Intramolecular Kinetic Isotope Effects in Alkane Hydroxylations Catalyzed by Manganese and Iron Porphyrin Complexes

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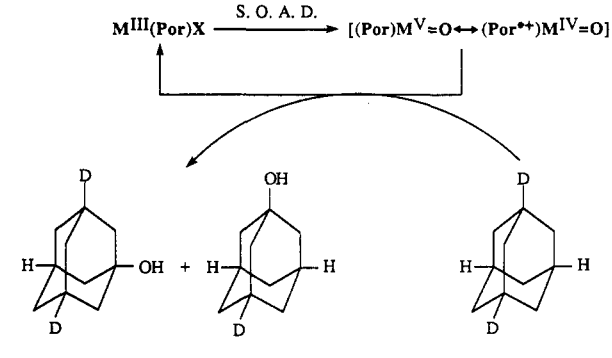
Received January 27, 1993. Revised Manuscript Received May 3, 1993

Abstract: Intramolecular kinetic isotope effects (KIEs) in alkane hydroxylations catalyzed by manganese and iron porphyrins have been studied with 1,3-dideuterioadamantane as substrate. This substrate is highly suitable for determination of primary isotope effects in metalloporphyrin-catalyzed hydroxylations: the high chemical reactivity of tertiary C–H (D) bonds avoids side reactions which complicate product analyses, and tertiary C–H and C–D bonds have the same steric and stereochemical environment. Kinetic isotope effects have been determined with adamantane-*1,3-d*$_2$ (98 atom % D) and iron and manganese complexes of *meso*-tetrakis(2,6-dichlorophenyl)porphyrin and *meso*-tetramesitylporphyrin [M^{III}(TDCPP)Cl and M^{III}(TMP)Cl,M^{III} = Fe or Mn] as catalysts. $KHSO_5$, NaOCl, and PhIO were used as simple oxygen atom donors. All KIE data were calculated taking into account isotope purity corrections and integrated scan calculations. The highest KIE values were obtained with Fe(TMP)Cl/NaOCl and Fe(TMP)-Cl/PhIO: 8.71 ± 0.20 and 7.52 ± 0.21, respectively. With $KHSO_5$, all KIEs are rather low, between 4.09 ± 0.17 and 4.74 ± 0.17 with Fe(TMP)Cl and Mn(TMP)Cl, respectively (values obtained with benzene as solvent). On one hand, these KIE values obtained with various metalloporphyrin catalysts associated with different oxidants suggest that the nature of the high-valent metal–oxo species is probably a "pure" metal–oxo species when iron porphyrins, especially Fe(TMP)Cl, are activated by NaOCl or PhIO. The leaving group of the oxidant is probably not involved in the rather symmetrical H-transfer transition state in these cases. On the other hand, active metal–oxo species generated by $KHSO_5$ regardless of the metalloporphyrin or by PhIO or NaOCl activated with manganese porphyrins might qualify as *metal–oxo like* species, since the leaving group of the oxidant is probably involved in the transition state which is consequently more bent than with catalytic systems generating a *pure metal–oxo* entity, as is the case for Fe(TMP)Cl associated with PhIO or NaOCl. The temperature dependence on KIE values obtained with different metalloporphyrin catalysts confirms the different transition state geometries between iron and manganese porphyrins and suggests that the high KIEs obtained with Fe(TMP)Cl associated with NaOCl or PhIO might be due to the possible contribution of a tunneling effect.

Introduction

Saturated alkane hydroxylations are catalyzed by cytochrome P-450 enzymes[1] and by iron and manganese tetraarylporphyrin complexes.[2] Both enzymatic and biomimetic hydroxylations involve the oxidative cleavage of a C–H bond by a high-valent metal–oxo species as the rate-determining step in alcohol formation (see Scheme I for a possible catalytic cycle of alkane hydroxylations by P-450 model systems). Large kinetic isotope effects (KIEs) accompanied by high retention of configuration at the carbon undergoing oxidation provided strong evidence for hydrogen atom abstraction in the oxygen-rebound mechanism.[4] Data on the magnitude of KIEs have been obtained by intermolecular or intramolecular isotope effect studies[5] (some examples have been summarized in Table I for oxidation catalyzed by cytochrome P-450 or by metalloporphyrins). The intramolecular approach is more accurate for the determination of primary

Scheme I. Adamantane-*1,3-d*$_2$ Hydroxylation Catalyzed by Different Metalloporphyrins Associated with Various Single Oxygen Atom Donors (PhIO, NaOCl, etc)[a]



AdOH-*d*$_2$ (MW 154) AdOH-*d*$_1$ (MW 153) Ad-*d*$_2$ (MW 138)

[a] The exact distribution of the two oxidant equivalents between the metal center and the ligand in the active form of the catalyst is still an open question (see refs 2 and 3). Another alternative proposal is a (Por)M^{IV}–O• complex.

