Aliphatic Hydroxylation Catalyzed by Iron(III) Porphyrins

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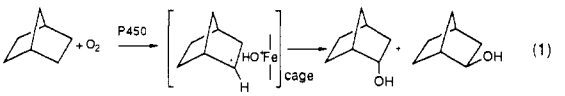
Abstract: Hydroxylation of aliphatic hydrocarbons with oxidants such as iodosobenzene can be effectively catalyzed with highly halogenated iron(III) porphyrins such as iron(III) tetrakis(2,6-dichlorophenyl)octabromoporphyrin. Hydroxylation of norbornane and tetraexodeuterionorbornane using this catalyst afforded good yields of products which consisted of 86:13:<1 and 84:16:<1 ratios of *exo*-norbornan-2-ol, *endo*-norbornan-2-ol, and 2-norbornanone, respectively. In the latter case both D_3 and D_4 exo and endo alcohols but only D_3 ketone were obtained. The primary isotope effect is 5. These results show that the reaction involves loss of stereochemistry and has a large isotope effect; the results are in agreement with those from a previous study of the same compounds using the enzyme cytochrome P-450. As in that case, this hydroxylation proceeds through a free-radical cage process. The hemin catalysis leads to a loss of stereospecificity similar to that in the enzyme-catalyzed reaction.

Introduction

Among organic reactions carried out in biological systems the hydroxylation of alkanes to alcohols, catalyzed by cytochrome P-450, seemed unprecedented in organic chemistry.[1,2] Most alkane oxidations lead to further oxidation to ketones and acids. It has therefore been interesting to develop model heme systems which duplicate these hydroxylations and to determine the mechanisms of the biomimetic reactions.[3-7]

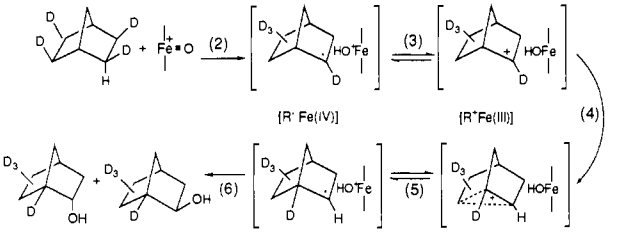
The large isotope effects,[3,4a,5] absence of carbocation types of skeletal rearrangements[4a] and loss of stereochemistry in the enzymatic process, has provided strong evidence for a radical cage, "rebound" mechanism.[3,4] An investigation of the products derived from the hydroxylation of [2.2.1]bicycloheptane (norbornane) and *exo,exo,exo,exo*-2,3,5,6-tetradeuterionorbornane by cytochrome P-450, carried out by Groves, McClusky, White, and Coon,[4a] afforded *exo*- and *endo*-norbornan-2-ols which, in the case of deuterated norbornane, contained D_3 and D_4 alcohols. Quantitative analyses of these products indicated substantial stereochemical loss at the reaction center as well as the primary isotope effect of 11.5 for the reaction. These results indicated a free-radical abstraction process. Abstraction of both exo and endo hydrogens along with some inversion of configuration were indicated.



(1)

The production of substantial *endo*-norbornan-2-ol led the authors to conclude that the reaction did not involve carbocation intermediates. However, reversible electron transfer within the cage is possible if the iron(III) partner has a sufficient potential. Norbornyl radical has an ionization potential of 6.6 eV.[8] The cation is bridged, and thus rearrangement can be expected to accompany reversible electron transfer (reaction 4).

With the development of robust hydroxylation catalysts having halogens substituted on both the phenyl and pyrrole position, Figure 1, it has become possible to carry out high yield and high turnover hydroxylations similar to those observed with the enzyme.[6,7]



We have therefore studied the kinetics and products of hydroxylation of cyclohexane, norbornane, and their alcohols in order to determine relative reactivities. Additionally, we have studied the hydroxylation of *exo,exo,exo,exo*-2,3,5,6-tetradeuterionorbornane, **7**, in the manner of Groves et al.[4a] except that the catalyst 2^+Cl^- was used with pentafluoroiodosobenzene (PFIB) as oxidant.

Experimental Section

Materials. Pentafluoroiodosobenzene (PFIB), iron(III), 3,6,9,12-tetrakis(2,6-dichlorophenyl)porphyrin chloride 1^+Cl^- and iron(III) tetrakis(2,6-dichlorophenyl)-1,2,4,5,7,8,10,11-octabromoporphyrin chloride 2^+Cl^- and the other hemins shown in Figure 1 were obtained from previous studies.[6,7] Norbornane (Aldrich) was distilled under argon from lithium aluminum hydride before use. Norbornadiene (Aldrich) was distilled under argon before use. Methylene chloride (Fisher Spectroanalytical grade), cyclohexane (Malinkrodt AR), 2,2,2-trifluoroethanol, methanol-d_1, D_2O, acetic acid-*d*, $CDCl_3$, azodicarbonamide, 30% NaOD in D_2O, norbornen-5-ol, cyclohexanol, *exo*-norbornan-2-ol, and *endo*-norbornan-2-ol (all from Aldrich) were used as received.

