6.8–8.3 (9 H, m), CH_3, 2.00 (6 H, s).

8-[(4-Methylphenyl)amino]-1-naphthalenesulfonate (1, X = 4-CH_3): same procedure as that used for **1**, X = 3,5-$(CH_3)_2$; yield, 1%. ^1H NMR (Me_2SO-d_6) (ppm): NH, 10.56 (1 H, s), aromatic H, 7.0–8.3 (10 H, m), CH_3, 2.23 (3 H, s).

8-[(3-Methylphenyl)amino]-1-naphthalenesulfonate (1, X = 3-CH_3): reaction, 72 h at 160 °C; purification, chromatography on silica (elution: benzene–methanol), crystallized three times from water; yield 12%. ^1H NMR (in Me_2SO-d_6) (ppm): NH, 10.60 (1 H, s), aromatic H, 6.6–8.3 (10 H, m), CH_3, 2.24 (3 H, s).

8-[(4-Fluorophenyl)amino]-1-naphthalenesulfonate (1, X = 4-F): reaction, 24 h at 170°C. The yellow precipitate obtained after addition of HCl was recrystallized three times from water, yield 6%. ^1H NMR (Me_2SO-d_6) (ppm): NH, 9.3 (1 H, s), aromatic H, 7.1–8.3 (10 H, m).

8-[(4-Chlorophenyl)amino]-1-naphthalenesulfonate (1, X = 4-Cl): reaction, 72 h at 140 °C. The material which precipitated after addition of 10% HCl was freed from AmNS by dissolution in water. The product was isolated by evaporation of the filtrate and recrystallized from a small amount of water; yield 2.5%. ^1H NMR (Me_2SO-d_6) (ppm): NH, 10.73 (1 H, s), aromatic H, 7.1–8.3 (10 H, m).

8-[(4-Phenoxyphenyl)amino]-1-naphthalenesulfonate (1, X = 4-C_6H_5O): reaction, 48 h at 170 °C. After addition of 10% HCl, the mixture was extracted with chloroform, the $CHCl_3$ evaporated, and the residue chromatographed on silica (elution: benzene–methanol); the yellow product was crystallized three times from water, yield 18%. ^1H NMR (Me_2SO-d_6) (ppm): NH, 10.66 (1 H, s), aromatic H, 6.9–8.3 (15 H, m).

8-[(4-Methoxyphenyl)amino]-1-naphthalenesulfonate (1, X = 4-CH_3O): reaction 48 h at 150–160 °C. The precipitate obtained after treatment with 10% HCl was dissolved in aqueous $NaHSO_3$ (1.4 M):Na_2SO_3 (0.08 M). The solution was brought to pH 3.0 with HCl and the precipitate recrystallized from 10% NaOH, yield 10%. ^1H NMR (Me_2SO-d_6) (ppm): NH, 10.1 (1 H, s), aromatic H, 7.0–8.3 (10 H, m), 4-OCH_3, 3.72 (3 H, s).

8-(Phenylamino)-1-naphthalenesulfonate as the ammonium salt (1, X = H) was obtained from Merck. The purity of 8-(phenylamino)-1-naphthalenesulfonates was established by TLC on silica gel in two different solvent systems: benzene:methanol (60:40) and chloroform:methanol (60:40). The important spectroscopic properties are: IR (KBr) 3550–3350 (broad band), 1610, 1510, 1450, 1240, 1180, 1130, 1050, 840 cm^{-1}; UV (various solvents) four absorption bands at 375 nm (ϵ 6000–7000), 355 (sh) (5000–7000), 270 (16 000–18 000), and 220 (42 000–48 000).

8-(Methylphenylamino)-1-naphthalenesulfonate (3, X = H): prepared according to Corey et al.,[35] recrystallized from 10% NaOH. ^1H NMR (Me_2SO-d_6) (ppm): 6.2–8.6 (11 H, m), 2.9 (3 H, s). UV (dioxane) λ_{max} (ϵ_{max}): 365 nm (2100), 340 sh, 255 (16 000).

8-[Methyl(3,5-dimethylphenyl)amino]-1-methoxysulfonylnaphthalene (4). 8-[(3,5-Dimethylphenyl)amino]-1-naphthalenesulfonate (**1**, X = 3,5-$(CH_3)_2$) (0.25 g, 0.8 mmol) and 0.11 mL (1.2 mmol) of dimethyl sulfate in acetone (10 mL) were refluxed for 4 h. Sodium carbonate (0.2 g, anhydrous) and dimethyl sulfate (0.2 mL) were then added, and the mixture was refluxed for 20 h. The solvent was removed under vacuum, the residue extracted with chloroform, the solution dried (Na_2SO_4), and the solvent evaporated. The residue was chromatographed on silica (elution: chloroform), giving the product in 20% yield, mp 123 °C. ^1H NMR ($CDCl_3$) (ppm): 6.2–8.6 (9 H, m), 3.45 (3 H, s), 3.25 (3 H, s), 2.2 (6 H, s). UV (dioxane) λ_{max} (ϵ_{max}): 385 nm (1300), 285 (10 600), 255 (15 000).

8-[Methyl(3,5-dimethylphenyl)amino]-1-naphthalenesulfonate (3, X = 3,5-$(CH_3)_2$). **4** and 1 M KOH/CH_3OH were refluxed for 15 min; the solution was acidified with H_2SO_4/CH_3OH. The precipitate was filtered off, filtrate evaporated, and the residue recrystallized three times from water. ^1H NMR (Me_2SO-d_6) (ppm): 6.2–8.6 (9 H, m), 3.0 (3 H, s), 2.0 (6 H, s). UV (dioxane) (λ_{max} (ϵ_{max})): 365 nm (1950), 345 sh, 252 (14 000).