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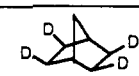
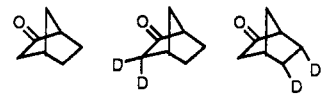
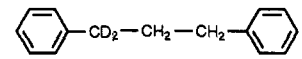
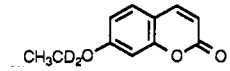
0002-7863/93/1515-7293$04.00/0

Table I. Kinetic Isotope Effects Associated with Alkane Hydroxylations by Cytochromes P-450 and Chemical Model Systems

entry	oxidation system[c] (t, °C)	substrate	k_H/k_D	ref
1	cytochrome P-450[a]		11.5 ± 1.0	4a
2	cytochrome P-450$_{cam}$[a]		3.8	6
3	cytochrome P-450		11	7
4	cytochrome P-450		12.8–14.0	8
5	cytochrome P-450 (37 °C)	anisole, methyl-d_3-anisole	10.5 ± 0.7	9
6	cytochrome P-450[a]	geraniol-*8,8*-d_2	8.0 ± 0.5	10
7	cytochrome P-450 (25 °C)	*n*-octane-*1,1,1*-d_3	11.77 ± 0.19	11
8	cytochrome P-450$_b$ (25 °C)	*n*-octane-*1,1,1*-d_3 *n*-octane-*1,1,8,8*-d_4 *n*-octane-*1,8*-d_2	primary: 9.10 ± 0.03 (d_3/d_4) 9.18 ± 0.28 (d_3/d_2) secondary: 1.14 ± 0.01 (d_3/d_4) 1.13 ± 0.10 (d_3/d_2)	12
9	cytochrome P-450$_c$ (25 °C)	*n*-octane-*1,1,1*-d_3 *n*-octane-*1,1,8,8*-d_4 *n*-octane-*1,8*-d_2	primary: 8.96 ± 0.17 (d_3/d_4) 7.69 ± 0.60 (d_3/d_2) secondary: 1.16 ± 0.02 (d_3/d_4) 1.25 ± 0.10 (d_3/d_2)	13
10	cytochrome P-450$_{LM2}$ (25 °C)		primary: 8.91 ± 0.12 (d_3/d_4) 9.02 ± 0.32 (d_3/d_2)	13
11	cytochrome-P-450$_{LM2}$ (25 °C)	(*R*)-(−)-phenylethane-*1-d* (*S*)-(+)-phenylethane-*1-d*	for *R* abstraction: 4.0 ± 1.3 for *S* abstraction: 19 ± 10	14
12	chiral binaphthyl iron porphyrin/PhIO (CH_2Cl_2)[a]	(*R*)-(−)-phenylethane-*1-d* (*S*)-(+)-phenylethane-*1-d*	for *R* abstraction: 6.4 for *S* abstraction: 6.4	15
13	FeTTPCl/PhIO (CH_2Cl_2) (0 °)	C_6H_{12}/C_5H_{10}, C_6D_{12}/C_5H_{10}	12.9 ± 1.0	4b
14	MnTTPPP(OAc)/PhIO(C_6H_6) (25°)	$CH_3CD_2CH_2CD_2CH_3$	3.5	16
15	MnTDCPPCl/$KHSO_5$(CH_2Cl_2)[a]	C_6H_{12}, C_6D_{12}	2.0 ± 0.2	17
	MnT*o*FPPCl/$KHSO_5$		2.5 ± 0.2	
	MnTF_5PPCl/$KHSO_5$		2.5 ± 0.2	
	MnTPPCl/$KHSO_5$		2.2 ± 0.2	
	MnTMPCl/$KHSO_5$		2.9 ± 0.2	
	FeTMPCl/$KHSO_5$		2.0 ± 0.2	
16	MnTPpyPP(OAc)/PhIO (C_6H_{12}/CH_2Cl_2 = 3/7)[a]	C_6H_{12}, C_6D_{12}	11.8	18
	MnTPpyPP($O_2C_8F_{15}$)/PhIO		5.7	
	MnTPpyPP($O_3SC_6F_{13}$)/PhIO		3.7	
17	Fe(Br_8TDCPP)Cl/PhIO (CH_2Cl_2)[a]		5	19
18	FeTMPCl/NaOCl(C_6H_6) (20.0 ± 0.1)	C_6H_{12}/C_5H_{10}, C_6D_{12}/C_5H_{10}	21.9 ± 1.9	20
	FeTMPCl/NaOCl(PhCl)		10.0 ± 0.4	
	FeTMPCl/NaOCl(PhCN)		10.2 ± 0.6	
	FeT*p*BuPPCl/NaOCl(C_6H_6)		21.1 ± 1.6	
	FeTPPCl/NaOCl(C_6H_6)		17.8 ± 2.3	
	FeT*p*FPPCl/NaOCl (C_6H_6)		14.4 ± 0.7	
	FeT*o*FPPCl/NaOCl(C_6H_6)		10.9 ± 0.9	
	FeT*o*FPPCl/NaOCl(PhCN)		6.0 ± 0.6	
	FeTF_5PPCl/NaOCl(C_6H_6)		10.6 ± 0.4	
	FeT*o*ClPPCl/NaOCl(C_6H_6)		10.7 ± 0.4	
	FeT*o*NO_2PPCl/NaOCl(C_6H_6)		9.3 ± 0.3	
19	MnTDCPPCl/MMPP(CH_2Cl_2)[a]	C_6H_{12}, C_6D_{12}[b]	2.1	21
	MnTMPCl/$KHSO_5$(CH_2Cl_2)	C_6H_{12}/C_8H_{16}, C_6D_{12}/C_8H_{16}	3.1	
	$MnCl_{12}$TMPCl/$KHSO_5$(CH_2Cl_2)		3.4	
	MnTDCPPCl/$KHSO_5$(CH_2Cl_2)		2.1 ± 0.2	
	$MnBr_8$TMPCl/$KHSO_5$(CH_2Cl_2)		2.3 ± 0.3	
	FeTDCPPCl/$KHSO_5$(CH_2Cl_2)		1.5 ± 0.7	
	$FeBr_8$TMPCl/$KHSO_5$(CH_2Cl_2)		1.2 ± 0.4	
	MnTDCPPCl/*n*Bu_4NHSO_5(CH_2Cl_2)		2.8 ± 0.6	
	$MnBr_8$TMPCl/*n*Bu_4NHSO_5(CH_2Cl_2)		4.9 ± 0.2	
	FeTDCPPCl/*n*Bu_4NHSO_5(CH_2Cl_2)		2.3 ± 1.2	
	$FeBr_8$TMPCl/*n*Bu_4NHSO_5(CH_2Cl_2)		2.9 ± 1.3	
	MnTDCPPCl/PhIO(CH_2Cl_2)		2.6 ± 0.4	
	$MnBr_8$TMPCl/PhIO(CH_2Cl_2)		1.8 ± 0.3	
	FeTDCPPCl/PhIO(CH_2Cl_2)		9 ± 3	
	$FeBr_8$TMPCl/PhIO(CH_2Cl_2)		7.7 ± 0.6	

