe(Por)X catalyst. The ratios are similar, only a factor of 2 difference, despite the very different steric and electronic properties of the catalysts. Under all conditions no acetophenone was detected. In a previous study we demonstrated that phenylacetaldehyde was relatively stable to oxidation to phenylacetic acid in the presence of excess styrene and that aldehyde was a primary product, not the result of epoxide rearrangement.[13]

Epoxidation of Substituted Styrenes. The effect of electronic and steric properties of the alkene on the partition number was probed through the epoxidation of four substituted styrenes with Fe(OCP)Cl and PFIB. Table V lists the partition numbers for para-substituted styrenes and 2,6-dimethylstyrene. The *p*-chloro- and *p*-methyl-substituted styrenes have partition numbers very similar to that of styrene whereas *p*-(trifluoromethyl)styrene has a somewhat smaller partition number.

Methyl substitution at the aryl 2- and 6-positions of styrene lowers the partition number by a factor of 4 compared to styrene. Unlike the other styrenes the *N*-alkylhemin from 2,6-dimethylstyrene retains a significant catalytic activity, only 6-fold lower than Fe(OCP)Cl. Due to the activity of the *N*-alkylhemin and

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Table VI. Product Distribution for Epoxidation of Substituted Styrenes

substituted styrene	% aldehyde[a]	epoxide/aldehyde Fe(OCP)Cl	epoxide/aldehyde Fe(PFP)Cl[b]
styrene	4	22	14
p-CH_3	10	9.4	13
p-Cl	4	27	17
p-CF_3	4	24	*c*
2,6-dimethyl	6	16	*c*

[a] Percent aldehyde/(aldehyde + epoxide). [b] From ref 13. [c] Not determined in previous work.[13]

Table VII. Partition Number Data for the Epoxidation of Vinylcyclohexane and Styrene by Fe(OCP)X (X = BF_4, Br, Cl)

olefin[a]	X: [Fe(OCP)X] (mM)	oxidant	partition no. A_∞	partition no. k_{cat}/k_{inact}
VCY	BF_4: 7.5–9.4	PFIB	330	310
VCY	BF_4: 9.4	PhIO	400	410
VCY	Br: 8.9	PFIB	270	250
VCY[b]	Cl: 2.7–12	PFIB	230	210
STY	BF_4: 1.2	PFIB	15000	15000
STY[b]	Cl: 2.7–3.5	PFIB	12000	13000

[a] All at 1 M olefin in CH_2Cl_2. VCY = vinylcyclohexane. STY = styrene. [b] Average values from Table III.

Table VIII. Competition of Styrene and Para-Substituted Styrenes and Oxidant Dependence

X[a]	oxidant PFIB	PhIO	LiOCl/PTC	mCPBA
CH_3	2.36	2.13	1.57	2.67
Cl	1.22	1.28	1.56	0.587
CF_3	0.381	0.315	0.479	0.118

[a] Ratio of *p*-X-styrene oxide to styrene oxide formed with Fe(OCP)Cl and the above oxidant. Styrene and *p*-X-styrene each 1 M in methylene chloride.

the formation of colored minor products that complicate the absorbance changes, the more accurate partition number in Table V is that from the computer fit. A possible explanation for the partition number sensitivity to ortho substitution and insensitivity to the para substituent will be presented in the Discussion.

Table VI lists epoxide/aldehyde ratios for the epoxidation of substituted styrenes by Fe(OCP)Cl with our previously reported[13] epoxide/aldehyde ratios for Fe(PFP)Cl. Consistent with our earlier report, the ratio for Fe(OCP)Cl is relatively insensitive to the electronic properties of the styrene. Once again, due to GC analysis difficulties, the data in Table V are for epoxide and aldehyde. Except for *p*-methylstyrene the fraction of aldehyde is less than 10% so the partition numbers are relatively unaffected by including aldehyde.

Effect of the Counterion on Partition Numbers. The crystal structures of Fe(TPP)X complexes show that the iron atom is displaced out of the porphyrin plane; the distance of this displacement from the center of the porphyrin varies as a function of the counterion.[14] For Fe(TPP)Cl a displacement of 0.39 Å is observed. With weakly coordinating anions, like SbF_6^- and ClO_4^-, the iron atom lies nearly in the plane of the porphyrin (0.15–0.30 Å) whereas with Br^- a large displacement (0.49 Å) is observed. The effect of the nature of the counterion on the partition numbers for vinylcyclohexane and styrene is shown in Table VII.

The partition numbers for vinylcyclohexane and styrene epoxidation with Fe(OCP)BF_4/PFIB are slightly larger than with Fe(OCP)Cl (230 and 12000 turnovers, respectively). With PhIO as the oxygen atom donor, the partition number for vinylcyclohexane is similar to that previously reported for Fe(OCP)Cl. The partition number observed for Fe(OCP)Br is identical with that of Fe(OCP)Cl. The apparent rate constants in all of these experiments are in the range of comparable experiments with Fe(OCP)Cl.[1c]

Table IX. Reactivity of Olefins Relative to Styrene

olefin[a]	Fe(OCP)Cl/PFIB[b]	mCPBA[b]
1-decene	0.14	0.71
vinylcyclohexane	1.5	1.1
methylenecyclohexane	1.2	33
2,6-dimethylstyrene[c]	0.30	0.33

[a] 1 M each in above olefin and in styrene unless noted otherwise. [b] Ratio of epoxide of above olefin to styrene oxide produced. [c] 0.5 M each in 2,6-dimethylstyrene and styrene.

Table X. Comparison of Apparent Rate Constants k_{cat} and k_{inact} for Alkenes Relative to Styrene

olefin	k_{cat}(rel)[a]	k_{inact}(rel)[b]	IP[c]
1-decene	0.14	14	9.43,[d] 9.51,[e] 9.59[f]
vinylcyclohexane	1.5	78	9.52[g]
methylenecyclohexane	1.2	17	9.17,[h] 8.94,[i] 8.97[j]
2,6-dimethylstyrene	0.30	1.3	8.49,[k] 8.65[l]
p-(trifluoromethyl)styrene	0.38	0.67	
styrene	1	1	8.48,[k] 8.50[l]
p-chlorostyrene	1.2	1.1	
p-methylstyrene	2.4	2.1	8.20[k]

[a] From Tables VIII and IX. [b] Calculated from the ratio of average partition numbers to styrene and k_{cat}(rel). [c] Ionization potentials for the alkenes. Method noted in parentheses in footnotes: photoionization (PI); photoelectron (PE). [d] Reference 16a. From 1-octene (PI). [e] Reference 16b. [f] Reference 16c. From 1-butene (PE). [g] Reference 16c. From 3-methyl-1-butene. [h] Reference 16c. From isobutylene. [i] Reference 16d (PE). [j] Reference 16a. [k] Reference 16e (PE). [l] Reference 16f (PE).

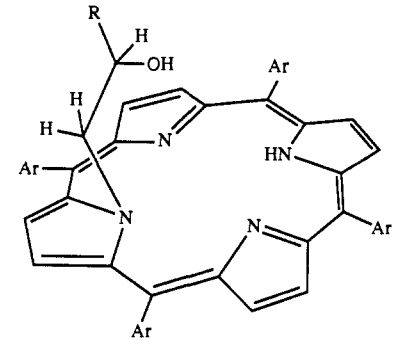

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Figure 2. Regiochemistry of *N*-alkylhemin formation.

Oxidant Dependence of Styrene Competitions. Table VIII lists ratios of epoxides formed when para-substituted styrenes and styrene are competitively oxidized by Fe(OCP)Cl and PFIB, PhIO, or LiOCl/BAC. Competitions with *m*-chloroperoxybenzoic acid were performed for comparison. The ratios provide a measure of the relative epoxidation reactivity [k_{cat}(rel)] of a substituted styrene compared to styrene. Plots of log k_{cat}(rel) versus the Hammett σ and σ^+ coefficients show better fit to σ^+ with the following ρ^+ values and correlation coefficients (R^2): PFIB, −0.86 (0.948); PhIO, −0.91 (0.930); LiOCl, −0.57 (0.744); mCPBA, −1.53 (0.998). Except for LiOCl the correlations are good. Although the data points are limited, it appears that the iodosylbenzenes exhibit similar selectivity. The smaller ρ^+ value for LiOCl/BAC suggests LiOCl forms a different active oxidant. The lower value could also be due to the more polar solvent conditions.[15]

Relative Reactivity of Alkenes. The relative epoxidation reactivities [k_{cat}(rel)] of the remaining olefins compared to styrene with the Fe(OCP)Cl/PFIB system and with mCPBA are listed

(14) (a) Hoard, J. L.; Cohen, G. H.; Glick, M. D. *J. Am. Chem. Soc.* **1967**, *89*, 1992. (b) Shelly, K.; Bartczak, T.; Scheidt, W. R.; Reed, C. A. *Inorg. Chem.* **1985**, *24*, 4325. (c) Reed, C. A.; Mashiko, T.; Bentley, S. P.; Kastner, M. E.; Scheidt, W. R.; Spartalian, K.; Lang, G. *J. Am. Chem. Soc.* **1979**, *101*, 2948. (d) Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1977**, *30*, 2655.

(15) Baldwin, J. E.; Kapecki, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4868.

in Table IX. The two systems exhibit very different selectivities in the epoxidation of the olefins. From the ratio of the partition number for a given terminal alkene compared to that of styrene and the relative reactivity of the olefin [k_{cat}(rel)], a relative inactivation reactivity [k_{inact}(rel)] for the terminal alkene compared to styrene can be calculated. The k_{inact}(rel) values are listed in Table X. Plots of log k_{inact}(rel) versus σ and σ^+ for the styrenes provide a better fit to σ^+ with a ρ^+ of −0.51 (R^2 = 0.897). For the other olefins in Table X it is clear there are no definite trends in either the k_{cat}(rel) or the k_{inact}(rel) compared to the olefin ionization potentials.[16] The absence of a trend, however, is not surprising since the olefins are not isosteric and so few olefins were studied.