Spectroscopic Measurements. A Cary Model 17 spectrophotometer was used to measure absorption spectra. A Perkin-Elmer Hitachi MPF-4 spectrofluorimeter with a corrected spectra attachment and a digital integrator was used. Quinine sulfate in 0.1 N H_2SO_4 (ϕ_F = 0.55) was the reference standard for quantum yield measurements.

Fluorescence Lifetimes. Fluorescence decay times were measured by the single photon counting technique as described previously.[11] Solvents were obtained from Merck: dioxane was spectroscopic grade, 1,2-ethanediol "zur Analyse", and glycerol for fluorescence microscopy. The last was handled in a glove bag under dry nitrogen. Water was triple distilled.

Photochemistry. The ammonium salt of 8-(phenylamino)-1-naphthalenesulfonate (**1**, X = H) (0.15 g, 0.6 mmol) in methanol (100 mL, spectroscopic grade) was irradiated at 360 nm for 2 weeks in a Rayonet reactor. The solvent was evaporated and the residue chromatographed on alumina (elution: chloroform), yielding 14 mg (0.06 mmol) of 1-(phenylamino)naphthalene (**5**): UV (methanol) λ_{max} (ϵ_{max}) 338 nm (8700), 252 (17 500); fluorescence λ_{max} (ϕ_F) dioxane 408 nm (0.45), methanol 428 nm (0.22); ^1H NMR ($CDCl_3$) (ppm) 6.9–8.1 (11 H, m), 5.2 (1 H, br s).

Registry No. 1 (X = 3-CF_3), 86747-90-2; **1** (X = 3-Br), 67472-73-5; **1** (X = 3-Cl), 86747-91-3; **1** (X = 4-Cl), 86747-92-4; **1** (X = 3-OCH_3), 86747-93-5; **1** (X = H), 17966-20-0; **1** (X = 4-F), 86747-94-6; **1** (X = 3-CH_3), 86747-95-7; **1** (X = 3,5-$(CH_3)_2$), 86747-96-8; **1** (X = 4-CH_3), 86747-97-9; **1** (X = 4-OCH_3), 86747-98-0; **1** (X = OPh), 86747-99-1; **3** (X = H), 86748-00-7; **3** (X = 3,5-$(CH_3)_2$), 86748-01-8; **4** (X = 3,5-$CH_3)_2$), 86748-02-9.

Supplementary Material Available: Spectroscopic data in Tables III, IV, and V (3 pages). Ordering information is given on any current masthead page.

Aliphatic Hydroxylation Catalyzed by Iron Porphyrin Complexes

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Abstract: The hydroxylation of unactivated alkanes has been observed in a catalytic system containing iodosylbenzene and various iron porphyrins. The yields and distributions of products have been found to be sensitive to the peripheral substitution pattern of the porphyrin. The oxidation of cyclohexane with chloro(5,10,15,20-tetra-*o*-tolylporphyrinato)iron(III) [Fe(TTP)Cl] gave a 31% yield of cyclohexanol and 6% cyclohexanone based on iodosylbenzene. Two samples of Fe(TTP)ClCl with differing atropisomeric composition gave different product ratios. The hydroxylation of cycloheptane under these conditions and in the presence of bromotrichloromethane gave 24% cycloheptanol and 18% bromocycloheptane. Steric selectivity was observed by comparing the hydroxylation of *cis*-decalin with Fe(TPP)Cl, Fe(TTP)Cl, Fe(TNP)Cl, and Fe(TMP)Cl. The hydrogen-isotope effect for cyclohexane hydroxylation by Fe(TTP)Cl was found to be 12.9 ± 1. A mechanism for hydroxylation is proposed on the basis of these results that involves initial oxidation of the iron porphyrin, hydrogen atom abstraction from the alkane, and rapid collapse of this radical to give the product alcohol and to regenerate the iron(III) catalyst.

The heme-containing monooxygenase cytochrome P-450 is known to oxidize a wide variety of organic compounds.[1] Among the more biologically significant of these processes are O- and N-dealkylation, olefin and arene epoxidation, and steroid hy-

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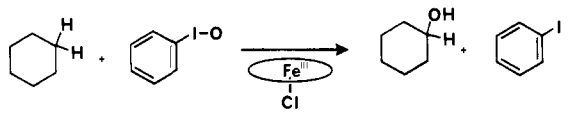
droxylation. the selective insertion of oxygen atoms into unactivated carbon–hydrogen bonds is particularly intriguing and has been without precedent in simple chemical systems. This consideration led us to investigate synthetic iron porphyrins as oxidation catalysts.

The seminal observation that alkyl hydroperoxides[2] and oxygen donors such as periodate[3] and iodosylbenzene[4] supported the cytochrome P-450 mediated oxidation of typical substrates has suggested the initial reduction of oxygen to a peroxide at the heme site. More speculative is the idea that the active oxygen species is a perferryl complex (FeO^{3+})[5] formed by oxygen atom transfer from the peroxide to iron(III). Alkyl hydroperoxides are known to react rapidly with iron(III) porphyrins, but all indications are that the metal complex serves only as an initiator of a free radical chain reaction of the hydroperoxide.[6] Accordingly, either the protoporphyrin IX of cytochrome P-450 has properties not mimicked by free porphyrins or the rapid free radical chain reactions of hydroperoxides in solution mask other modes of reactivity. This latter interpretation suggested iodosylbenzene as an oxygen source in metalloporphyrin-catalyzed oxygen-transfer reactions. Homolytic and heterolytic reaction paths of peroxides have long been recognized. While the reductive cleavage of hydrogen peroxide in acidic, aqueous media has been shown to generate hydroxyl radicals,[7] the same oxidant as well as peroxy acids decompose heterolytically in nonaqueous[8] solvents like acetonitrile. By contrast, the structure of iodosylbenzene indicates that it could be a peroxide mimic for heterolytic reactions but not for homolytic pathways. We describe here aliphatic hydroxylation reactions catalyzed by synthetic iron porphyrin complexes.[9,10]

Results and Discussion

The Hydroxylation Reaction. The reaction of iodosylbenzene with chloro(5,10,15,20-tetraphenylporphyrinato)iron(III) [Fe(TPP)Cl] at room temperature in the presence of excess cyclohexane was found to produce cyclohexanol and cyclohexanone in a ratio of 15:1 in a combined yield of 8%. Although quantitatively



inefficient, this oxidation showed that an unactivated carbon–hydrogen bond could be hydroxylated by this system under mild conditions. The insignificant amount of ketone is unusual for an oxidation reaction.

m-Chloroperoxybenzoic acid was a much less effective oxidant, producing only a 2% yield of cyclohexanol. Under these conditions, the deeply colored porphyrin solution became colorless, thus indicating oxidation of the porphyrin ring.