Sodium azodicarboxylate was prepared by slowly adding 8 g of azodicarbonamide to a 75-mL solution of 30% NaOD in D_2O with stirring at 0 °C. After 1.5 h the reaction was allowed to warm to room temperature and filtered. The remaining solid was carefully washed under N_2 with 3 × 20 mL of MeOD and dried under vacuum to give 8.2 g (94%) of yellow powder.

***exo,exo,exo,exo*-2,3,5,6-Tetradeuterionorbornane, 7**, was prepared using a modified version of Baird's procedure.[9] To 8 g (0.05 mol) of dried sodium azodicarboxylate was added 10 mL of dry methanol-d_1 followed by 1.2 mL (10 mmol) of norbornadiene. This mixture was stirred in an ice bath for 5 min after which a solution of 8 mL of acetic acid-*d* in 10 mL of methanol-d_1 was slowly added over 40 min. After stirring for 4 h, 10 mL of D_2O was slowly added. The resulting precipitate was filtered leaving 1.0 g (82%) of a white solid [^{1}H NMR (300 MHz, $CDCl_3$) δ 2.2 (2 H, s), 1.2 (2 H, s), 1.1 (4 H, s)]. A sample of the crude norbornane was purified by sublimation at 35 °C in the presence of $CaSO_4$ as a desiccant. NMR spectrum showed less than 2% norbornane exo hydrogen.

***exo,exo*-5,6-Dideuterionorbornan-2-ol, 11**, was prepared similarly.[9] To 400 mg (2.4 mmol) of dried sodium azodicarboxylate was added 2

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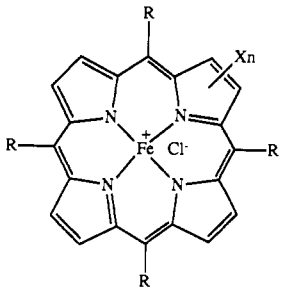


Catalyst	Xn	R	Ref
1^+Cl^-	H_8	2,6 diClPh	6a
2^+Cl^-	Br_8	2,6 diClPh	6b
3^+Cl^-	H_8	C_6F_5	--
4^+Cl^-	F_7H	2,6 diClPh	6b, 9
5^+Cl^-	Cl_8	C_6F_5	9b
6^+Cl^-	F_8	C_6F_5	7

Figure 1. Structure of catalysts.

Table I. Preparative Oxidation of Cyclohexane[a]

concn of cyclohexane (M)	% yield[b] cyclohexanol	% convn[c]	alcohol/ketone
0.1	41	25	9
0.5	62	7	13
1.0[d]	76	4.5	23
2.0[d]	82	2.5	31
5.0[d]	93	1	37

[a] Conditions: 2^+Cl, 10^{-3} M, PFIB, "0.06 M", in dichloromethane at 25 °C. [b] Based upon C_6F_5I produced. [c] Based upon cyclohexane. [d] No hemin destruction.

Table II. Stability of Halogenated Catalysts[a]

hemin	percent hemin loss	hemin	percent hemin loss
1^+Cl^-	100	4^+Cl^-	25
2^+Cl^-	90	5^+Cl^-	20
3^+Cl^-	100	6^+Cl^-	<20

[a] Condition: hemin, 10^{-3} M was mixed with 0.03 M PFIB in dichloromethane and agitated until the PFIB dissolved or the color bleached.

Table III. Kinetics of Hydroxylation of Norbornane and Cyclohexane and Epoxidation of Norbornene[a]

catalyst	substrate	concn (M)	k_2 (10^3 M^{-1} s^{-1})	catalyst loss (%)
2^+Cl	norbornane	0.65	9.5	35
2^+Cl	norbornane	1.0	9.5	15
2^+Cl	norbornane	2.0	9.3	7
2^+Cl	norbornane	2.8	9.8	6
2^+Cl	cyclohexane	2.0	8.0	
2^+Cl	norbornene	0.5	9.2	0
1^+Cl	norbornene	0.5	26	0

[a] Conditions: solvent $CH_2Cl_2/CF_3CH_2OH/H_2O$ at a 90:9:1 ratio by volume; catalyst concentration 5–16 × 10^{-6} M, PFIB 10^{-3} M, temperature 25 °C.

mL of dry methanol-d_1 followed by 100 mg (0.9 mmol) of norbornen-5-ol (mixture of exo and endo isomers). This mixture was stirred in an ice bath for 5 min after which a solution of 2 mL of acetic acid-*d* in 2 mL of methanol-d_1 was slowly added over 10 min. After stirring for 2 h, 5 mL of D_2O was added, and the resulting solution was extracted with CH_2Cl_2 (2 × 10 mL) and dried over $MgSO_4$.