N-Alkylhemin Regiochemistry. Traylor and co-workers were the first to report the isolation of *N*-alkylhemin **1** (Figure 2; Ar = 2,6-dichlorophenyl, R = neopentyl) in a P-450 model system consisting of Fe(OCP)Cl and PFIB.[17] Only the regioisomer with the terminal carbon attached to nitrogen was observed; the same regiochemistry was reported for P-450.[4] Using the same model system as Traylor, we observed that the epoxidation of 1,1-disubstituted alkenes and even styrenes resulted in the formation of *N*-alkylhemins. We characterized the adducts of 3-methyl-1-butene and isobutylene and observed the regiochemistry to be the same as reported by Traylor. Mass spectral data for the adduct of 2,6-dimethylstyrene and Fe(OCP)Cl were also provided.[1b]

The other regioisomer, attachment to the more hindered carbon, has been observed by Mansuy and colleagues during the epoxidation of 1-butene by Fe(TpClPP)Cl and PhIO.[18] In these adducts, the 2-position is attached to the pyrrolic nitrogen and the 1-position is oxidized to a carboxylate. After being heated in acid, the *N*-alkylporphyrin decarboxylates to provide an *N*-propylporphyrin.[18b] They attributed the different regiochemistry between Fe(OCP)Cl and Fe(TpClPP)Cl to steric effects. Mansuy has also characterized *N*-alkylhemins formed in the epoxidation of *trans*-2-hexene with Fe(TpClPP)Cl and found them to be stereospecific additions of the alkene to the pyrrolic nitrogen and iron-oxo.[18c] Traylor and co-workers have reported the formation of unstable *N*-alkylhemins during the epoxidation of several internal alkenes.[19]

The Fe(OFP)Cl and Fe(PFP)Cl catalysts should have steric properties similar to that of Fe(TpClPP)Cl (Table I), yet the fluorinated porphyrins are much more electron poor than Fe(TpClPP)Cl (Table II). With both PFIB and PhIO, Fe(PFP)Cl yields only the primary *N*-alkylhemin during the epoxidation of 1-butene at 0 °C. The high-field pair of doublet of doublets at −4.0 to −4.2 ppm (each one proton) is definitive evidence for the primary *N*-alkylhemin **1** (Ar = pentafluorophenyl, R = ethyl) in Figure 2 as the major product; no other *N*-alkylporphyrins, especially an *N*-propylporphyrin, were detected.

The same regiochemistry (**1** (Ar = 2,6-difluorophenyl, R = ethyl); Figure 2) was observed for Fe(OFP)Cl and 1-butene supported by either PFIB or iodosylbenzene. The *N*-(2-hydroxyalkyl)porphyrin, obtained by 5% HCl/methanol demetalation of the *N*-alkylhemin at 50 °C, exhibits a high-field multiplet at −4.3 ppm (two protons). Acetylation of the hydroxyl group with acetic anhydride/HCl yielded the *N*-(2-acetoxyalkyl)porphyrin whose ^{1}H NMR displays a well-resolved pair of doublet of doublets at −4.2 and −4.3 ppm (each one proton) consistent with the primary *N*-alkylporphyrin regiochemistry.

Stereochemistry of N-Alkylhemin Formation. The stereochemistry of epoxidation and hemin N-alkylation has been reported by Ortiz de Montellano and co-workers[4] for P-450 and by ourselves for the Fe(OCP)Cl/PFIB model system.[1b] The epoxidation of *trans*-1-deuterio-1-octene by P-450 resulted in the formation of an *N*-alkylhemin and the isolation of exclusively the *trans*-1-deuterio epoxide. Dealkylation of the *N*-alkyl substituent led to the isolation of an epoxide with inverted stereochemistry at the terminal carbon. This stereochemistry is consistent with a syn addition to the alkene followed by an inversion on dealkylation. Direct observation of the stereochemistry of the *N*-alkylporphyrin was not possible in the natural system.

We reported that the epoxidation of either *cis*- or *trans*-deuterio-3-methyl-1-butene by Fe(OCP)Cl/PFIB resulted in the formation of exclusively the *cis*- and *trans*-1-deuterio epoxides, respectively.[1b] The syn stereochemistry of the hemin N-alkylation was determined by acidic demetalation of the *N*-alkylhemin under the conditions of Traylor and co-workers (3:1 acetic acid/HCl) and analysis of the metal-free *N*-alkylporphyrins by ^{1}H NMR.

The *N*-alkylhemin isolated from the epoxidation of 3-methyl-1-butene exhibits an NMR spectrum with a high-field pair of doublet of doublets at −4.2 and −4.4 ppm for the methylene attached to the pyrrolic nitrogen. The *N*-alkylporphyrins from *cis*- and *trans*-1-deuterio-3-methyl-1-butene each display a doublet in the −4 to −4.5 ppm region, indicating a highly stereospecific (>95%) addition to the alkene. The actual stereochemistry (syn or anti) was determined from the doublet coupling constants, 11 Hz for the *trans*-1-deuterioalkene and 2 Hz for the *cis*-1-deuterioalkene. Since the bulky isopropyl group would favor a conformation of the *N*-alkyl substituent which places the isopropyl group anti to the pyrrolic nitrogen of the bulky porphyrin, the 11- and 2-Hz coupling constants require an anti and gauche, respectively, placement of the protons on the 1-methylene and the 2-methine. Both conformations result from a syn addition to the alkene double bond. The stereochemistry of isolated epoxides for each deuterated alkene also indicated a stereospecific (>95%) syn addition to the alkene. The deuterated 3-methyl-1-butenes isolated from reaction mixtures showed no detectable isomerization.

Yield of N-Alkylhemins. In each of our isolations only enough oxidant was added for ~50% conversion to minimize oxidative destruction of the *N*-alkylhemin. As a result, no yields were determined for the above adducts. We and others[17,18] have observed the yields for isolated *N*-alkylporphyrins to be less than quantitative.

Traylor reported a yield of 53% for the *N*-alkylhemin formed during the epoxidation of 4,4-dimethyl-1-pentene and PFIB.[17] In their study, only 63 equiv of PFIB was used. Unless the partition number for this olefin is considerably smaller than that for 1-decene (130 turnovers/N-alkylation), we would have expected a maximum theoretical yield of about 50% under their conditions. In a later study by Traylor and co-workers 260 equiv of PFIB/Fe(OCP)Cl was used, but the yield of *N*-alkylhemin was not reported.[19a] This number resembles our partition number of 230 turnovers for vinylcyclohexane. Mansuy reported a yield of 60% for the methyl ester of his 1-butene adduct of Fe(TpClPP)Cl.[18b]

During our isolation attempts we also find that the yields are less than quantitative; for the vinylcyclohexane adduct of Fe(OCP)Cl we have obtained a yield of 70%. The ^{1}H NMR spectrum of the *N*-alkylporphyrin indicates several persistent impurities, so the 70% yield is probably a high estimate. Analysis of the reaction mixture indicated the presence of 280 equiv of epoxide. Since we have determined the partition number for vinylcyclohexane to be 230 turnovers, the N-alkylation should have been complete.

In addition to the isolated *N*-alkylporphyrin, a significant amount of Fe(OCP)X was obtained when the demetalated *N*-alkylhemin was chromatographed. The presence of starting catalyst could be due to incomplete N-alkylation of the porphyrin,

(16) (a) Demeo, D. A.; El-Sayed, M. A. *J. Chem. Phys.* **1970**, *52*, 2622. (b) Watanabe, K.; Nakayama, T.; Mottle, J. *J. Quant. Spect. Radiat. Transfer* **1962**, *2*, 369. (c) Dewar, M. J. S.; Worley, S. D. *J. Chem. Phys.* **1969**, *50*, 654. (d) Demo, D. A.; Yencha, A. J. *J. Chem. Phys.* **1970**, *53*, 4536. (e) Kobayashi, T.; Yokota, K.; Nagakura, S. *J. Elect. Spect. Rel. Phenom.* **1973**, *3*, 449. (f) Maier, M. P.; Turner, D. W. *J. Chem. Soc., Faraday Trans. 2* **1973**, *69*, 196.

(17) Mashiko, T.; Dolphin, D.; Nakano, T.; Traylor, T. G. *J. Am. Chem. Soc.* **1985**, *107*, 3735.

(18) (a) Mansuy, D.; Devocelle, L.; Artaud, I.; Battioni, J. P. *Nouv. J. Chim.* **1985**, *9*, 711. (b) Artraud, I.; Devocelle, L.; Battioni, J. P.; Girault, J. P.; Mansuy, D. *J. Am. Chem. Soc.* **1987**, *109*, 3782. (c) Artaud, I.; Devocelle, L.; Gregoire, N.; Battioni, J. P.; Mansuy, D. *Recl. Trav. Chim. Pays-Bas.* **1987**, *106*, 336.

(19) (a) Traylor, T. G.; Nakano, T.; Miksztal, A. R.; Dunlap, B. E. *J. Am. Chem. Soc.* **1987**, *109*, 3625. (b) Traylor, T. G.; Miksztal, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 2770. (c) Traylor, T. G.; Miksztal, A. R. *J. Am. Chem. Soc.* **1989**, *111*, 7443.

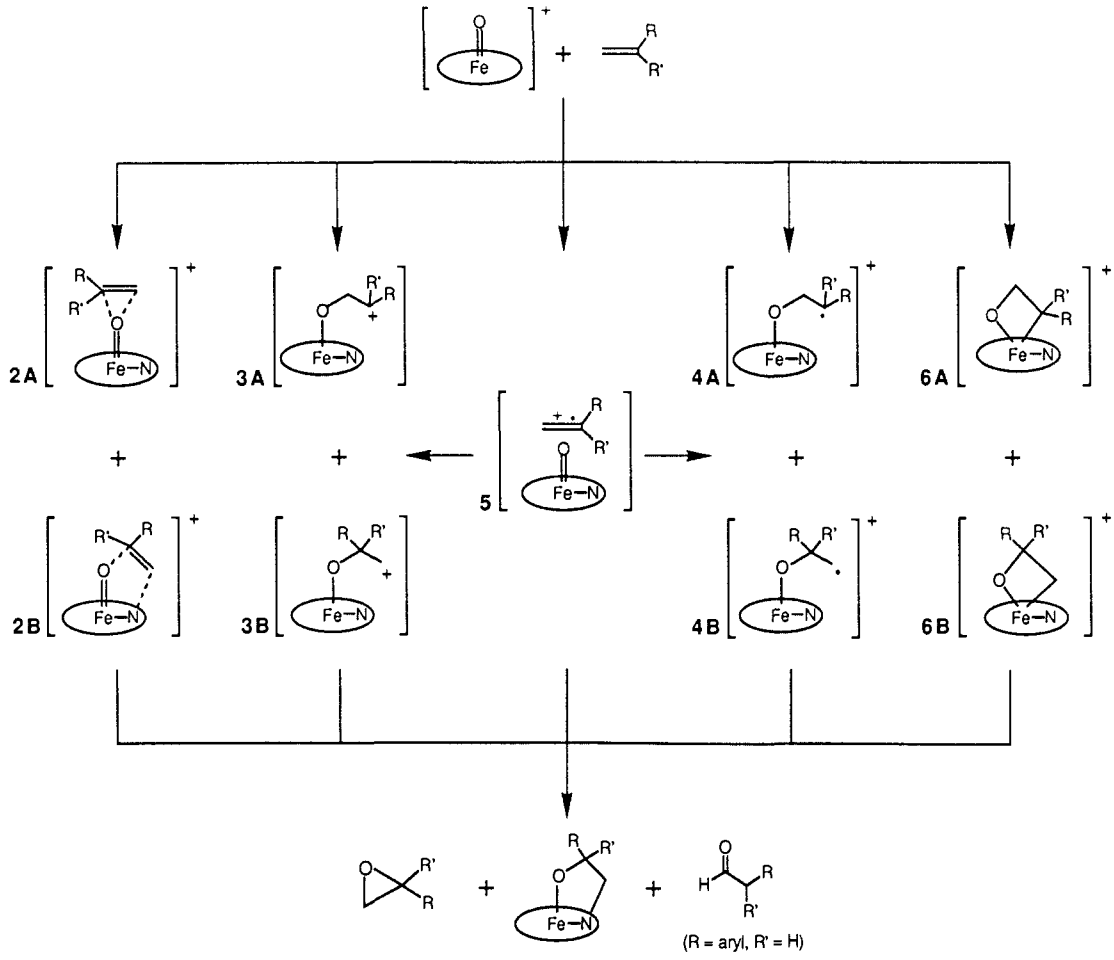

Figure 3. Proposed mechanisms for olefin epoxidation and heme N-alkylation.

to dealkylation of the primary *N*-alkylhemin under the harsh demetallation conditions, or to the decomposition of a less stable secondary *N*-alkylhemin. Simple *N*-alkylhemins are known to be dealkylated by nucleophiles.[20] It is possible that small amounts of unstable secondary *N*-alkylhemins are formed with the hemins we have studied and we have failed to isolate them.