Replacing Fe(TPP)Cl with chloro(5,10,15,20-tetra-(*o*-tolyl-porphyrinato)iron(III) [Fe(TTP)Cl] in the oxidation of cyclohexane with iodosylbenzene caused a 3-fold increase in the amount of oxidized products formed. Treatment of Fe(TTP)Cl with aqueous sodium hydroxide followed by chromatography on basic alumina produced two bands of approximately equal proportions. The more mobile band, A, was red and was assigned a μ-oxo dimer structure structure since its absorption spectrum was similar to that of $(FeTPP)_2O$ (α,β band region 565, 610 nm). IR analysis revealed a band at 865 cm^{-1} which is diagnostic for iron μ-oxo compounds,[11] and treatment with HCl caused a conversion back to the spectrum of Fe(TPP)Cl.

The second chromatography band, B, was green, and its visible spectrum was unlike that of the starting chloride or the μ-oxo dimer. This product also was converted to Fe(TTP)Cl upon treatment with HCl. Apparently, part of the Fe(TTP)Cl treated with NaOH formed μ-oxo dimers, and the remaining portions formed the corresponding hydroxo complex, Fe(TTP)OH.[12]

Table I. Ferric Porphyrin–Iodosylbenzene Oxidations of Cyclohexane

ferric porphyrin	catalyst, mmol	iodosyl-benzene, mmol	cyclo-hexanol,[a] %	cyclo-hexanone,[a] %
Fe(TPP)Cl	0.044	0.4545	7.6	0.50
Fe(TTP)Cl mixture	0.058	0.455	22	2.4
Fe(TTP)Cl (B) band	0.040	0.455	31	6

[a] Yield is based on iodosylbenzene.

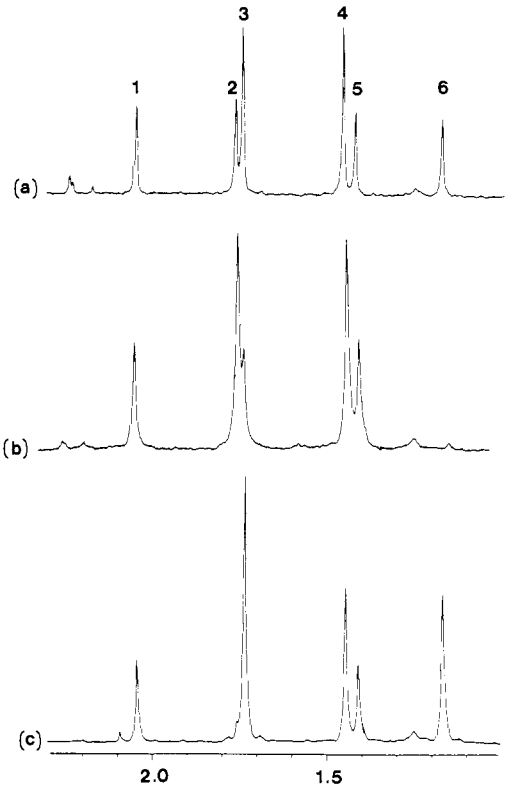


Figure 1. ^1H NMR spectra at 360 MHz of the bis(pyridyl) adducts of Fe(TTP): $\alpha,\alpha,\alpha,\alpha$ (peak 2), $\alpha,\alpha,\alpha,\beta$ (peaks 1, 4, and 5), $\alpha,\beta,\alpha,\beta$ (peak 6), $\alpha,\alpha,\beta,\beta$, (peak 3): (a) mixture of atropisomers, (b) chromatography fraction A, (c) chromatography fraction B.

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Table II. Atropisomeric Composition of A and B Fractions from Fe(TTP)Cl

isomer	band A, %	band B, %	original mixture, %
$\alpha,\alpha,\alpha,\alpha$	28	0	12.5
$\alpha,\alpha,\alpha,\beta$	56	40	50
$\alpha,\beta,\alpha,\beta$	0	20	12.5
$\alpha,\alpha,\beta,\beta$	14	40	25

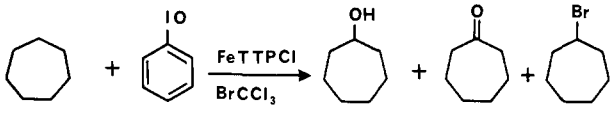
Table I compares the results for cyclohexane hydroxylation by Fe(TTP)Cl prepared from the B fraction with Fe(TPP)Cl and the Fe(TTP)Cl mixture. It is apparent from the data that the B fraction of Fe(TTP)Cl was a more efficient hydroxylation catalyst than Fe(TTP)Cl. Analysis of the B catalyst after completing 10 reactions with iodosylbenzene did not show any evidence of porphyrin decomposition.