Instruments. Product analysis was performed on a Varian 3700 gas chromatograph equipped with a 10% carbowax 20 M on 80/100 Supelcoport column and a flame ionization detector. Deuterium content of samples was determined on the HP-5890 GC equipped with HP-5988A mass spectrometer. The GC column was HP carbowax 20 M. Quantitative analysis of deuterionorbornan-2-ol (M^+D_3, M^+D_4) was determined by selected ion monitoring (SIM) method, i.e. during the data acquisition period, instead of monitoring whole range of *m/z* value, we only selectively monitored *m/z* = 96.0–96.3, 97.0–97.3, 98.0–98.3, 99.0–99.3. This method can give greater sensitivity. Kinetics and other spectrophotometric measurements were recorded on a Kontron Uvikon 810 spectrophotometer interfaced with a Celerity computer.

Table IV. Relative Reactivities of Substrates toward the "Oxene" Derived from Reaction of 1^+Cl^- or 2^+Cl^- with PFIB at 25 °C[a]

catalyst	substrate A	substrate B	rel reactivity ratio (A/B) actual	corrected[b]
1^+Cl^-	norbornene	cyclohexane	1000	12000
1^+Cl^-	norbornane	cyclohexane	0.60	1.7[c] (1.4)[d]
1^+Cl^-	cyclohexanol	*endo*-norbornan-2-ol	2.8	2.8
1^+Cl^-	cyclohexanol	*exo*-norbornan-2-ol	0.4	0.4
1^+Cl^-	*endo*-norbornan-2-ol	*exo*-norbornan-2-ol	7.0[e]	7.0[e]
1^+Cl^-	*endo*-norbornan-2-ol	norbornane	4.0[e]	16[c] (20)[d,e]
1^+Cl^-	cyclohexanol	cyclohexane	0.96[e]	11[e]
2^+Cl^-	norbornane	cyclohexane	0.72	2.2[c]
2^+Cl^-	**7**	cyclohexane	0.19	
2^+Cl^-	norbornane	**7**	3.8	

[a] Conditions: total substrate concentration 2 M, PFIB 0.3 M, catalyst 2 × 10^{-3} M except for the first entry in which the catalyst concentration was 8 × 10^{-5} M and PFIB concentration was 0.0045 M. The solvent was dichloromethane in which PFIB is insoluble. [b] These values are corrected for the number of equivalent hydrogens available except as noted below. [c] The statistical correction is four for only the exo hydrogens of norbornane. [d] This correction includes the form endo hydrogens at 1/7, the reactivity of the exo hydrogens bringing the statistical number to five hydrogens. [e] These values are derived from ketone formation; diols are also formed but not analyzed here. [f] These values are derived from those above.

Table V. Yields of Norborneols and Norbornanone from Hemin-Catalyzed Oxidations of Norbornane and *exo*-2,3,5,6-Tetradeuterionorbornane[a]

catalyst	substrate	exo alcohol **8**	endo alcohol **9**	ketone **10**	exo/endo	yield[b] (%)
1^+Cl^-	norbornane	90	6.4	3.6	14	40
1^+Cl^-	**7**	81	17	2	4.8	30
2^+Cl^-	norbornane	86	13	<1	6.7	82
2^+Cl^-	**7**	84	16	<1	5.3	79
P-450[c]	norbornane	77	23		3.3	
P-450[c]	**7**	43	57		0.75	

[a] See Experimental Section for conditions. [b] The yield is for all products. Products are reported as the percentages of total products. All yields are based upon pentafluoroiodobenzene produced and are corrected for GC response factors. [c] The data are from ref 4a.

Procedures. Oxidation of norbornane by 1^+Cl^- and PFIB (typical oxidation procedure). To a small test tube were added 10 mg (0.104 mmol) of sublimed norbornane and 100 μL of a CH_2Cl_2 solution of 1^+Cl^- (3.1 × 10^{-5} mmol). To this was added 1 mg (3.2 × 10^{-3} mmol) of PFIB. The tube was sealed with a rubber septum and shaken with the aid of a Vortex mixer for 2 min. Gas chromatographic (GC) analysis of the mixture showed that *exo*-norbornan-2-ol (90%), *endo*-norbornan-2-ol (6.4%), and 2-norbornanone (3.6%) had been produced in 40% yield (see Table V) based on perfluoroiodobenzene formed. The UV–vis spectrum of the reaction mixture indicated that 70% of the catalyst had been destroyed. Competitive oxidations of hydrocarbons, alcohols and ethers were carried out and analyzed in a similar manner.