Discussion

In our previous papers[1a,b] we have shown that the synthetic hemin/iodosylarene systems are viable models for the suicide inactivation of P-450 by terminal olefins. The epoxidation of 1-alkenes, 1,1-disubstituted alkenes, and styrenes leads to the irreversible formation of *N*-alkylhemins that possess significantly diminished catalytic activity. From our studies of this model system we have obtained information about the mechanisms of epoxidation and N-alkylation. A variety of mechanisms have been proposed for epoxide and *N*-alkylhemin formation for both P-450 and the model systems: a concerted addition structure **2**, acyclic cation **3** or radical **4**, electron transfer from the olefin to the iron–oxo **5**, and oxametallacycles **6**. These mechanisms are shown in Figure 3.

We believe either a concerted addition or a short-lived acyclic intermediate is most consistent with the stereospecificity and sensitivity to electronic effects that we have observed. Addition of an alkene to the iron–oxo **2A** or to the oxo and the hemin nitrogen **2B** could result in the formation of either epoxides or *N*-alkylhemins, respectively. Transition states **2A** and **2B** are shown in more detail in Figures 4 and 5. The stereochemistry for epoxidation and N-alkylation and the insensitivity of the partition numbers to the electronic properties of the catalyst and olefin would be consistent with such a mechanism. Both the

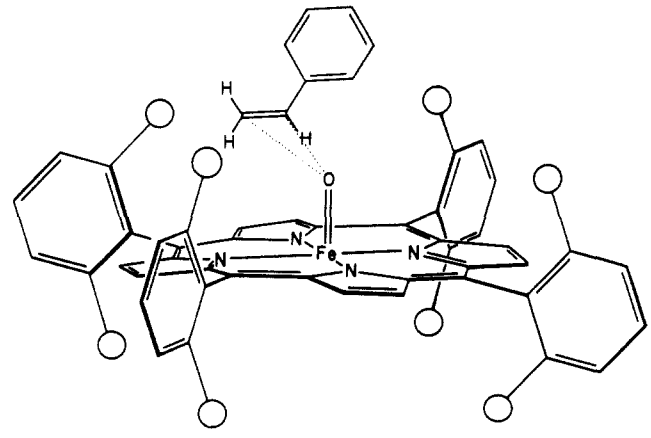

Figure 4. Transition-state geometry **2A** for epoxide formation.

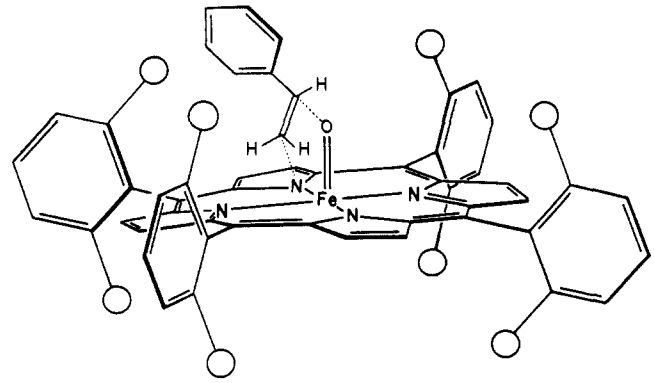

Figure 5. Transition-state geometry **2B** for *N*-alkylhemin formation.

(20) Schauer, C. K.; Anderson, O. P.; Lavallee, D. K.; Battioni, J. P.; Mansuy, D. *J. Am. Chem. Soc.* **1987**, *109*, 3922.

structure of the alkene and modest electronic effects could influence the transition-state geometry and lead to the factor of a 100 in the range of partition numbers we have observed. The formation of phenylacetaldehydes as major products during the epoxidation of substituted styrenes requires the presence of acyclic cation **3A** or radical **4A** as an intermediate at least for the rearrangement to aldehydes; these species could also be intermediates in olefin epoxidation and N-alkylation. Traylor has suggested that electron transfer from the alkene to the iron–oxo, as in **5**, may precede the formation of the acyclic species **3** and **4**.[21] Two regioisomers of an oxametallacycle, **6A** and **6B**, may also be intermediates in epoxidation and N-alkylation.[18,22] Each of these possible mechanisms will be discussed in light of the regiochemistry and stereochemistry of N-alkylation, the partition number studies, and the relative reactivities of alkenes.

Regiochemistry and Stereochemistry of N-Alkylation. With a variety of 1-alkenes (1-butene, 1-hexene, 1-octene, 3-methyl-1-butene, vinylcyclohexane, and isobutylene) and hemins (Fe(OCP)Cl, Fe(OFP)Cl, and Fe(PFP)Cl) and either pentafluoroiodosylbenzene (PFIB) or iodosylbenzene as oxygen atom donors, we have isolated only the *N*-alkylhemin regioisomer with the pyrrolic nitrogen attached to the primary carbon of the terminal alkene (Figure 2). Traylor and Dolphin and co-workers originally reported the isolation of an *N*-alkylhemin in the Fe(OCP)Cl/PFIB system and observed only the primary regioisomer.[17] This regiospecificity is the same as reported for the *N*-alkylhemins isolated for P-450.[4] In the epoxidation of 1-butene by Fe(TpClPP)Cl/PhIO, Mansuy and co-workers observe only *N*-alkylhemin products consistent with attachment of the pyrrolic nitrogen to the 2-position of the alkenes.[18] The different regiospecificity with Fe(TpClPP)Cl may be due to electronic effects and not to steric effects, as suggested by Mansuy, since we observed the unhindered but more electron-poor Fe(OFP)Cl provided only the primary *N*-alkylhemin.

Both Mansuy and Traylor have reported the formation of *N*-alkylhemins during the epoxidation of internal alkenes; from our studies we cannot exclude the possibility that a secondary *N*-alkylhemin forms, and we have not succeded in isolating it. The stability of the *N*-alkylhemins and the reproducibility of the partition numbers that we observe require that either the secondary *N*-alkylhemins are rapidly forming and reverting to starting catalyst, leading to the gradual accumulation of the primary *N*-alkylhemins, or the secondary *N*-alkylhemins are stable and are formed in a constant ratio with the major regioisomer, the primary *N*-alkylhemin. Traylor has observed the apparent reversible formation of *N*-alkylhemins with some internal alkenes including norbornene and a caged diene.[19,21] For terminal alkenes, the secondary *N*-alkylhemin could be the kinetic product whereas the primary *N*-alkylhemin could be the stable, thermodynamic product. The less than quantitative yields of isolated *N*-alkylporphyrins (50–70%) suggests that either the primary *N*-alkylhemin partially decomposes or a minor, unstable secondary *N*-alkylhemin completely decomposes under the conditions of acidic demetalation.

We have observed the stereochemistry of both *N*-alkylhemin formation and epoxidation to be rigorously a syn addition to the alkene when *cis*- and *trans*-1-deuterio-3-methyl-1-butene were used as substrates in the Fe(OCP)Cl/PFIB system. This sterochemistry confirms the indirect stereochemical study performed by Ortiz de Montellano for P-450, where the stereochemistry was determined by analyzing the epoxide generated by dealkylation of the *N*-alkylhemin.[4] The stereochemistry observed for the model system and P-450 requires that closure of an acyclic intermediate **3B** or **4B** to form an *N*-alkylhemin or epoxide must be rapid compared to bond rotation.

Partition Number Studies. The first paper in this series reported a further study of the mechanism of *N*-alkylhemin formation in the Fe(OCP)Cl/PFIB model system, which we previously reported.[1a,b] The rates of olefin epoxidation and hemin N-alkylation were both found to be first order in Fe(OCP)Cl from computer fitting to epoxidation and spectral data. Unlike P-450, the *N*-alkylhemins formed in the epoxidation of terminal aliphatic alkenes by Fe(OCP)Cl were observed to retain diminished epoxidation activity; only the *N*-alkylhemins from styrene and substituted styrenes were inactive as epoxidation catalysts. From computer fitting we obtained values for the apparent rate constants 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}). The efficiency of the N-alkylation has been referred to as the partition number and reflects the number of productive turnovers of the catalyst to form epoxide per N-alkylation event. Partition numbers were measured either by the amount of epoxide formed when N-alkylation was complete or by the ratio k_{cat}/k_{inact} with fit rate constants. Although the rate constants k_{cat} and k_{inact} exhibited considerable variation between experiments, the partition numbers were highly reproducible (10–20%) for reactions performed under comparable reaction conditions. In this and the previous papers we have probed the sensitivity of the partition numbers to (1) the reaction conditions, (2) the terminal alkene structure, (3) the nature of the hemin catalyst, and (4) the oxygen atom donor.

The partition numbers are insensitive to alkene and hemin concentrations, the presence of additives (1-hexene oxide, cyclooctene, and phenylacetaldehyde), and the solvent. In the previous paper we reported the partition numbers for 1-decene and vinylcyclohexane with the Fe(OCP)Cl catalyst and PFIB as a function of the concentrations of catalyst and olefin. Olefin concentration changes by a factor of 20 and catalyst concentration changes by a factor of 5 had no effect on the partition numbers for the two olefins. The insensitivity of the partition number for 1-decene to the presence of 1-hexene oxide (0.1 M) demonstrated that N-alkylation of the hemin occurred during olefin oxidation and not as a result of alkylation by the product epoxides. The similarity of partition numbers for 1-decene in the presence or absence of cyclooctene demonstrated that both N-alkylation and epoxidation pathways were affected in the same way by the added alkene. Although aldehydes are observed to accelerate the rate of olefin epoxidation in the hemin/iodosylarene systems, the addition of phenylacetaldehyde to a standard vinylcyclohexane partition number experiment had no effect on the partition number but did accelerate both the rates of N-alkylation and epoxidation. The origin of the rate acceleration is not clear but may be due to heterogeneous processes. In methylene chloride and acetonitrile the partition numbers for vinylcyclohexane are identical, whereas in benzene the partition number is about 50% larger. The insensitivity of partition numbers to the above changes in reaction conditions suggests that the pathways of olefin epoxidation and hemin N-alkylation may have similar mechanisms.