Samples of the B band, the A band, and the Fe(TTP)Cl mixture were treated with HCl and then converted into the respective ferrous bis(pyridyl) adducts by sodium sulfite reduction in the presence of excess pyridine. The ^{1}H NMR spectra of the methyl region of these ferrous bis(pyridyl) adducts are shown in Figure 1. The pattern displayed by the original mixture is exactly that expected for a statistical distribution of four possible atropisomers of $(FeTPP)(Pyr)_2$. A similar pattern has been observed by Walker et al.[13] for the diamagnetic nickel complex of TTP. The methyl absorptions of band A and band B are clearly different, and by combining the normalized intensities of these two spectra, the spectrum of the original mixture is reproduced.

It is reasonable to assume that the $\alpha,\beta,\alpha,\beta$ atropisomer would have greater difficulty forming the μ-oxo dimer than the $\alpha,\alpha,\alpha,\alpha$ isomer, due to steric interactions.[14] Making only this assumption, it was possible to assign all of the methyl resonances of $FeTTP(Pyr)_2$ and to determine atropisomeric composition of the A and B fractions.

As indicated in Table II, the more efficient B catalyst is enriched in the $\alpha,\beta,\alpha,\beta$ and $\alpha,\alpha,\beta,\beta$ atropisomers. The A band is depleted in the $\alpha,\beta,\alpha,\beta$ atropisomer and contains only a minor amount of the $\alpha,\alpha,\beta,\beta$ atropisomer. This indicates that the $\alpha,\alpha,\beta,\beta$ and $\alpha,\beta,\alpha,\beta$ atropisomers are responsible for the increased hydroxylation efficiency of Fe(TTP)Cl.

Oxidation of cycloheptane by iodosylbenzene and Fe(TTP)Cl in the presence of bromotrichloromethane produced 24% cycloheptanol and an 18% yield of cycloheptyl bromide. The presence



of brominated product is significant, since it is known that bromotrichloromethane reacts with radicals to form alkyl bromides.[15] Accordingly, the intermediacy of alkyl radicals during the oxidation is indicated. The amount of bromide produced cannot necessarily be taken as an indication of how many radicals escaped the solvent cage since trichloromethyl radicals produced might have induced a chain reaction generating cycloheptyl bromide via a completely separate route.

Selectivity and Stereospecificity. Table III lists the results from the oxidation of adamantane with iodosylbenzene and three iron porphyrins: Fe(TPP)Cl, Fe(TTP)Cl, and chloro(5,10,15,20-tetramesitylporphrinato)iron(III) [Fe(TMP)Cl].

From these data, it is apparent that there was a high degree of selectivity for tertiary centers over secondary centers; also, the ratio is dependent on the catalyst used. With increasing substitution of the porphyrin peripheral groups, the relative reactivity

Table III. Ferric Porphyrin-Iodosylbenzene Oxidation of Adamantane

catalyst	1-adamantanol,[a,b] %	2-adamantanol, %	2-adamantanone, %	tertiary:secondary selectivity[c]
Fe(TPP)Cl	13	<1	nil	48
Fe(TTP)Cl	39	5	1	20
Fe(TMP)Cl	7.5	2	nil	11

[a] Yield based on iodosylbenzene. [b] Typical amounts of reactants; ferric porphyrin, 0.070 mmol; iodosylbenzene, 0.455 mmol; adamantane, 2.90 mmol. [c] Corrected to a per-hydrogen relative reactivity.

Table IV. Hydroxylation[a] of *cis*-Decahydronaphthalene by Iron Porphyrins-Iodosylbenzene

ferric porphyrin	*cis*-9-decalol,[b,c] %	1-decalols, %	2-decalols, %
Fe(TPP)Cl	4	0.3	0.3
Fe(TTP)Cl	30	5.6	8.0
Fe(TNP)Cl	27	5.8	8.2
Fe(TMP)Cl	3.6	2.2	6.4

[a] Ketones were also produced in low yield (see Experimental Section). [b] Yields based on iodosylbenzene. [c] Typical amounts of reactants: iodosylbenzene, 0.455 mmol; ferric porphyrin, 0.05 mmol; *cis*-decahydronaphthalene, 1.93 mmol.

of tertiary and secondary hydrogens decreased from 48:1 to 11:1. Fe(TTP)Cl was again the most efficient catalyst.

Hydroxylation of *cis*-decahydronaphthalene with Fe(TPP)Cl and iodosylbenzene produced mainly *cis*-9-decalol in a modest yield. Significantly, only a small amount of *trans*-9-decalol was produced, indicating that the hydroxylation had occurred with retention of configuration at carbon.

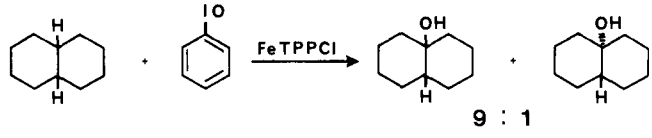


Table IV summarizes the results of the oxidation of *cis*-decahydronaphthalene catalyzed by four iron porphyrins: Fe(TPP)Cl, Fe(TTP)Cl, Fe(TMP)Cl, and chloro(5,10,15,20-tetra-1-naphthylporphyrinato)iron(III) [Fe(TNP)Cl]. The data indicate that the selectivity of the oxidation changed as a function of the structure of the ferric porphyrin. In the case of Fe(TMP)Cl, the most hindered porphyrin, most of the oxidation occurred at the least sterically hindered methylene of *cis*-decahydronaphthalene. As expected, the reactivity pattern of Fe(TNP)Cl and Fe(TTP)Cl were similar since these porphyrins are similarly shaped. The dependence of the distribution of products on the structure of the catalyst can be ascribed to a reaction occurring near or at the iron center of the porphyrin. The regioselectivity observed as a function of the steric nature of the oxidant is similar to the reported chlorination of pentane with the highly hindered *N*-chloro-2,2,6,6-tetramethylpiperidine.[16]

Use of the red band, A, obtained from the chromatography of Fe(TTP)Cl as a catalyst for the oxidation of *cis*-decahydronaphthalene caused greatly diminished yields (7%) of *cis*-9-decalol compared to the unchromatographed mixture. Heating band A at 153 °C (refluxing DMF solution) for 3 h, followed by purification, restored its original activity. Thus the original statistical mixture of atropisomers that contained the $\alpha,\beta,\alpha,\beta$ and $\alpha,\alpha,\beta,\beta$ atropisomers was more efficient than the porphyrin mixture depleted in those compounds.