Oxidation of **7** (0.9 M in CH_2Cl_2) using 1^+Cl^- (7 × 10^{-4} M CH_2Cl_2 solution) and 1.3 mg (4.2 × 10^{-3} mmol) of PFIB by the above procedure produced, upon interpretation of the GC results, a 31% yield (based upon perfluoroiodobenzene; see Table V) of deuterated *exo*-norbornan-2-ol (81%), deuterated *endo*-norbornan-2-ol (17%), and deuterated 2-norbornanone (2%). The deuterium content of each product was not determined.

The relative reactivities of norbornane and **7** catalyzed by 2^+Cl^- were determined by oxidizing each in competition with cyclohexane. Into a vial containing 10^{-2} mmol of 2^+Cl^- was added a mixture of norbornane (0.1 mmol) and cyclohexane (0.1 mmol) followed by enough CH_2Cl_2 to make up a 100-μL solution. GC/MS and GC analysis of the mixture were done in a carbowax 20 M column before and after addition of 1.5 mg (0.05 mmol) of PFIB to the mixture. From the amounts of products we determined the relative reactivities of norbornane and cyclohexane (0.72) and the relative reactivities of **7** and cyclohexane (0.19). Therefore the ratio of reactivities of norbornane and **7** is 3.8:1. The *exo*- to *endo*-norbornan-2-ol ratio from norbornane oxidation is 6.7, and the ratio from **7** oxidation is 3.7. Table VI lists the mass spectra of the products.

In a separate experiment we deliberately overoxidized **7** to produce enough deuterio-2-norbornanone to analyze for deuterium content. The GC/MS spectrum (70 eV) showed relative intensities for *m/z* = 113

Table VI. Relative Intensities of the $M^+ - H_2O$ (HOD) Ions from the Mass Spectrum of the Deuterated Exo and Endo Alcohols Produced by Catalytic Hydroxylation of 7 with 2^+Cl^- and PFIB in CH_2Cl_2

m/e	(D_1) 95	(D_2) 96	(D_3) 97	(D_4) 98	$\%D_n$
8 from **7**			100[a]	26.7[a]	83% D_3, 17% D_4
calcd for $D_3/D_4 = 5.25$			100	27.2	
9 from **7**			47.5[a]	100[a]	13% D_3, 87% D_4
calcd for $D_3/D_4 = 0.16$			47.5	100	
exo-**11**[b]	33.2	100	8.6		>95% D_2
endo-**11**[b]	33.2	100	8.6		>95% D_2

[a] The values are from the averages of 5 runs. [b] See ref 13.

(M^+D_3) and 114 (M^+D_4) of 38 and 0, respectively.

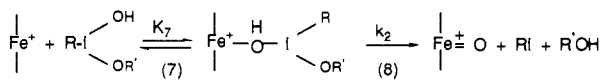
Kinetic Measurements. The reaction rates were determined by following the loss of PFIB, whose disappearance was followed by the loss of absorbance at 285 nm (ϵ = 1674).[10] The solvent system employed consisted of a mixture of methylene chloride, 2,2,2-trifluoroethanol, and water in a 90/9/1 ratio by volume. In a typical experiment a solution of norbornane or norbornene and catalyst was placed in a quartz cuvette followed by the addition of a solution of oxidant in the same solvent. The rate of decrease of the oxidant absorbance at 285 nm was measured. The resulting first-order rate constant was then divided by the catalyst concentration to produce the desired second-order rate constant. In each of the hydroxylation experiments the amount of catalyst destroyed during the reaction was determined by measuring the absorbance of the Soret band at 453 nm.[11]

Results and Discussion

Catalyst Efficiency. The stability of the halogenated hemin catalysts toward destruction during hydroxylations as well as the selectivity toward alcohol formation can be seen in Table I. Carrying out the reaction at 1% conversion of cyclohexane to cyclohexanol results in 93% yield of cyclohexanol based upon the oxidant with a 37:1 ratio of alcohol to ketone. This seems to be a more selective hydroxylation than other metal-catalyzed hydroxylations, and, since even more stable catalysts are now available (see below), even more efficient hydroxylations of less reactive alkanes can be expected.

The unusual stabilities of some of the catalysts are seen in Table II which describes oxidations of dichloromethane. The catalysts 4^+Cl, 5^+Cl, and 6^+Cl having halogens on the pyrrole rings are especially resistant to oxidative destruction.