As we reported in the previous paper and our preliminary communication, we have observed that the partition numbers are highly sensitive to the structure of the terminal alkene but relatively insensitive to the electronic properties of para-substituted styrenes. The average partition numbers we have observed for terminal olefins in the Fe(OCP)Cl/PFIB system are the following: 1-decene, 130 turnovers; vinylcyclohexane, 230 turnovers; methylenecyclohexane, 830 turnovers; styrene, 12 000 turnovers; 2,6-dimethylstyrene, 3000 turnovers; *p*-(trifluoromethyl)styrene, 6900 turnovers; *p*-chlorostyrene, 14 000 turnovers; *p*-methylstyrene, 14 000 turnovers. The range of partition numbers is over 100-fold; both steric and modest electronic effects are probably responsible for the observed range. The partition numbers for vinylcyclohexane and 1-decene are surprisingly very similar to the partition numbers reported for P-450 with allylisopropylacetamide (200–300 turnovers) and 2,2,2-trifluoroethyl vinyl ether (100–300 turnovers).[2,3]

Although the partition numbers do show a sensitivity to the structure of the terminal alkene, the sensitivity for the para-substituted styrenes is less than what we would have expected. The range in partition numbers (Table V) is only a factor of 2 between the electron-poor *p*-(trifluoromethyl)styrene and the

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(22) Collman, J. P.; Kodadek, T.; Raybuck, S. A.; Brauman, J. I.; Papazian, L. M. *J. Am. Chem. Soc.* **1985**, *107*, 4343.

electron-rich *p*-methylstyrene. The similar partition numbers suggest that the pathways of epoxidation and N-alkylation have similar sensitivities to alkene electronic properties and may have similar transition states. For the styrenes we observe significant amounts of phenylacetaldehydes (5–10%), but the ratio of epoxide to aldehyde is relatively insensitive to the electronic properties of the styrenes (Table VI). In an earlier paper[13] we argued that this insensitivity was inconsistent with acyclic cation **3A** as an intermediate. Since this ratio would depend on the relative rates of ring closure compared to hydrogen migration, the effect of substituents on the branching between epoxide and aldehyde from **3A** would be difficult to predict.

The 4-fold lower partition number for 2,6-dimethylstyrene compared to styrene surprised us since we expected the severe steric encumbrance of the alkene would make *N*-alkylhemin formation less favorable. This lowering may be due to the twisted structure of 2,6-dimethylstyrene. Ultraviolet absorbance spectra suggest that the ring of the olefin is twisted 50–54° with respect to the plane of the aryl ring.[23] A similar dihedral angle has been estimated by photoelectron spectroscopy.[16e] Despite the twisting out of the plane of the ring, the ionization potential for 2,6-dimethylstyrene is reported to be close to that of styrene.[16e,f] From CPK models, we infer that transition-state geometry **2A** for a concerted addition of the nonplanar 2,6-dimethylstyrene to the oxo forces a methyl group into the porphyrin ring. To minimize the interactions of the alkene methyl groups with the porphyrin, the alkene would favor the transition-state geometry in **2B** where the methyl groups lie in the cleft between the *meso*-aryl rings. Since **2B** is the geometry required for N-alkylation, the preference for transition-state **2B** over **2A** could result in the lowered partition number that we observe.

In this paper we observed only small changes in partition numbers with significant variations in the electronic properties of the iron porphyrin catalyst. The electrochemical oxidation potentials for the iron(III)–chloro and zinc derivatives of OFP and PFP show that OFP is much more electron rich than the isosteric PFP. Similarly, OCP and NOCP are isosteric, yet the iron(III)–chloro and zinc derivatives are more difficult to oxidize than OCP. The three hemins Fe(OFP)Cl, Fe(OCP)Cl, and Fe(OBP)Cl exhibit similar oxidation potentials but possess very different steric properties as the *cis*-olefin/*trans*-olefin selectivities indicate (Table I).

Although the isosteric pairs of hemins Fe(OFP)Cl/Fe(PFP)Cl and Fe(OCP)Cl/Fe(NOCP)Cl exhibit significantly different electronic properties, the partition numbers are very similar for the two hemins in each pair. In the epoxidation of methylenecyclohexane, the hemin Fe(PFP)Cl has a partition number only modestly larger than the more electron-rich hemin Fe(OFP)Cl; vinylcyclohexane and styrene have the same partition numbers for both hemins. For the electronegative hemin Fe(NOCP)Cl the partition numbers for styrene and vinylcyclohexane are actually lower (7200 and 150 compared to 12 000 and 210, respectively, Table III), indicating a more efficient N-alkylation of Fe(NOCP)Cl compared to Fe(OCP)Cl. Even the electron-rich Fe(TMP)Cl apparently has a partition number similar to that of the more electronegative Fe(OCP)Cl.[1b]

The absence of a significant electronic effect on the partition numbers is in contrast with Traylor's study of Fe(β-Br_8OCP)Cl, which suggested that increasing the electronegativity of the porphyrin should increase the partition number.[5,6c,d] They observed no N-alkylation of Fe(β-Br_8OCP)Cl by 4,4-dimethyl-1-pentene under conditions they used to isolate the 4,4-dimethyl-1-pentene adduct of Fe(OCP)Cl.[17] The number of catalyst turnovers was not given in this paper, however, so we cannot compare its turnover numbers with the partition numbers we have measured. The red-shifted spectrum of Fe(β-Br_8OCP)Cl with its Soret at 453 nm may have made detection of an *N*-alkylhemin more difficult. If an *N*-alkylhemin of Fe(β-Br_8OCP)Cl was formed, it might also be unstable under reaction conditions, as we observed for the *N*-alkylhemin formed with α-methylstyrene, or unstable toward oxidative bleaching as we have observed for the *N*-alkylhemins of Fe(NOCP)Cl and Fe(TMP)Cl.

The steric properties of the porphyrins also have only a modest effect on the partition numbers. From cis/trans competitions, Fe(OBP)Cl and Fe(OCP)Cl appear to have similar steric properties, and the partition numbers are identical for these catalysts with all three olefins. The cis/trans selectivity is lower for Fe(OFP)Cl compared to Fe(OCP)Cl, which is consistent with the smaller van der Waals radius for fluorine.[9] The porphyrin Fe(OFP)Cl has partition numbers somewhat lower than those of Fe(OCP)Cl and Fe(OBP)Cl; for styrene the partition number is about half that observed for Fe(OCP)Cl and Fe(OBP)Cl. The slightly lower partition numbers for the less encumbered Fe(OFP)Cl and Fe(PFP)Cl are consistent with the sterically demanding transition-state geometry **2B** becoming more favorable. We predicted methylenecyclohexane might have a much greater interaction with the aryl substituents in Fe(OBP)Cl, on the basis of CPK models, yet the partition numbers were nearly identical for the two catalysts with all three olefins. The cleft between the two aryl rings is apparently large enough that substitution of chlorine for bromine has little effect on the accessibility of the pyrrolic nitrogens.

Ostovic and Bruice recently reported partition numbers for the Fe(OBP)Cl-catalyzed epoxidation of terminal alkenes with PFIB.[24] They obtained partition numbers for 1-hexene (80 turnovers), vinylcyclohexane (130 turnovers), and 2,4,4-trimethyl-1-pentene (280 turnovers) by determining the amount of epoxide present when the N-alkylation was judged as complete from unquenched reaction aliquots. They also reported no N-alkylation of Fe(OBP)Cl by styrene up to 250 turnovers. The value they reported for vinylcyclohexane is somewhat lower than that which we have measured (200 turnovers) for Fe(OBP)Cl under similar reaction conditions. The partition number for 2,4,4-trimethyl-1-pentene is significantly different from that which we measured for another 1,1-disubstituted alkene, methylenecyclohexane (1000 turnovers); the two alkenes may, however, possess different enough properties to account for the differences in the partition numbers. We prefer our method of determining partition numbers, which utilizes a fit to epoxidation and spectral data to determine the partition number for each catalyst and alkene. In contrast, their method neglects the catalytic activity of the *N*-alkylhemin, uses unquenched reaction aliquots to follow spectral changes, and uses the extinction coefficient for the 1-hexene *N*-alkylhemin to determine the extent of N-alkylation for the other alkenes.

As Figure 3 in our previous paper[1a] demonstrates, the determination of a partition number is sensitive to the choice of N-alkylation end point. In each of our experiments we used triphenylphosphine-quenched reaction aliquots to monitor spectral changes and determine the end point. We observed significant changes in the spectra of reaction aliquots on quenching, changes that we attributed to the reduction of oxidized forms of the catalyst and *N*-alkylhemin. In fact, the Soret extinction coefficients we measured for the *N*-alkylhemins of Fe(OBP)Cl were larger than for Fe(OBP)Cl; Bruice reports the *N*-alkylhemins to have a *lower* extinction coefficient. We feel that the method Bruice used to determine partition numbers may have led to an early end point and, thus, lower partition numbers than those we obtained using computer fitting. The absence of an *N*-alkylhemin up to 250 turnovers of styrene, reported by Bruice, is not surprising since we have reported styrene to have a large partition number (12 000–14 000 turnovers).[1] At 250 turnovers only a negligible fraction of the catalyst (<2%) would have been converted to *N*-alkylhemin.

In the previous paper[1a] we observed that the partition number for vinylcyclohexane and Fe(OCP)Cl showed a sensitivity to the nature of the oxygen atom donor: hypochlorite, 610 turnovers; iodosylbenzene (PhIO), 360 turnovers; PFIB, 230 turnovers. If all three oxygen atom donors generated the same active iron–oxo, then we would have expected the partition numbers to be completely insensitive to the nature of the donor. The sensitivity to

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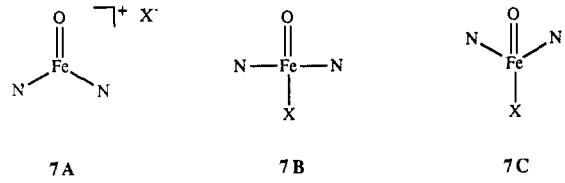

7A 7B 7C

Figure 6. Metal–porphyrin ring geometries.

the nature of the donor suggests that either the oxo intermediates possess different steric or electronic properties or the oxidant has a more complex role than simply generating the iron–oxo, for example inducing or inhibiting *N*-alkylhemin formation. The cis/trans selectivities (Table I) and the epoxide/aldehyde ratios (Table IV) for both PhIO and PFIB oxidants with Fe(OCP)Cl are essentially the same. From competitions of para-substituted styrenes with styrene, we obtained similar Hammett correlations with PhIO ($\rho^+ = -0.91$) and PFIB ($\rho^+ = -0.86$), but the correlation was very different with hypochlorite ($\rho^+ = -0.51$). It appears that PFIB and PhIO generate an iron–oxo with essentially the same steric and electronic properties, whereas the oxo from hypochlorite possesses significantly different electronic properties.