Similar to the oxidation of *cis*-decahydronaphthalene with Fe(TPP)Cl, oxidation with Fe(TNP)Cl or Fe(TTP)Cl produced an insignificant amount of *trans*-9-decalol.

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Kinetic Isotope Effect. The kinetic isotope effect for hydroxylation by the Fe(TTP)Cl–iodosylbenzene system was measured for the oxidation of a mixture of cyclohexane and cyclopentane. The alcohols and ketones that were produced were used to obtain the relative reactivity of these compounds. This was repeated by using cyclohexane-d_{12} in place of cyclohexane to obtain a value of k(cyclohexane-d_{12})/k(cyclopentane). The ratio of these relative rate determinations gives a k_H/k_D for cyclohexane of 12.9 ± 1.0. The value produced in this way is a composite of primary and secondary effects but still indicative of substantial C–H bond breaking in the transition state for oxygen transfer.

Mechanism. The most notable aspect of these iron porphyrin catalyzed hydroxylation reactions is the facility with which the unactivated C–H bond is broken under such mild conditions.[17-19] Several lines of evidence suggest that the oxidation had radical character. Most convincing is the influence of the free radical trap bromotrichloromethane on the product distribution in the oxidation of cycloheptane. The tertiary to secondary relative reactivities (25–48:1) were in a range expected of free radical abstraction reactions and are very similar to the selectivity of a bromine atom.[20] Likewise, the large hydrogen isotope effect can be accommodated by a free radical abstraction mechanism.[21]

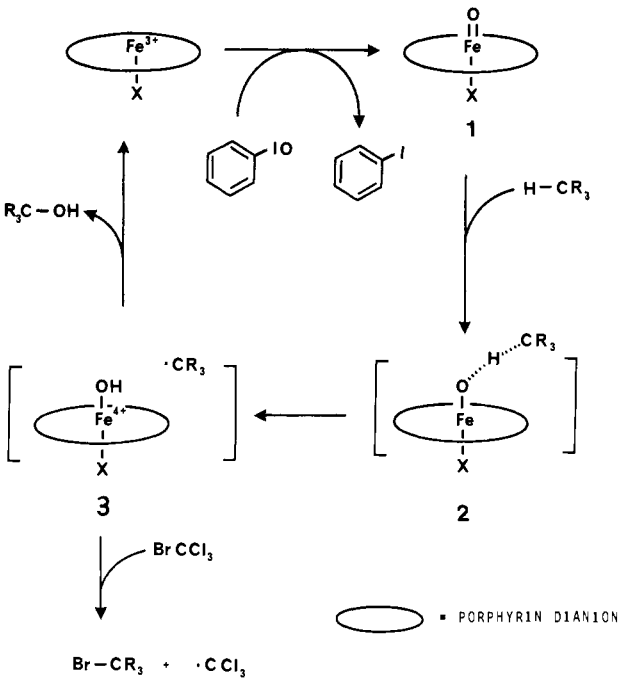
The tertiary to secondary carbon–hydrogen bond relative reactivity is inconsistent with a hydride abstraction mechanism for the oxidation. The value of 25–48:1 does not approximate the large difference in rates found by solvolysis reactions. For example, tertiary bromides solvolyze approximately 10^3 times faster than secondary bromides.[22] This argument has been offered by Wiberg[23] to explain results for the chromic acid oxidation of alkanes.

The oxidation of norcarane by Fe(TTP)Cl and iodosylbenzene also provided evidence against a carbonium path. The isomeric 2-norcaranols were produced in 10.3% yield based on iodosylbenzene consumed. By contrast, the hydrolysis of the dinitrobenzoate ester of 2-norcaranol produced cyclohepten-4-ol via a cationic cyclopropylcarbinyl–homoallyl ring opening.[24]

The hydroxylation of *cis*-decahydronaphthalene proceeded with retention of stereochemistry at the tertiary center. This indicates that the radical formed from the cis -hydrocarbon did not have time to equilibrate before collapse to the product alcohol. The same effect has been observed for the trapping of a decalyl radical generated by peroxyester decarboxylation.[25]

The results from the oxidation of norcarane provide similar information. Boikess[26] has examined the free radical chlorination of norcarane with molecular chlorine and the photoinduced reaction with *tert*-butyl hypochlorite. It was concluded that the cyclohexenyl methyl radical was the major rearrangement product of the 2-norcaranyl radical. The oxygenation of norcarane by ozone adsorbed on silica gel has been shown to give unrearranged alcohols.[27]

Scheme I



A mechanism for the hydroxylation reaction catalyzed by the ferric porphyrins and accommodating the observed selectivity, retention of stereochemistry, and kinetic isotope effect is shown in Scheme I. This mechanism is essentially the same as that one of us has proposed[28] for the oxidation of alkanes by cytochrome P-450. Abstraction of a hydrogen atom by an oxidized iron porphyrin and hydroxo ligand transfer to the resulting radical is the simplest way to explain the product alcohol. The large hydrogen isotope effect supports the symmetrical transition state depicted in structure **2** for the hydrogen abstraction.[21]

Two additional possibilities for oxygen transfer to the carbon radical in **3** are deprotonation of the hydroxo group and carbon radical addition to the resultant oxoiron(IV) complex[29] and carbon radical addition to *iron* followed by a reductive elimination.