The overall rates of hydroxylation and epoxidation are independent of substrate type or concentration. This can be seen in the plots of concentration of oxidant, expressed as absorbance at 285 nm versus time in Figure 2. The traces for separate norbornene and norbornane oxidations are superimposed. The second-order rate constants for oxidations of norbornane, cyclohexane, and epoxidation of norbornene using 1^+Cl^- and 2^+Cl^- catalysts are listed in Table III. Although independent of the type of substrate the rate constants show a dependence on catalyst structure as we had previously indicated.[11] In the two-step process of eqs 7 and 8, the oxygen-transfer step (k_2) is more dependent upon the hemin structure than is the preequilibrium (K_7), consistent with previous findings.[12] Otherwise the more electronegative hemin should give a faster rate of reaction.



Finding that relative reactivities of substrates cannot be easily obtained by direct measurement, we have used competitive experiments to establish these reactivities. Oxidation of various mixtures of alkanes and alcohols to low conversion and analysis of the products allows direct calculation of relative rates. These and turnovers, based upon pentafluoroiodobenzene produced, are listed in Table IV. One of the interesting findings in this study is that the exo to endo abstraction ratio $k^{ab}_{exH}/k^{ab}_{enH}$ for norborneols

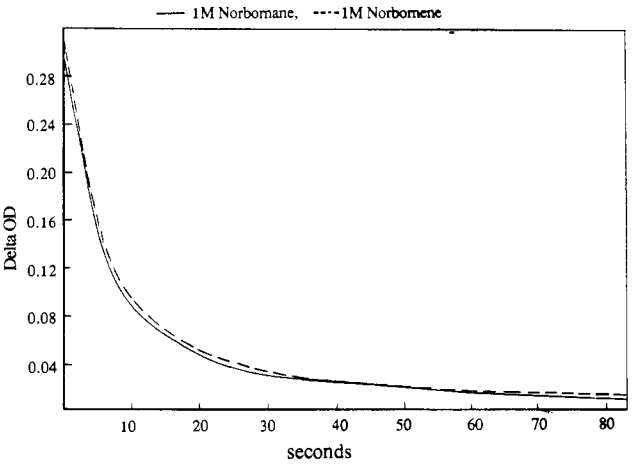
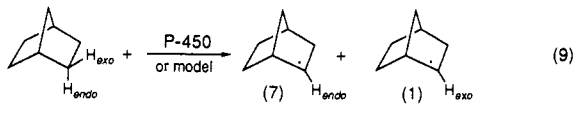
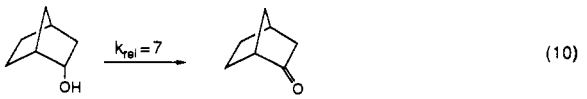


Figure 2. Plots of absorbance versus time after mixing adding PFIB in the CH_2Cl_2, CF_3CH_2OH, and H_2O solvent (90:9:1) to a solution of 2^+Cl^- and substrate to bring concentrations to 1.6×10^{-5} M in 2^+Cl^-, 10^{-3} M in PFIB, and 1 M in substrate: (–) substrate norbornane and (––) substrate norbornene.

is similar to the product ratios found in both the model and the enzymatic oxidation of norbornane.[4] It also becomes clear from





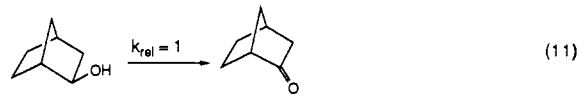
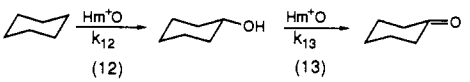
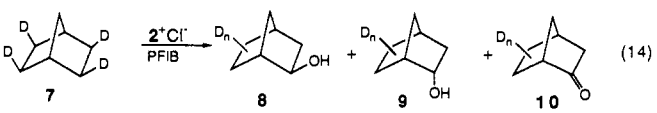


Table IV why cytochrome P-450 and model systems can achieve hydroxylation without further oxidation. The abstraction of a hydrogen α to an alcohol function is only about 10 times faster than that from alkanes. For example the actual relative rates $k_{13}/k_{12} \cong 1$ (11 on a per hydrogen basis).



Stereochemistry. Oxidations of norbornane and tetradeuterionorbornane were carried out using both 1^+Cl^- and 2^+Cl^- as catalysts, and the products were analyzed by gas chromatography. The yields and composition of products are shown in Table V along with those from the enzyme oxidation. The oxidation of norbornane catalyzed by 2^+Cl gives a product ratio exo/endo = 6.7 compared to 3.3 for the enzyme reaction. In both norbornane and tetradeuterionorbornane (**7**) oxidation a higher exo/endo product ratio was obtained with the hemin catalyst. The decrease in exo/endo alcohol ratio with exo deuterium substitution for the hemin-catalyzed hydroxylations closely parallels results with the P-450 enzyme system.[4a] Substitution of the exo hydrogens by deuterium results in reduced reactivity and an alteration of product ratios. These changes provide the means of determining the kinetic isotope effect and the stereospecificity of the reaction.