The differences in the partition numbers for the three oxidants may be due to the position of the iron atom with respect to the porphyrin ring: the iron atom could be above (**7A**), in (**7B**), or below (**7C**) the plane of the porphyrin (Figure 6). For hypochlorite, the iron–oxo could have a highly solvated counterion and the iron atom might be displaced toward the oxo ligand as in **7A**. This displacement would increase the nitrogen–oxo distance compared to an iron–oxo in the plane or below the plane and, thus, favor epoxidation over N-alkylation. If the out-of-plane displacement of the iron atom is similar to that in Fe(TPP)Cl or Fe(TPP)Br, then the nitrogen–oxo distance could change by as much as 0.5 Å between **7A** and **7C**.[14] The increase in partition numbers for iodosylbenzene could be due to a weakening of the Fe–X bond through coordination of iodosylbenzene [X = PhI(X)O$^-$]; such coordination is known for manganese porphyrins with iodosylbenzene and would be less favorable for PFIB.[25] The similarity of the partition numbers for different counterions (Table VII) suggests the Fe(TPP)X crystal structure displacements are not retained in the iron–oxo.

Despite the very different properties of the model system compared to P-450, the partition numbers are very similar for 1-alkenes for both systems. The insensitivity of partition numbers to the steric and electronic properties of the hemin suggests that changes in the steric properties of the P-450 active site may have little effect on the efficiency of the suicide event beyond exclusion of the substrate. The sensitivity to the nature of the oxygen atom donor, however, suggests that changes in the character of the iron–oxo may affect the partition numbers. It would be interesting to compare the efficiency of N-alkylation for P-450 under "shunt" conditions to that of the reconstituted systems studied by Walsh and Ortiz de Montellano.[2,3] Since chloroperoxidase performs several P-450-like oxidations, it would be interesting if it also undergoes the suicide event.

Relative Reactivities of Terminal Alkenes. Competitive epoxidations of each of the terminal alkenes with styrene have provided relative reactivities for epoxidation [k_{cat}(rel)] and N-alkylation [k_{inact}(rel)] for each of the alkenes used in this study (Tables IX and X) compared to styrene. For the aliphatic alkenes there is no trend for either k_{cat}(rel) or k_{inact}(rel) with the ionization potentials of the alkenes. Vinylcyclohexane and styrene have very similar reactivities [k_{cat}(rel) = 1.5] despite their very different electronic properties. The smaller partition number for 2,6-dimethylstyrene is due to a decreased rate of epoxidation [k_{cat}(rel) = 0.30] and a somewhat increased rate of N-alkylation compared to styrene (Table X). For *p*-chlorostyrene and *p*-methylstyrene, increases in k_{cat}(rel) are matched by comparable increases in k_{inact}(rel) (Table X) and the partition numbers are the same as styrene; for *p*-(trifluoromethyl)styrene the rate of epoxidation is affected more by the substitution than N-alkylation, resulting in a slightly lower partition number.

Both the relative rate constants for epoxidation and N-alkylation for the para-substituted styrenes can be fit to the Hammett σ^+ constants. The ρ^+ values obtained for epoxidation with PhIO (−0.91) and PFIB (−0.86) are in good agreement with those previously reported for similar hemin systems.[26,27] Although the fits are poor, the relative N-alkylation rate constants exhibit a smaller ρ^+ of −0.51; thus, the formation of *N*-alkylhemins is less sensitive to the electronic properties of the styrenes than is epoxidation. For hypochlorite as the oxygen atom donor, the correlation is poor but the ρ^+ of −0.59 that we have measured resembles Meunier and co-workers' value for the Mn(TMP)Cl/NaOCl epoxidation of styrenes ($\rho^+ = -0.46$).[28]

Traylor[26] has measured a ρ^+ of −0.84 for the soluble PFIB system with Fe(OCP)Cl, and Lindsay-Smith[27] has obtained a ρ^+ value of −0.93 for the heterogeneous iodosylbenzene and Fe(TPP)Cl system. Traylor and co-workers have argued their ρ^+ value resembles the −0.7 value obtained by Fox and Chen for the photooxidation of substituted 4-stilbenes on a semiconductor surface, which is a reaction proposed to proceed through an olefin–radical-cation intermediate.[29] The same reference, however, reports the much lower ρ^+ of −0.37 for the photooxidation of para-substituted styrenes.

Hammett correlations have been reported for a variety of reaction types and show a broad range of ρ^+ values depending on the character of the reaction. Radical reactions like hydrogen atom abstraction from substituted toluenes by phenyl radical and by chlorine atoms yield small ρ^+ values, −0.1 and −0.66, respectively.[30] The hydration of styrenes exhibits a large ρ^+ value (−3.21 to −4.51) consistent with the cationic character of the reaction.[31] The epoxidation of styrenes by mCPBA in 1,2-dichloroethane has been reported to have a ρ^+ value of −1.3, similar to our value of −1.5 in methylene chloride.[32] The reaction between substituted styrenes and diphenylketene yields a ρ^+ of −0.73; a concerted mechanism was proposed for this reaction.[15] A ρ^+ value of −0.89 was observed in the ozonolysis of styrenes.[33] The Criegee mechanism proposed for ozonolysis of alkenes involves a concerted [3+2] cycloaddition of ozone to the double bond.

The sensitivity of epoxidation and N-alkylation to substituent effects in our study resembles that of reactions believed to be concerted additions. Thus, we believe a concerted mechanism with a transition state possessing some sensitivity to polar effects of the olefin would be consistent with our data. *N*-Alkylhemin formation could be considered a [3+2] cycloaddition of the olefin and the N—Fe=O group. Concerted mechanisms for N-alkylation and epoxidation would also be consistent with the reported oxenoid character of the iron–oxo.[34]

Discussion of Possible Mechanisms for Epoxidation and N-Alkylation. Any mechanisms proposed for N-alkylation and epoxidation in this system must account for (1) the high degree of regiospecificity and stereospecificity of *N*-alkylhemin formation, (2) the dependence of partition numbers on the structure of the terminal olefin, (3) the insensitivity of the partition numbers to changes in reaction conditions (olefin concentration, catalyst concentration, additives, and the solvent), (4) the relative reactivities of olefins in epoxidation and N-alkylation, and (5) the formation of phenylacetaldehydes for the styrenes.

The stereochemistry and relative insensitivity of the branching to the electronic properties of either the catalyst or olefin suggest

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epoxidation and N-alkylation are concerted reactions, but the observation of substituted phenylacetaldehydes requires a separate, parallel reaction involving an acyclic intermediate. Aldehyde formation is a significant pathway in the epoxidation of styrenes (5–10% of the turnovers) whereas N-alkylation occurs in only 0.01% of the turnovers. It is possible that epoxidation and N-alkylation are concerted reactions but that aldehyde formation proceeds by an acyclic intermediate. However, since aldehyde formation also exhibits an insensitivity to the electronic properties of para-substituted styrenes, it is likewise possible that all three reactions—epoxidation, N-alkylation, and rearrangement to aldehydes—could proceed through a short-lived acyclic intermediate. Such an intermediate could exhibit retention of olefin stereochemistry in epoxidation and N-alkylation if its lifetime was short compared to the rate of bond rotation. The transition state for such an intermediate, however, would have to exhibit very little bond formation, an early transition state, to account for the relatively narrow range of the partition numbers, only a factor of 100, and the modest sensitivity to the electronic properties of the olefin.

For a concerted addition, the dependence of partition numbers on the nature of the alkene could be due to steric and modest electronic effects on the transition state for olefin addition to the oxo. Groves and co-workers have considered several transition states for olefin epoxidation by iron porphyrins and iodosylbenzene.[35] The geometry in **2A** (Figure 4) was proposed since it was consistent with the high *cis*-olefin/*trans*-olefin selectivities exhibited by the hemin catalysts. In this transition state the double bond of the alkene is parallel to the plane of the porphyrin and perpendicular to the iron–oxo axis. The angle of approach of the alkene would depend on the steric properties of the alkene and the hemin catalyst. Transition-state geometry **2B** (Figure 5) has the p orbitals of the double bond in the same plane as the iron–oxo and pyrrolic nitrogen. Groves suggested that this approach was less favorable than **2A** for epoxidation since a competition between cycloheptene and methylenecyclohexane was observed to yield a 4.5/1 ratio of epoxides. With chromic acid the two olefins are epoxidized at the same rate. Either epoxide or *N*-alkylhemin formation could occur from transition-state geometry **2B**, whereas epoxide would be the product from **2A**. Both steric and electronic effects could govern the ability to proceed via transition-state **2B** versus **2A** and lead to the observed range of the partition numbers.

In addition to phenylacetaldehyde formation, there is considerable evidence for acyclic intermediates in other oxidations by the model systems and by P-450. Rearrangements during the epoxidation of norbornene, *trans*-cyclooctene, hexamethyl(Dewar benzene), a caged diene, and *cis*-stilbene have been reported by Traylor and Bruice and their co-workers.[21,36] They have proposed either direct formation of acyclic intermediates **3** and **4** or electron transfer to form olefin–radical cation **5** followed by trapping to form an acyclic intermediate as possible mechanisms for these reactions. Acyclic intermediates have also been invoked for P-450 for the rearrangements that occur during the metabolism of aromatic substrates (NIH shift), trichloroethylene, vinylidene chloride, and *trans*-1-phenyl-1-butene.[37] Ortiz de Montellano has also proposed an acyclic intermediate for the formation of *N*-alkylhemins by P-450.[38]

If epoxide, aldehyde, and *N*-alkylhemin formation proceed through acyclic intermediates **3** or **4**, then the acyclic intermediates must be short-lived and their formation must be exothermic with an early transition state. The stabilities of acyclic cation **3A** and radical **4A** (Figure 3) increase for the series of olefins vinylcyclohexane (R = cyclohexyl, R = H) < methylenecyclohexane [R–R′ = $(CH_2)_5$] < styrene (R = C_6H_5, R′ = H) since the cation or radical center is secondary, tertiary, and benzylic, respectively, for the three olefins. In contrast, the stabilities of cation **3B** or radical **4B** change very little since they are primary cations or radicals and are isolated from the substitution by a carbon atom. Thus, the energy differences between the **A** and **B** regioisomers increase in the direction we observe for the partition numbers for the three olefins: vinylcyclohexane (230) < methylenecyclohexane (830) < styrene (10 000). Although this appears to support an acyclic intermediate, the magnitude of the differences in the partition numbers is less than would be expected on the basis of relative stabilities of the intermediates. For example, the partition number for styrene is only 50-fold larger than that for the essentially isosteric vinylcyclohexane, yet the energy difference between a secondary and a benzylic radical is about 10 kcal/mol.[39] If the ratio of epoxidation to N-alkylation reflected the relative stabilities of **4B** for the two olefins, then the partition number for styrene would be expected to be $\sim 10^6$-fold larger than that for vinylcyclohexane. The energy differences would be even greater for cationic intermediates **3A** and **3B**. The "small" 50-fold difference between styrene and vinylcyclohexane demands that the transition states for the formation of the two acyclic intermediates **4A** and **4B** cannot differ by any more than 2–3 kcal/mol. Such a small energy difference would only be possible if the formation of the acyclic intermediate was exothermic with an early transition state.