Occasional escape of the radical is indicated by the effects of the free radical traps, oxygen and bromotrichloromethane, on the distribution of products. The oxidation of norbornane in the presence of carbon tetrachloride did not produce norbornyl chloride, and *cis*-decahydronaphthalene was hydroxylated stereospecifically. Accordingly, the radicals produced in these cases by hydrogen abstraction are efficiently scavenged by the iron porphyrin.

In related studies,[28b] we have shown that the allylic hydroxylation of 1,2-dideuteriocyclohexene with the Fe(TPP)Cl–iodosylbenzene system occurred with partial (37%) scrambling of the allylic sites. This observation can be explained by considering the greater stability and expected lifetime of an allylic radical and the relatively modest molecular motion required to cause positional scrambling. Consequently, this system had a greater opportunity to rearrange before being captured by the hydroxoiron porphyrin.

The oxidation of cyclohexene in the presence of methanol produced 3-cyclohexenyl methyl ether in addition to epoxide and

(17) Subsequent to our report on this iron porphyrin–iodosylbenzene reaction, we and others have demonstrated improved yields for hydroxylation with manganese porphyrins: (a) Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6375–6377. (b) Hill, C. L.; Schardt, B. C. *Ibid.* **1980**, *102*, 6374–6375. (c) Chang, C. K.; Ebina, F. *J. Chem. Soc., Chem. Commun.* **1981**, 778–779.

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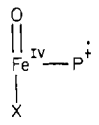
(29) An iron(IV) porphyrin species has recently been described: Chin, D.-H.; Balch, A. L.; LaMar, G. N. *J. Am. Chem. Soc.* **1980**, *102*, 1446–1448.

allylic alcohol. Whereas this observation could indicate the intermediacy of a carbocation, the results also be explained by a ligand transfer mechanism.[30] Thus, in the presence of methanol, methoxy ligand transfer could occur in the recombination part of the mechanism.

We have presented elsewhere evidence that the reactive species generated upon the oxidation of iron porphyrin complexes is an iron(IV) porphyrin cation radical (**4**).[31]

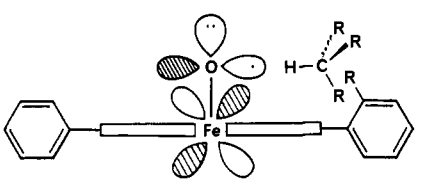


4

This species in an S = $^3/_2$ state would be expected to have one electron in the d_{xz} and d_{yz} iron orbitals. Mixing of these orbitals with the filled oxygen p orbitals, p_x and p_y, would be expected to produce two singly occupied, antibonding d_π–p_π orbitals. To the extent that the unpaired electron density in this orbital is on the oxygen, such ferryl species may have oxy radical character. Further, the approach of an abstractable hydrogen atom should be directed toward the p orbital on oxygen and parallel to the plane of the porphyrin ring, rather than perpendicular to it, to allow interaction of the electrons in the C–H bond with the singly occupied Fe–O orbital.

The sensitivity of these hydroxylation reactions to relatively small changes in the steric environment of the porphyrin periphery is adequately explained by a stereoelectronic preference for parallel approach. Inspection of the space-filling models reveals no indication of nonbonded interactions between an *o*-methyl substituent and saturated substrates such as adamantane or *cis*-decalin with a perpendicular approach.

By contrast, the parallel approach depicted in **5** requires significant contact between the *o*-methyl substituent and the substrate.



5

One of the more enigmatic aspects of fatty acid hydroxylation by certain forms of cyclochrome P-450 is the observed selectivity for ω and $\omega - 1$ hydroxylation. The stereoelectronic effect suggested here in combination with a sufficiently encumbered active site could provide a rationale for this selectivity with such a conformationally mobile substrate. Further, a requirement for parallel approach would provide a molecular basis for the construction of a stabilizing or site-directing heme environment.

This work was begun to develop a synthetic biomimic of cytochrome P-450 activity. The most challenging of these oxidations, aliphatic hydroxylation, has now been demonstraed. In addition, to the extent that the iron porphyrin/iodosylbenzene system described here accesses reactivity intermediates related to the P-450 catalytic cycle, the enzymic activity can be understood in simple chemical terms.

Experimental Section

General. Analytical gas chromatography was done on Varian Instrument Models 1200, 2400, or 3700 equipped with flame ionization detectors. Capillary gas chromatography was done on a Varian 3700 instrument. Peak areas were measured by electronic integration with a Hewlett-Packard 3380A or Spectra Physics SP4100 reporter–integrators. Mass spectra were taken on a Finnigan 4021 gas chromatograph/mass spectrometer. NMR spectra were taken of a Varian T-60A, JOEL PS-100, or Brüker WM 360 NMR spectrometer. Chemical shift values are reported relative to Me_4Si. Infrared spectra were taken on a Beckman IR 4240, Perkin-Elmer 457, or 727B instrument. Visible spectra were measured on a Varian Cary 219 spectrometer. Extinction coeffs. were measured by dissolving an appropriate amount of the compound in 100 mL of solvent and then successively diluting this solution to achieve absorbance values of less than 1 for each band. Methylene chloride was purified by distillation from phosphorus pentoxide. Elemental analyses were done by Galbraith Microanalytical Laboratories.

Porphyrins. 5,10,15,20-Tetraphenylporphyrin was either purchased from Aldrich or synthesized according to the method of Alder et al.[32] *meso*-Tetraphenylchlorin was removed by treatment with dicanodichloroquinone (DDQ) according to the method of smith et al.[33] Purification was achieved by chromatography on silica silica gel (Woelm, activity 1) or alumina (Woelm, basic or neutral, activity 3) using dry methylene chloride.

5,10,15,20-Tetramesitylporphyrin [(TMP)H_2]. Mesitaldehyde was synthesized via the method of Höft et al.,[35] bp 108 °C (6 mmHg). 5,10,15,20-Tetramesitylporphyrin was synthesized by the method of Badger et al.[36] (and repeated by Eaton and Eaton[37]) with the following modifications. Hydrated zinc acetate was dehydrated by heating for 3–4 h at 100 °C (hood) and then cooled in a desiccator. Pyrrole was distilled before use and pyridine was dried over KOH for 3 days before distillation.