We have deliberately overoxidized the alcohol to produce a small amount of ketone as a probe for reactions 3–5. Because half of the cationic rearrangement product would have the deuteriums rearranged away from C_2 as shown below. The parent ion would display an M + 4 peak. Only the M + 3 peak was detected.

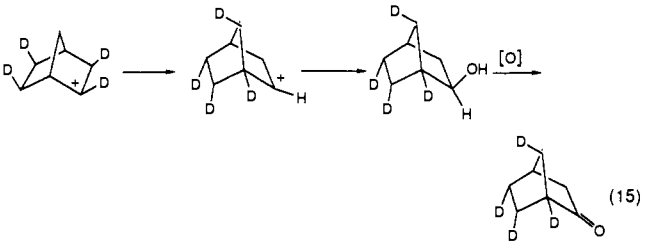
(10) Traylor, T. G.; Marsters, J. C., Jr.; Nakano, T.; Dunlap, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 5537.
(11) Traylor, T. G.; Xu, F. *J. Am. Chem. Soc.* **1988**, *110*, 1953.
(12) Traylor, T. G.; Lee, W. A. *J. Am. Chem. Soc.* **1984**, *106*, 755.

Table VII. Deuterium Content of Products from Oxidation of Tetradeuterionorbornane (**7**)[a]

catalyst	total D_3	total D_4	D_3/D_4	**8**-D_3	**8**-D_4	**9**-D_3	**9**-D_4	**10**-D_3[b]
2$^+Cl^-$	68	32	2.1	83	17	13	87	100
P-450	37	63	0.6	75	25	0.9	91	

[a] All values are percentages of the noted deuterium content in the product indicated or in the total alcohol product except for the ratio D_3/D_4 which refers to total D_3 and D_4 alcohols. [b] 2-Norbornone was formed by deliberately over oxidizing **7**.

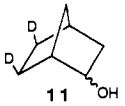
Therefore such rearrangement does not occur in this hydroxylation. We further conclude that the electron transfer of eq 3 is probably not involved.[13] Groves has provided other evidence against carbocation formation.[4b]



(15)

We can determine stereospecificity from the ratios of exo to endo alcohols produced along with the deuterium content of each alcohol using the method developed by Groves et al.[4a] Additionally, the relative rates of oxidation of norbornane and **7**, taken with the above, afford isotope effects as well as abstraction and collapse ratios.

Mass spectral studies of deuterated norborneols have shown that not only do the exo and endo alcohols have identical fragmentation patterns but that negligible deuterium loss occurs from carbon 2 or 3 upon loss of water from the parent ion.[14,15] Therefore, the D_3 or D_4 containing derivatives of **8** and **9** will show identical $M^+ - H_2O$ (HOD) fragment intensities displaced by 1 and 2 mass units from the $M^+ - H_2O$ (HOD) peak of **11**.[4a]



11

The deuterium content of the various products of oxidation of **7** with **2**$^+Cl^-$ or cytochrome P-450 as catalysts are calculated from Table VI and the corresponding data of ref 4a and displayed in Table VII. From this data, previous workers calculated 14% leakage to endo product from exo abstraction. The amount of endo D_3 alcohol divided by the total D_3 alcohol affords the corresponding exo → endo leakage for our oxidation.

$$100F_{\text{exo}\rightarrow\text{endo}} = \frac{0.13 \times 0.21}{(0.13 \times 0.21) + (0.83 \times 0.79)} \times 100 = 4\% \quad (16)$$

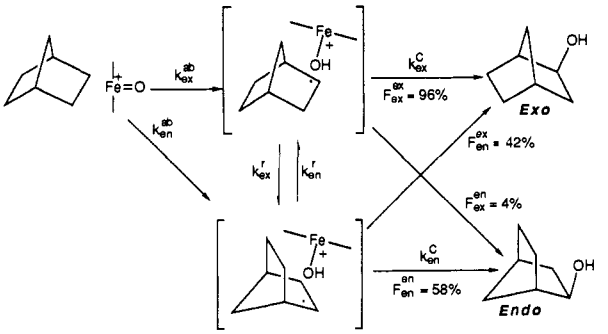
Similarly, the

$$\text{endo} \rightarrow \text{exo leakage, } 100F_{\text{endo}\rightarrow\text{exo}} = 42\% \quad (17)$$

These leakages, being not quite statistical, require an intermediate cage process represented as a free-radical cage in Scheme I.