The insensitivity of partition numbers to the electronic properties of the para-substituted styrenes and of the hemin catalysts is also consistent with an early transition state. Less than a factor of 2 difference (Table V) in the partition numbers of *p*-(trifluoromethyl)styrene and styrene is observed, yet the stabilities of the regioisomers of intermediates **3** and **4** should be very different. The lack of a significant change in the partition numbers for the electron-poor hemins Fe(PFP)Cl and Fe(NOCP)Cl compared to Fe(OFP)Cl and Fe(OCP)Cl is also consistent with an early transition state, since the branching should be less sensitive to the nucleophilicity of the pyrrolic nitrogens.

Traylor and co-workers have presented evidence for olefin–cation-radical intermediate **5**, which can collapse to acyclic cations **3** or radicals **4**. The rearrangement of hexamethyl(Dewar benzene) and a caged diene and the formation of both *exo*- and *endo*-epoxides of norbornene are consistent with the initial formation of **5** followed by trapping of the radical cation by the oxo.[19,21] They have suggested that **5** may be a common intermediate for rearrangements and epoxide formation. The olefin competitions in our study, however, show similar rate constants for the epoxidation of olefins with very different electronic properties. The ionization potentials for vinylcyclohexane and styrene differ by ~1 eV, yet the ratio of epoxides in a 1/1 competition is 1.5/1 favoring vinylcyclohexane oxide (Table IX). Methylenecyclohexane and styrene differ by ~0.5 eV, yet a 1.2/1 ratio of methylenecyclohexane oxide to styrene oxide is observed. If electron transfer to form an olefin–radical-cation intermediate occurs, then the electron transfer must be exothermic and the transition state early, to explain the lack of selectivity between olefins.

Sawyer and co-workers have reported the preparation of a high-valent oxo, formulated as $[Fe^{II}(OCP\ radical\ cation)(O)]^+$, by the oxidation of $Fe(OCP)ClO_4$ with mCPBA, PFIB, or O_3 at −35 °C.[34] The reduction potential for this species was reported to be +1.27 V vs SCE. A similar high-valent species was observed as a transient by Gold and co-workers.[40] The oxidation potentials for the alkenes used in our study are all positive of the potential reported by Sawyer: +1.9 V for 4-methylstyrene[41] and +2.8 V for 1-octene[42] (vs SCE). Considering the very positive redox potentials for the 1-alkenes, the formation of an olefin–radical cation should be an endothermic process and epoxide formation

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should be more sensitive to the alkene redox potential than we observe. For this reason we believe a discrete olefin–radical-cation intermediate is inconsistent with our data.

Bruice and co-workers have probed the mechanism of hemin-catalyzed oxidations with *cis*-stilbene and a radical clock as substrates.[36,43] They observed significant isomerization and rearrangement of *cis*-stilbene consistent with an acyclic intermediate.[36] The lifetime of possible acyclic radicals or olefin–radical cations was probed with a substituted 1,2-dicyclopropylethylene. No oxygen-containing rearrangement products were detected; Bruice argued that this requires the rate of closure to epoxide to be $\geq 2 \times 10^{12}$ s^{-1}, which suggests that a neutral radical like **4** is not a likely intermediate. If the observed nonpolar rearrangement products were due to an olefin–radical-cation **5**, then the rate of epoxide formation from such an intermediate would have to be $\geq 2 \times 10^{11}$ s^{-1}. With such a rate constant Bruice has argued the free energy of an olefin–radical cation would approach that of the transition state for epoxide formation.[43]

Oxametallacycles have been suggested as possible intermediates in olefin epoxidation and in the formation of *N*-alkylhemins. Sharpless and co-workers first proposed an oxametallacyclic intermediate for the epoxidation of olefins by a chromium–oxo and for the cis hydroxylation of olefins by OsO_4.[44] For the latter reaction a concerted addition to the two oxo ligands was considered less favorable since the oxo–oxo distance is approximately 2 Å. For the formation of *N*-alkylhemins an oxo–nitrogen distance of more than 2 Å is expected on the basis of the Fe–N distance from the crystal structure of Fe(TPP)Cl[14a] and the Fe=O distance of 1.64 Å from the study of horseradish peroxidase compound I.[45] Distortions of the porphyrin and movement of the iron atom, however, could significantly decrease the nitrogen–oxo distance; thus, a concerted mechanism is not excluded.

We previously reported kinetic evidence that was consistent with the reversible formation of an olefin–oxo intermediate, which we proposed to be an oxametallacycle.[13,22] In the preceding paper we discussed alternative explanations for these kinetic observations that do not require the presence of a reversibly formed intermediate. Despite the absence of kinetic evidence for an intermediate, an oxametallacycle should still be considered as a possible intermediate for olefin epoxidation and N-alkylation.[1b,13,18,22] A metallacyclic intermediate could have two regioisomers, **6A** and **6B**. Either **6A** or **6B** could lead to epoxide, but iron to nitrogen migration from **6B** would be required for the formation of the primary *N*-alkylhemins we[1b] and Traylor[17] have isolated. The secondary *N*-alkylhemins observed by Mansuy and co-workers could result from isomer **6A**.[18] The severe steric interactions for a metallacycle, as reported by Bruice,[7b] make this pathway unlikely for the internal olefins and the hindered catalysts. An oxametallacycle would be consistent with the modest electronic effects and the high stereo- and regiospecificity we have observed, but we would have expected the steric properties of the catalyst and olefin to have had a greater effect on the partition numbers.

Several characterized oxametallacyclobutanes are now known, and none exhibit any ability to eliminate to form epoxide.[46] Bergman and co-workers have isolated an oxametallacycle from the deprotonation of $Cp^*Ir(CH_2C(CH_3)_2OH)(Cl)(P(CH_3)_3)$.[46a] Whinnery and Bercaw have reported the formation of stable metallaoxetanes $Cp^*_2Ta(CH_2CH(R)O)(CH_3)$ through the reaction of $Cp^*_2Ta(=CH_2)(CH_3)$ with benzaldehyde or *p*-formaldehyde. They have also reported that the deoxygenation of epoxides, the microscopic reverse of olefin epoxidation, by $Cp^*_2Ta(=X)(H)$ [X = CH_2, C_6H_4, and CHC_6H_5] to form $Cp^*_2Ta(=O)(XH)$ proceeds with retention of stereochemistry and without any evidence for an oxametallacyclic intermediate.[46c] An oxametallacycle has been characterized crystallographically from the reaction of a platinum(0) complex and tetracyanoethylene oxide.[47a] The presence of an oxametallacycle in the reaction between iron atoms and ethylene oxide in an argon matrix has been interpreted from FTIR studies.[47b] Dolphin has shown that a β-hydroxy-substituted alkyliron(III) porphyrin, two oxidation states below a putative iron(V) oxametallacyclic intermediate, decomposes in the presence of base to form an epoxide.[47c] The only evidence for an organometallic intermediate in olefin epoxidation by cytochrome P-450, presumably an iron–alkylidene formed via an oxametallacycle, follows from the observation by Groves and his colleagues of a 95% loss of the deuterium label when (*E*)-1-deuteriopropylene was epoxidized by reconstituted $P\text{-}450_{LM2}$ in H_2O.[48]

It is tempting to try to account for all of the products of metalloporphyrin-catalyzed olefin oxidations by a single, unifying mechanism, but parallel reaction pathways with different mechanisms must also be considered. Comparisons between metalloporphyrin epoxidation systems must be made with care since the mechanism may change depending on the nature of the metal, the presence and type of axial base, the steric and electronic properties of the porphyrin, the nature of the oxygen atom donor, the reaction conditions, and the nature of the olefin substrate. Mechanisms ranging from a fully concerted reaction to a stepwise reaction involving an initial electron transfer may all be possible depending on the nature of the system. For olefin epoxidation and heme N-alkylation we favor a concerted mechanism; we cannot exclude, however, the formation of a short-lived, acyclic intermediate. In addition to providing information about the mechanisms of these reactions, our studies have shown that the synthetic hemins are viable models for the suicide inactivation of P-450 by terminal olefins and have provided insight into the behavior of the enzyme.

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; the styrenes were distilled and used immediately. *p*-(Trifluoromethyl)styrene was prepared from trifluoro-*p*-tolualdehyde according to the procedure of Bercaw and co-workers.[49] The porphyrins H_2OFP, H_2TMP, $H_2(TpClPP)$, and $H_2(OCP)$ were prepared either by the Rothemund method or, more recently, by the method of Lindsey and co-workers.[50] H_2PFP was purchased from Aldrich. Epoxide standards were prepared by *m*-chloroperoxybenzoic acid (mCPBA) oxidation of the olefins.

Deuterated Alkenes. *trans*-1-Deuterio-3-methyl-1-butene was prepared from 3-methyl-1-butyne via hydroboration with 9-BBN.[51] A solution of 9-BBN (0.1 mol) in THF was added by cannula to the alkyne (0.2 mol) in THF at 0 °C over 30 min. After complete addition the solution was stirred at 0 °C for 12 h. The solvent and excess alkyne were then removed under vacuum. Treatment of the solid with acetic acid-d_1 (prepared from D_2O and acetic anhydride) at 5 °C for 3 h and distillation yielded *trans*-1-deuterio-3-methyl-1-butene (>95% trans-d_1).

cis-1-Deuterio-3-methyl-1-butene was prepared from 1-deuterio-3-methyl-1-butyne. Deprotonation of 3-methyl-1-butyne by *n*-butyllithium (1.1 equiv) followed by deuteration with a solution of D_2O in THF at 0 °C yielded the alkyne-d_1. Hydroboration with 9-BBN, as above, followed by protonation with glacial acetic acid and distillation yielded *cis*-1-deuterio-3-methyl-1-butene (>95% cis-d_1).