Anhydrous zinc acetate (21.3 g, 0.12 mol), mesitaldehyde (50 g, 0.337 mol), pyrrole (21.4 g, 0.337 mol), and pyridine (42.5 g, 44 mL) were divided equally among three glass tubes with constricted necks (~50-mL capacity). These tubes were sealed under argon, and the solid $Zn(OAc)_2$ was dissolved by careful heating with a heat gun. The tubes were then immersed in an oil bath and heated to 175 ± 5 °C for 72 h.

The tarry product was washed with acetone to give relatively pure Zn(TMP) as insoluble purple crystals. This material was dissolved in methylene chloride and washed with 10% HCl and with 10 10% sodium bicarbonate. Removal of chlorin was achieved by refluxing the crude (TMP)H_2 in methylene chloride (300 mL) with DDQ (1 g) for approximately 6 h. Chromatography on basic alumina using dry methylene chloride afforded 2.9 g (4.5%) of porphyrin: ^{1}H NMR ($CDCl_2$) δ 8.62 (8 H, s), 7.30 (8 H, s), 2.61 (12 H, s), 1.86 (48 H, s), −2.51 (2 H, m).

Ferric Porphyrin Complexes. (TPP)H_2 was metalated with $Fe^{+2}Cl_2 \cdot 4H_2O$ in refluxing DMF according to the method of Kobayashi et al.[38] The product was recrystallized from methylene chloride and petroleum ether.

Fe(TTP)Cl has been reported by LaMar and Walker.[39] (TTP)H_2 was metalated by the same procedure as (TPP)H_2. Fe(TTP)Cl: vis (CH_2Cl_2) λ_{max} 375 nm (ϵ 58 700 cm^{-1} M^{-1}), 416 (109 000), 507 (14 100), 576 (3250), 660 (2490), 690 (2620).

(TNP)H_2 was metalated in the same manner as (TPP)H_2. The μ-oxo dimer of this compound has been reported by Straub et al.[40] Fe(TNP)Cl: vis (CH_2Cl_2) λ_{max} 378 nm (ϵ 61 500 cm^{-1} M^{-1}), 422 (107 900), 509 (14 700), 582 (4330), 654 (3490), 682 (3200).

(TMP)H_2 was metalated in exactly the same manner as (TPP)H_2. The metalloporphyrin crystallized from the DMF solution upon cooling. This compound was dissolved in methylene chloride and washed with 10% HCl to ensure the complete conversion to the chloride. The product was recrystallized from methylene chloride/ethanol. Fe(TMP)Cl: vis (CH_2Cl_2) λ_{max} 375 nm (ϵ 57 600 cm^{-1} M^{-1}), 417 (440 000), 509 (16 130), 576 (3860), 664 (3000), 694 (3241). Anal. Calcd for $C_{56}H_{52}N_4FeCl$: C, 77.10; H, 6.01; N, 6.42. Found: C, 77.25; h, 6.15; N, 6.34.

Iodosylbenzene. Iodosylbenzene was prepared either by the hydrolysis of iodobenzene diacetate or iodobenzene dichloride with aqueous sodium hydroxide. Iodobenzene dichloride was synthesized by the method of

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Lucas and Kennedy.[41] Iodobenzene diacetate was either purchased from Aldrich or synthesized from iodobenzene and 40% peroxyacetic acid (FMC Corporation) by the method of Sharefkin and Saltzman.[42] Both methods produce iodosylbenzene having a purity of nearly 99%. The product was dried at 0.5 mmHg and room temperature overnight. Since iodosylbenzene will slowly disproportionate, care was taken to keep the compound cold (refrigerator), and new material was made approximately every three months. *Caution*: Iodosylbenzene explodes at 210 °C.

Iodosylmesitylene was prepared by the method of Sharefkin and Saltzman.[42]

Chromatography of Fe(TTP)Cl. Fe(TTP)Cl (0.10 g) was dissolved in methylene chloride (20 mL) and rapidly stirred, open to air, for 1.5 h with 10% NaOH (20 mL). The phases were separated and the porphyrin solution loaded onto a column of alumina (basic, activity 3.5, Woelm) and eluted with dry methylene chloride (200 g of alumina was used in a column with a 3-cm diameter). The first band off the column was red (0.0373 g), and the second band was green (0.050 g).

Samples for NMR spectroscopy were prepared by washing a methylene chloride solution of the compound with 10% HCl and then removing the solvent under vacuum (aspirator). In NMR tubes approximately 10 mg of the green band, the red band, and mixture were dissolved in $CDCl_3$ (0.6 mL). Pyridine (0.25 mL), D_2O (0.2 mL), and enough sodium sulfite to saturate the D_2O were added. The tubes were vigorously shaken. ^1H NMR (360 MHz) methyl region of $FeTTP(Pyr)_2$ δ (rel intensity) 2.419, (1), 1.791, (1), 1.758, (2), 1.459, (2), 1.419, (1), 1.715, (1).

Reaction of Iodosylbenzene with Cyclohexane Catalyzed by Fe(TTP)Cl. Iodosylbenzene (0.100 g, 0.455 mmol) was added over 1 h to a solution of cyclohexane (1 mL, 9.26 mmol) and Fe(TTP)Cl (0.044 g, 0.058 mmol) in methylene chloride (5 mL). Cyclohexene oxide was used as an internal standard. The mixture was analyzed by GLPC (Carbowax 20 M, 100 °C initially, then increased at 1 °C min). Cyclohexanol (10.85 min) was produced in 22% yield, cyclohexanone (7.45 min) in 2.4% yield, and iodobenzene (16.87 min) in 74% yield based on iodosylbenzene. Cyclohexene oxide had a retention time of 4.08 min.