If we assign $k^r_{en} = k^r_{ex} \cong k^r$ then the total rate (as a first-order k) of disappearance of the radical pair from exo abstraction is given by the rate of direct collapse k^c_{ex} plus the rate of rotation times the fraction of rotated product giving alcohol. The fraction

Scheme I[a]



[a] The rate constants, k^x_y, represents process x from the position y, exo (ex) or endo (en): abstraction = ab, rotation = r, collapse to product, c.

of exo radical pair which gives exo product is then obtained from the following equations.

$$F^{ex}_{ex} = \frac{k^c_{ex}}{k^c_{ex} + k^r F^{en}_{en}} \quad \text{or} \quad 0.96 = \frac{k^c_{ex}}{k^c_{ex} + k^r\left(\dfrac{k^c_{en}}{k^c_{en} + k^r}\right)} \quad (18)$$

$$F^{en}_{en} = \frac{k^c_{en}}{k^c_{en} + k^r F^{ex}_{ex}} \quad \text{or} \quad 0.58 = \frac{k^c_{en}}{k^c_{en} + k^r\left(\dfrac{k^c_{ex}}{k^c_{ex} + k^r}\right)} \quad (19)$$

Therefore

$$\frac{k^c_{ex}}{k^r} = 8$$

and by similar methods

$$\frac{k^c_{en}}{k^r} = 0.6$$

The exo radical pair collapses to product 13 times faster than does the endo pair, and the rotation is 1.5 times faster than endo collapse.

Green[16] and Kopecky[17] showed that α-phenethyl radicals, generated from α-azophenylethane, rotate in the cage about 14 times faster than they combine and six times faster than they diffuse from the cage at low viscosities. In our case the collapse of the exo radical pair exceeds rotation by at least a factor of 8, and the collapse of endo radical pair is 0.6 times of rotation. We provide no evidence concerning diffusion from the cage, but it must be less important than in alkyl radical combinations because collapse is faster. Nevertheless, Groves et al.[18] have reported products of halogen abstraction during hydroxylation, indicating some escape from the cage.

The faster collapse of the [R•Fe=O] cage might explain the reported retention of configuration in the hydroxylation of *trans*-decalin,[19,20] where the 9-decalyl radical might be expected to rotate more slowly than the 2-norbornyl radical.

The stereospecificities of the reaction can be assessed from the amount of deuterium in the exo or the endo alcohols. If the reaction involved retention of configuration at both positions, then

(13) The electron transfer would only be detected for endo abstraction which would require a rotation of the radical in order to detect rearrangement. A more definitive experiment would require endo deuterium substitution in norbornane.
(14) Holmes, J. L.; McGillivary, D. *Org. Mass. Spectrom.* **1973**, *7*, 559.
(15) Jelus, B. L.; Dalrymple, D. L.; Michnowicz, J.; Munson, B. *Org. Mass. Spectrom.* **1978**, *13*, 163.
(16) Greene, F. D.; Berwick, M. A.; Stowell, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 867.
(17) Kopecky, K. R.; Gillian, T. *Can. J. Chem.* **1969**, *47*, 2371.
(18) Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6377.
(19) Lindsay-Smith, J. R.; Sleath, P. R. *J. Chem. Soc., Perkins Trans.* **1983**, 1165.
(20) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243.

the exo alcohol would contain 100% D_3 and the endo alcohol would contain 100% D_4 forms. Complete loss of stereochemistry in solution can be assumed for free norbornyl radicals in solution. In this case both exo and endo alcohols would contain the observed statistical amounts of D_3 and D_4, i.e., 68% D_3. The observed amount of D_3 in the exo alcohol is 87% indicating a (100 − 87)/(100 − 68) × 100 = 53% loss of stereochemistry. By similar reasoning the endo alcohol lost 20% of stereospecificity. This partial loss of stereochemistry is best explained with the cage return, "rebound" of the [R•HO⁺Fe] pair as suggested by Groves.[4a]

Isotope Effects and Relative Abstraction Rates. The relative reactivities of norbornane and **7** catalyzed by $\mathbf{2}^+Cl^-$ (Table IV) are the combination of exo and endo hydrogen (deuterium) reactivities. If we neglect secondary deuterium isotope effects we can express the relative reactivities of the protio- and deuterionorbornanes in terms of abstraction rate constants.

$$\frac{k_{\text{norbornane}}}{k_7} = \frac{k^{ab}_{exH} + k^{ab}_{enH}}{k^{ab}_{exD} + k^{ab}_{enH}} = 3.8 \qquad (20)$$

The ratio of $k^{ab}_{exD}/k^{ab}_{enH}$ is equal to the ratio of the total yield of D_3 alcohols divided by the total yield of D_4 alcohols (see Table VII).