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Methods. ^{1}H NMR spectra were recorded either on a Varian XL-400 or on a Nicolet NMC300. A Cary 219 spectrophotometer or a Hewlett-Packard 8450A diode array spectrophotometer (2-nm resolution) was used for electronic spectra. Elemental analyses were obtained from Chemical Analytical Services, University of California at Berkeley, Berkeley, CA. Mass spectra were recorded at the Mass Spectrometry Resource, School of Pharmacy, University of California at San Francisco, San Francisco, CA.

Analyses of reaction mixtures were performed on a Hewlett-Packard HP-5880A gas chromatograph equipped with nitrogen carrier gas and FID detector. The packed columns used were either a 10% OV-101 on Chromosorb W-HP 80/100 or a 10% PEG-20M on Supelcoport 80/100, each 6 ft in length.

A Princeton Applied Research wave generator (Model 175) and potentiostat (Model 173) were used for electrochemical measurements. All electrochemical measurements were performed in an inert-atmosphere drybox. Electrolyte solutions were prepared by dissolving tetrabutylammonium chloride in methylene chloride (distilled from P_2O_5 and degassed) to make a 0.2 M solution; this solution was passed through alumina (neutral, activity I). The small-volume electrochemical cell (2–3 mL) consisted of a platinum rotating disk electrode (EDI-Tacussel) placed between the auxillary (platinum wire) and reference (silver wire) electrodes. Both the auxillary and reference electrodes were isolated from bulk solution by a vycor fritted chamber. All measured $E_{1/2}$ values were reversible. At the end of each electrochemical experiment a few milligrams of ferrocene was added to the porphyrin solution to reference $E_{1/2}$ values to the ferrocenium couple.

H_2OBP. This porphyrin, originally prepared by Bruice and co-workers[7b] by a Rothemund condensation, was prepared under the conditions of Lindsey and co-workers.[50b] Because the extreme insolubility of this porphyrin made its manipulation difficult, it was handled in its trifluoroacetic acid protonated form. After chromatography of the crude porphyrin on silica with CH_2Cl_2, trifluoroacetic acid (5 mL), and water (20 mL) were added to the eluent and the solvent was removed under vacuum. After filtration of the aqueous suspension and washing with water, 240 mg of crystals of H_2(OBP) (0.176 mmol, 9% yield) was dried to remove residual CF_3COOH.

Anal. Found for H_2(OBP): C, 42.52; H, 1.82; N, 4.36. Calcd: C, 42.42; H, 1.78; N, 4.5. UV–vis [λ_{max}, nm (CH_2Cl_2)]: 406 (sh), 422 (Soret), 516, 542 (sh), 592. ^{1}H NMR ($CDCl_3$/CF_3COOD): 8.58 (s, 8 H, β-pyrrolic), 8.10 (d, 8.4 Hz, 8 H, *meso*-aryl), 7.64 ppm (t, 8 Hz, 4 H, *meso*-aryl).

Preparation of 2-Nitro-5,10,15,20-tetrakis(2,6-dichlorophenyl)-21*H*-23*H*-porphine [H_2NOCP]. (A) Preparation of Zn(NOCP). The preparation of Zn(NOCP) followed Crossley and co-workers' procedure for the nitration of Cu(TPP).[52] In a 500-mL round-bottom flask was added gaseous nitrogen dioxide (2.2 equiv) via gas-tight syringe to a solution of 125 mg of Zn(OCP) (0.131 mmol) in 250 mL of CH_2Cl_2; a color change from pink to green was instantaneous. After being stirred for 2 h at room temperature, the solution was reduced to dryness and chromatographed on alumina (neutral, activity I, deactivated 5% (w/w) with water) with 1/1 CH_2Cl_2/toluene to 2/1 CH_2Cl_2/toluene eluent. All products except for Zn(NOCP) remained at the column origin. Addition of cyclohexane to the eluent and removal of the solvent yielded 93 mg of Zn(NOCP) (0.0932 mmol) in 71% yield. UV–vis [λ_{max}, nm (CH_2Cl_2)]: 430 (Soret), 564. ^{1}H NMR ($CDCl_3$): 8.99 (s, 1 H, β-pyrrolic, nitro substituted), 8.68–8.60 (m, 6 H, β-pyrrolic), 7.78–7.60 ppm (m, 12 H, *meso*-aryl).

(B) **H_2NOCP.** Demetalation of Zn(NOCP) (66.8 mg, 0.0669 mmol) by treatment with trifluoroacetic acid for 1 h followed by workup with ammonium hydroxide and crystallization from CH_2Cl_2/heptane yielded 44.6 mg (71%) of H_2(NOCP). Anal. Found for H_2NOCP: C, 56.26; H, 2.39; N, 7.28. Calcd: C, 56.50; H, 2.26; N, 7.49. UV–vis [λ_{max}, nm (CH_2Cl_2)]: 425 (Soret), 522, 562. ^{1}H NMR ($CDCl_3$): 8.90 (s, 1 H, β-pyrrolic, nitro substituted), 8.76–8.70 (m, 4 H, β-pyrrolic), 8.53 (s, 2 H, β-pyrrolic), 7.81–7.70 (m, 12 H, *meso*-aryl), −2.49 ppm (br s, 2 H, NH).

General Procedure for the Preparation of Fe(Por)X. Each Fe(Por)Cl was prepared by metalation with $FeBr_2$ in refluxing dimethylformamide or 1,2-dichlorobenzene containing a small amount of 2,4,6-collidine as a base. The progress of the reaction was followed by thin-layer chromatography (TLC); when metalation was complete, the solvent was removed at reduced pressure and the remaining solid was dissolved in CH_2Cl_2 and filtered to remove iron salts. The CH_2Cl_2 solution was then chromatographed on alumina with 5% methanol/CH_2Cl_2. The eluent was stirred with 5% HCl (for X = Cl) and dried over NaCl for 2 h; Fe(OCP)Br was similarly prepared by stirring with 5% HBr and drying over NaBr. The Fe(Por)X were recrystallized by layering heptane or cyclohexane onto a CH_2Cl_2 solution of the Fe(Por)X. Metathesis of Fe(OCP)Cl with $AgBF_4$ in refluxing benzene under inert atmosphere yielded Fe(OCP)BF_4, which was recrystallized from CH_2Cl_2/acetonitrile. All Fe(Por)X were dried at 100 °C (10^{-5} mmHg) for several hours.

Fe(OBP)Cl.[7b] 81% yield. Anal. Found for Fe(OBP)Cl: C, 40.37; H, 1.89; N, 4.03. Calcd: C, 39.58; H, 1.51; N, 4.20. UV–vis [λ_{max}, nm (log ϵ) (CH_2Cl_2)]: 421 Soret (4.91), 511 (4.00).

Fe(OCP)Cl.[6a] UV–vis [λ_{max}, nm (log ϵ) (CH_2Cl_2)]: 368 (4.71), 418 Soret (5.06), 509 (4.13), 581 (3.67), 648 (3.68).

Fe(OCP)Br. UV–vis [λ_{max}, nm (log ϵ) (CH_2Cl_2)]: 388 sh (4.81), 419 Soret (4.94), 512 (4.14), 586 (3.60), 654 (3.59).

Fe(OCP)BF_4. UV–vis [λ_{max}, nm (log ϵ) (CH_2Cl_2)]: 412 Soret (5.22), 478 sh (4.24), 594 (4.05).

Fe(NOCP)Cl. 70% yield. Anal. Found for Fe(NOCP)Cl: C, 53.13; H, 2.27; N, 6.76. Calcd: C, 51.58; H, 1.87; N, 6.84. UV–vis [λ_{max}, nm (log ϵ) (CH_2Cl_2)]: 356 (4.68), 428 Soret (4.94), 510 (4.11).

Fe(OFP)Cl.[7a] UV–vis [λ_{max}, nm (log ϵ) (CH_2Cl_2)]: 366 (4.75), 412 Soret (5.05), 505 (4.12), 576 (3.66), 638 (3.69).

Fe(PFP)Cl.[6b] UV–vis [λ_{max}, nm (log ϵ) (CH_2Cl_2)]: 350 (4.80), 411 Soret (5.08), 504 (4.09), 629 (3.77).

General Procedure for Preparation of Zn(Por). Zn(TpClPP) was prepared in chloroform with an ethanolic solution of zinc acetate. The remaining Zn(Por) were prepared in refluxing 1,2-dichlorobenzene with anhydrous zinc chloride and 2,4,6-lutidine.

Zn(OBP). ^{1}H NMR (CD_2Cl_2): 8.75 (s, 8 H), 8.06 (d, 8.4 Hz, 8 H), 7.58 ppm (t, 8.4 Hz, 4 H). UV–vis [λ_{max}, nm (CH_2Cl_2)]: 402 sh, 424 Soret, 432 sh, 556, 564.

Zn(NOCP). ^{1}H NMR ($CDCl_3$): 8.99 (s, 1 H), 8.68–8.60 (m, 6 H), 7.78–7.60 ppm (m, 12 H). UV–vis [λ_{max}, nm (CH_2Cl_2)]: 430 Soret, 564.

Zn(OFP). ^{1}H NMR ($CDCl_3$): 8.97 (s, 8 H), 7.78 (m, 4 H), 7.38 ppm (t, 8 H). UV–vis [λ_{max}, nm (CH_2Cl_2)]: 414 Soret, 544.

Zn(PFP). ^{1}H NMR ($CDCl_3$): 9.05 ppm (s). UV–vis [λ_{max}, nm (CH_2Cl_2)]: 413 Soret, 543, 577.

Zn(TpClPP). ^{1}H NMR ($CDCl_3$): 8.93 (s, 8 H), 8.12 (d, 8.2 Hz), 7.73 ppm (d, 8.2 Hz). UV–vis [λ_{max}, nm (CH_2Cl_2)]: 419 Soret, 547.

Procedure for Kinetics of Epoxidation and N-Alkylation. The procedure used to determine partition numbers and apparent rate constants was the same as that previously reported.[1a]

Competition Experiments. Competitions between pairs of olefins were performed by preparing an equimolar solution by weight of the two alumina-purified olefins (styrenes were distilled) and dissolving the mixture in CH_2Cl_2 with an internal standard. For the iodosylbenzenes this solution was added to the solid oxidant. Sufficient Fe(Por)Cl catalyst was added to ensure all epoxidation was performed by Fe(Por)Cl and not an *N*-alkylhemin. Soon after addition of the Fe(Por)X catalyst (2-mL total volume), an aliquot was removed and quenched in a dilute PPh_3 solution. When the oxidant had been consumed in the reaction vial, 100 μL of a 1 M PPh_3 solution was added and the reaction was analyzed by gas chromatography. Early reaction aliquots provided the same epoxide ratio as the quenched reaction vials.