Repeating this reaction with less iodosylbenzene (0.05 g) and Fe(TTP)Cl (0.035 g, 0.046 mmol) produced cyclohexanol in 34% yield, cyclohexanone in 3% yield, and iodobenzene in 84% yield. The results from the other catalysts are given in Table I.

Reaction of Iodosylbenzene with Cycloheptane Catalyzed by Fe(TTP)Cl in the Presence of Bromotrichloromethane. Iodosylbenzene (0.100 g, 0.455 mmol) was slowly added over 1 h to a solution of cycloheptne (1.0 mL, 8.26 mmol), bromotrichloromethane (1 mL, 10.0 mmol), and Fe(TTP)Cl (0.049 g, 0.064 mmol) in methylene chloride (4 mL). The cycloheptane was first purified by placing under hydrogen with Pd/C (atmospheric pressure) overnight and then passed through a column of activated alumina (activity 1, basic, Woelm). Cyclohexanone was used as an internal standard and the mixture was analyzed by gas chromatography (DEGS, 110 °C initial then increased at 0.5 °C/min). Cycloheptanol (14.99 min) was produced in 24% yield, cycloheptyl bromide (8.76 min) in 18% yield, cycloheptanone (11.87 min) in 3.6% yield, and iodobenzene (12.96 min) in 91% yield based on iodosylbenzene.

Reaction of Iodosylbenzene with Adamantane Catalyzed by Ferric Porphyrins. Iodosylbenzene (0.100 g, 0.455 mmol) was added over 1 h to a solution of adamantane (0.400 g, 2.90 mmol) and ferric porphyrin (0.04 g). The products were analyzed by GLPC (DEGS, 135 °C). 1-Adamantanol (8.49 min), adamantanone (10.25 min), and 2-adamantanol (11.37 min) were produced as deduced by comparison to authentic samples. The results for the catalysts used are in Table III.

Reaction of Iodosylbenzene with *cis*-Decahydronaphthalene Catalyzed by Ferric Porphyrins. The procedure described below is for the reaction catalyzed by Fe(TTP)Cl and is typical for all the reactions.

Iodosylbenzene (0.100 g, 0.455 mmol) was added over 1 h to a solution of *cis*-decahydronaphthalene (0.30 mL, 1.93 mmol) and Fe(TTP)Cl (0.035 g, 0.046 mmol) in methylene chloride (5 mL). At the end of addition the products were analyzed by GLPC (Carbowax 20 M, 135 °C). Adamantanone was used as an internal standard. Samples of the oxidation products were prepared for GLPC/MS analysis by removing the methylene chloride under reduced pressure and adding pentane (5 mL) to dissolve the products and leave the insoluble catalyst. Filtration, followed by removal of the pentane under reduced pressure, produced a dark oil. This oil was distilled in a short-path distillation apparatus (oil bath 120 °C, 0.05 mmHg). The volatile material was collected on a dry ice cooled condenser in the short-path still.

Analysis by GLPC revealed three major products. The major product, some of which was isolated by column chromatography, was assigned to be *cis*-9-decalol by comparison with an authentic sample: ^1H NMR ($CDCl_3$) δ 1.5 (m); IR (CCl_4) 3607 (w), 2993 (s), 1452 (m); mass spectrum, 111 (base), 154 (M^+).

Reaction of Iodosylbenzene with Norcarane Catalyzed by Fe(TTP)Cl. Iodosylbenzene (0.100 g, 0.455 mmol) was added over 1 h to a solution of norcarane (0.50 mL, 4.43 mmol) and Fe(TTP)Cl (0.040 g, 0.053 mmol). Analysis by GLPC (Carbowax 20 M, 10 °C initial then increased 1 °C/min) showed three peaks after iodobenzene (6.89 min). The first peak (8.24 min) coinjected with authentic *syn*-2-norcaranol,[45] the second peak (10.16 min) was characterized as *anti*-2-norcaranol (GLPC/MS), and the third peak (10.16 min) was characterized as 2-norcaranone by GLPS/MS.

Determination of the Kinetic Isotope Effect for the Oxidation of Cyclohexane by Fe(TTP)Cl/Iodosylbenzene. Fe(TTP)Cl (0.030 g, 0.039 mmol) was dissolved into methylene chloride (6 mL), purged with dry nitrogen (15 min) at ambient temperature, and then cooled to 0 °C. Cyclopentane (0.50 mL, 5.35 mmol) and cyclohexane (0.50 mL, 4.63 mmol) were syringed into the flask and the purging discontinued, but a positive pressure of nitrogen was maintained. Iodosylbenzene (0.100 g, 0.455 mmol) was slowly added over a 1-h period. The mixture was stirred for 15 min and then a sample removed for GLPC analysis (DEGS, 90 °C).

The reaction was repeated with cyclohexane-d_{12} (Aldrich, 99.5%-*d*) instead of cyclohexane.

Acknowledgment. Financial support of this research by the National Institutes of Health (GM 25923) and the National Science Foundation (CHE-77-21849) is gratefully acknowledged. The National Science Foundation provided funds for the purchase of a NMR spectrometer.

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(44) See Lund et al. and Benyon et al. (Lund, E.; Budzikiewicz, H.; Wilson, J. M.; Djerassi, C. *J. Am. Chem. Soc.* **1963**, *85*, 941–949. Benyon, J. H.; Saunders, R. A.; Williams, A. E. *Appl. Spectrosc.* **1960**, *14*, 95) for mass spectra of the decalones. The identity of the decalols can be inferred from the decalone mass spectra.

(45) A sample of the 2-norcaranol was obtained from J. Kruper. It was synthesized by the method of Dauben (Dauben, W. G.; Berezin, G. H. *J. Am. Chem. Soc.* **1963**, *85*, 468–472).