$$\frac{\sum D_3\text{prod.}}{\sum D_4\text{prod.}} = \frac{k^{ab}_{exD}}{k^{ab}_{enH}} = 2.1 \pm 0.3 \qquad (21)$$

Combining eqs 22 and 21 provides the relative rates of abstraction of the exo and endo hydrogens.

$$\frac{k^{ab}_{exH}}{k^{ab}_{enH}} = 10.8 \pm 1.4 \qquad (22)$$

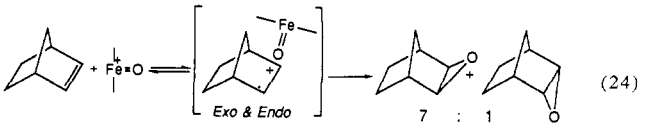
It follows that the isotope effect for abstraction is given by the following equation.

$$\frac{k_H}{k_D} = \frac{k^{ab}_{exH}}{k^{ab}_{exD}} = \frac{\sum D_4\text{prod.}}{\sum D_3\text{prod.}} \times \frac{k^{ab}_{exH}}{k^{ab}_{enH}} = 5 \pm 1 \qquad (23)$$

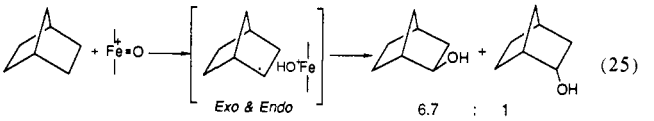
While not as large as the kinetic isotope effect reported for the enzyme, this value of k_H/k_D is similar to that which we have found for cyclohexane hydroxylation using this catalyst.[21]

It is interesting to compare the exo/endo product ratios (or derived radical collapse ratios) obtained in norbornane hydroxylation with those from norbornene epoxidation. The similarities in the observed product ratios using the catalyst $\mathbf{2}^+Cl$ are strikingly close, 7 vs. 6.7.

Since both reactions are proposed to proceed through the iron(IV) radical cage (perhaps the same iron species if Fe^+OH rapidly deprotonates) and both organic moieties are reactive



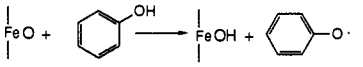
(24)



(25)

radicals, the reactions are reasonably considered to be alike. We consider this as additional evidence for electron transfer in alkene epoxidation involving these electronegative catalysts, a process discussed in detail elsewhere.[2,22]

These results begin to reveal something of the difference between the "oxo" (Fe(IV)) and "oxene" (Fe(IV) radical cation). The former is unable to abstract an electron from a norbornyl radical (and from comparison of ionization potentials could not abstract an electron from an alkene) but is capable of collapse with a radical at diffusion-controlled rate. These results also lead to the conclusion that Fe=O could not abstract an electron from phenols, and yet it surely reacts with phenols, suggesting that the reaction is probably one of radical abstraction.



(26)

Conclusion

The hydroxylation of alkanes with synthetic hemins as catalysts, large hydrogen isotope effects, relative reactivities, and partial loss of stereospecificity are consistent with free-radical abstraction followed by cage collapse and inconsistent with either direct insertion or the intermediary of carbocations. In all regards, the model oxidations qualitatively resemble the enzyme hydroxylation.

Acknowledgment. We are grateful to the National Science Foundation, Grant No. CHE 87-21364 and the National Institutes of Health, Grant No. PHS AM07233 for support.

Registry No. $\mathbf{1}^+Cl^-$, 91042-27-2; $\mathbf{2}^+Cl^-$, 107053-17-8; $\mathbf{3}^+Cl^-$, 36965-71-6; $\mathbf{4}^+Cl^-$, 138061-11-7; $\mathbf{5}^+Cl^-$, 134131-11-6; $\mathbf{6}^+Cl^-$, 121605-75-2; **7**, 3574-60-5; **8**-d_3, 138061-08-2; **8**-d_4, 138061-09-3; **9**-d_3, 138230-65-6; **9**-d_4, 138230-66-7; **10**-d_3, 138061-10-6; *exo*-**11**, 28956-13-0; *endo*-**11**, 28956-12-9; D_2, 7782-39-0; PFIB, 14353-90-3; norbornadiene, 121-46-0; sodium azodicarboxylate, 5954-19-8; azodicarbonamide, 123-77-3; *exo*-norbornen-5-ol, 2890-98-4; *endo*-norbornen-5-ol, 7782-39-0; cyclohexane, 110-82-7; (−)-norbornene, 279-23-2; norbornene, 498-66-8; *endo*-norbornan-2-ol, 497-36-9; *exo*-norbornan-2-ol, 497-37-0; cyclohexanol, 108-93-0.

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