For the hypochlorite epoxidations the olefins, internal standard, and catalyst were combined in CH_2Cl_2 (total volume 2 mL), and a LiOCl solution (1 mL, ~0.3 M) was added. After the mixture was stirred vigorously for a few minutes, an aliquot was removed and quenched; the vial was then allowed to stir for 1 h, at which time the CH_2Cl_2 layer was removed and quenched.

General Procedure for Isolation of *N*-Alkylporphyrins. A solution of 10–20 mg of Fe(Por)Cl and 1-butene (2–4 M) in 50 mL of CH_2Cl_2 at 0 °C was stirred as solid PhIO or PFIB was added in small portions (25–50 mg). The progress of N-alkylation was followed by TLC (SiO_2, 5% methanol/CH_2Cl_2). When a significant green spot was observed, approximately 50% or greater of added Fe(Por)Cl, the solvent was removed at reduced pressure. The hemin was then demetalated with either 5% HCl/methanol at 50 °C for 1 h or 5/1 acetic anhydride/HCl at 5 °C for 12 h. The green acidic solution was neutralized with ammonium hydroxide at 0 °C and extracted with CH_2Cl_2. Chromatography (1–5% tetrahydrofuran/CH_2Cl_2 for Fe(OFP)Cl adducts or 1/1 toluene/hexane for Fe(PFP)Cl adducts) yielded the free base *N*-alkylporphyrins below.

21-(2-Acetoxybutyl)-5,10,15,20-tetrakis(pentafluorophenyl)-23*H*-porphine and 21-(2-Hydroxybutyl)-5,10,15,20-tetrakis(pentafluorophenyl)-23*H*-porphine. These adducts were isolated with PhIO as the oxidant and under the acetic anhydride/HCl or HCl/methanol demetalation conditions, respectively.

(A) 2-Acetoxybutyl. Mass spectral analysis showed (M + H)$^+$ at 1089 (calcd M$^+$ 1088.13). ^{1}H NMR (C_6D_6): −4.04 (dd, J_{AB} = 15 Hz, J_{AX} = 5.1 Hz, 1 H, NCH_AH$_B$CH$_X$(OAc)CH$_2$CH$_3$), −3.91 (dd, J_{AB} = 15 Hz, J_{BX} = 5.1 Hz, 1 H, H_B), −2.1 (br s, 1 H, NH), −1.2 (m, 1 H, CH_2), −1.00 (t, 7.4 Hz, 3 H, CH_3), −0.6 (m, 1 H, CH_2), 7.57 (d, 4.8 Hz, 1 H, β-pyrrolic), 7.66 (d, 4.7 Hz, 1 H, β-pyrrolic), 8.67–8.55 (m, 4 H, β-

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pyrrolic), 8.75 ppm (pair of d, 1.9 Hz). Impurities in the 0.8–2.0 ppm region prevented assignment of the acetyl and H_X signals.

(B) 2-Hydroxybutyl. Mass spectral analysis indicated a $(M + H)^+$ at 1047 (calcd M^+ 1046). UV-vis [λ_{max}, nm]: 426, 518, 533, 604. ^1H NMR (C_6D_6): −4.17 (dd, J_{AX} = 4.3 Hz, J_{AB} = 15 Hz, 1 H, $NCH_AH_BCH_X(OH)CH_2CH_3$), −4.07 (dd, J_{BX} = 8.6 Hz, J_{AB} = 15 Hz, 1 H, H_B), −2.06 (br s, 1 H, NH), −1.6 (m, 1 H, CH_2), −1.2 (m, 1 H, CH_2), −0.9 to −1.0 (d and t, 4 H, OH and CH_3), 0.62 (br s, 1 H, H_X), 7.55 (d, 4.6 Hz, 1 H, β-pyrrolic), 7.58 (d, 4.8 Hz, 1 H, β-pyrrolic), 8.57 (d, 4.9 Hz, 1 H, β-pyrrolic), 8.61 (d, 4.8 Hz, 1 H, β-pyrrolic), 8.73–8.66 ppm (unresolved pair of doublet of doublets and singlet, 4 H, β-pyrrolic).

21-(2-Acetoxybutyl)-5,10,15,20-tetrakis(2,6-difluorophenyl)-23*H*-porphine and 21-(2-Hydroxybutyl)-5,10,15,20-tetrakis(2,6-difluorophenyl)-23*H*-porphine. The *N*-alkyl hemin was demetalated with 10% HCl/methanol at 50 °C for 1 h. Treatment of the product with acetic anhydride (5 mL) and 1 mL of concentrated HCl yielded the acetylated porphyrin after neutralization and chromatography. The isolated product was free any alkyl impurities when $PhIO_2$ was used as the oxidant.

(A) 21-(2-Acetoxybutyl). Mass spectral analysis showed $(M + H)^+$ at 873 (calcd M^+ 872.2). UV-vis [λ_{max}, nm (CH_2Cl_2)]: 424, 517, 553, 605. ^1H NMR ($CDCl_3$): −4.34 (dd, 1 H, J_{AB} = 15 Hz, J_{AX} = 3.7 Hz, $NCH_AH_BCH_X(OCOCH_3)CH_2CH_3$), −4.20 (dd, 1 H, J_{AB} = 15 Hz, J_{BX} = 3.7 Hz, H_B), −2.32 (s, 1 H, NH), −1.22 (m and t, 4 H, CH_2CH_3), −0.56 (m, 1 H, CH_2), 1.42 (s, 3 H, acetate), 1.77 (br m, 1 H, H_X), 7.22–7.47 (m, 8 H, *meso*-aryl), 7.73–7.77 (m, 4 H, *meso*-aryl), 7.87 (s, 2 H, β-pyrrolic), 8.63, 8.60, 8.53, 8.49 (4 d, 4 H total, β-pyrrolic), 8.85 ppm (s, 2 H, β-pyrrolic).

(B) 21-(2-Hydroxybutyl). UV-vis [λ_{max}, nm (CH_2Cl_2)]: 425, 516, 552, 605. ^1H NMR ($CDCl_3$): −4.27 to −4.30 (m, 2 H, $NCH_2CH(OH)CH_2CH_3$), −2.21 (s, 1 H, NH), −1.26 to −1.28 (m, 1 H, CH_2), −0.81 to −0.86 (t and m, 4 H, CH_2CH_3), −0.54 (quartet, 1 H, OH), 0.67 (m, 1 H, CH(OH)), 7.24–7.43 (m, 8 H, *meso*-aryl), 7.73–7.78 (m, 4 H, *meso*-aryl), 7.83 (s, 2 H, β-pyrrolic), 8.50 (m, 2 H, β-pyrrolic), 8.61 (m, 2 H, β-pyrrolic), 8.83 ppm (s, 2 H, β-pyrrolic).

Yield of 21-(2-Hydroxy-2-cyclohexylethyl)-5,10,15,20-tetrakis(2,6-dichlorophenyl)-23*H*-porphine. A solution of Fe(OCP)Cl (14 μmol) in CH_2Cl_2 containing 2 M vinylcyclohexane and dodecane as an internal standard was stirred at room temperature, and 350 equiv of PFIB was added in small portions. On consumption of the oxidant essentially all the catalyst was present as a green pigment by TLC as above. Gas chromatographic analysis of the reaction indicated 280 equiv of epoxide was formed (86% yield based on PFIB added). The solvent was removed at reduced pressure, and the porphyrin was dissolved in 3/1 acetic acid/HCl and stored at 5 °C for 24 h. After the solution was neutralized with NH_4OH at 0 °C and extracted with CH_2Cl_2, the product was chromatographed on flash silica (CH_2Cl_2 to 3% diethyl ether/CH_2Cl_2). Only one migrating band was observed; the dark material at the column origin could only be eluted with methanol/CH_2Cl_2. The yield was 70% based on starting catalyst. By ^1H NMR the isolated compound was similar to that of 3-methyl-1-butene, which we previously reported.[1b] ^1H NMR ($CDCl_3$): −4.40 (dd, 1 H), −4.15 (dd, 1 H), −2.3 to −2.4 (m, 1 H), −2.1 (br s, 1 H), −1.65 to −1.7 (br m, 2 H), −1.1 to −1.2 (br s, 1 H), −0.54 (d, 1 H), −0.15 to −0.35 (br m, 4 H), 0.4–0.0 (m, 3 H), 7.5–8.0 (m, 14 H), 8.37–8.50 (4 d, 4 H), 8.75 ppm (s, 2 H).

Stereochemistry of Heme N-Alkylation. The *N*-alkylporphyrins formed during the epoxidation of deuterated 3-methyl-1-butene by Fe(OCP)Cl/PFIB were isolated by demetalation with 3/1 acetic acid/HCl. The deuterated *N*-(2-hydroxy-3-methylbutyl) substituted porphyrins were analyzed by ^1H NMR and mass spectrometry. The ^1H NMR spectra of both *cis*- and *trans*-1-deuterio-3-methyl-1-butene adducts resembled the spectrum for the protio adduct and differed only in the −4 to −4.5 ppm region as we previously reported.[1b] Mass spectra of the deuterated adducts exhibited a molecular ion of $(M + H)^+$ at 978 compared to the protio-olefin adduct molecular ion $(M + H)^+$ of 977.

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Supplementary Material Available: Tables (1S–3S) showing partition numbers for individual experiments with three olefins (vinylcyclohexane, methylenecyclohexane, and styrene) and with the five hemin catalysts whose averages are reported in Table III (3 pages). Ordering information is given on any current masthead page.

Chemistry of Tricarbonyl Hemiketals and Application of Evans' Technology to the Total Synthesis of the Immunosuppressant (−)-FK-506

Todd K. Jones,* Robert A. Reamer,* Richard Desmond, and Sander G. Mills*

Contribution from the Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065-0900. *Received September 29, 1989. Revised Manuscript Received December 7, 1989*

Abstract: Details of model studies probing the chemistry of the tricarbonyl region of FK-506 are presented, and their use in designing a successful route to this immunosuppressant is outlined. Applications of asymmetric oxazolidinone alkylation/aldol methodology to a convergent, highly flexible synthesis of the C_{10}–C_{18} fragment and to improvements in the preparation of the C_{20}–C_{34} segment are also discussed.

FK-506, **1**, isolated from *Streptomyces tsukubaensis* (no. 9993),[1] is a unique 21-member macrolactam that possesses exceptional biological activity[2] and an array of challenging structural features, in particular an unusual α,β-diketo amide hemiketal system. The immunosuppressive potency of **1** has been shown to be superior to that of cyclosporin A in the inhibition of delayed hypersensitivity responses in a variety of allograft transplantation

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