[a] No data about reaction temperature. [b] KIE were calculated on substrate conversion. [c] TPP, *meso*-tetraphenylporphyrin dianion; T*o*ClPP, *meso*-tetrakis(*o*-chlorophenyl)porphyrin dianion; T*o*FPP, *meso*-tetrakis(*o*-fluorophenyl)porphyrin dianion; T*p*FPP, *meso*-tetrakis(*p*-fluorophenyl)porphyrin dianion; T*o*NO_2PP, *meso*-tetrakis(*o*-nitrophenyl)porphyrin dianion; TPP, *meso*-tetra-(*o*-tolyl)porphyrin dianion; TPpyPP, *meso*-tetrakis(4-pyridylphenyl)porphyrin dianion; TF_5PP, *meso*-tetrakis(pentafluorophenyl)porphyrin dianion; T*p*BuPP, *meso*-tetrakis(*p-tert*-butylphenyl)porphyrin dianion; TMP, *meso*-tetramesitylporphyrin dianion; Br_8TMP, *meso*-tetramesityl-β-octabromoporphyrin dianion; Cl_{12}TMP, *meso*-tetrakis(3-chloro-2,4,6-trimethylphenyl)-β-octachloroporphyrin dianion; TDCPP, *meso*-tetrakis(2,6-dichlorophenyl)porphyrin dianion; Br_8TDCPP, *meso*-tetrakis(2,6-dichlorophenyl)-β-octabromoporphyrin dianion; MMPP, magnesium salt of the monoperoxyphthalic acid, hexahydrate.

intrinsic isotope effects, because in enzyme-catalyzed reactions kinetic effects are often influenced by pre- or postcatalytic steps not involving the C–H bond cleavage itself. Additional stereochemical factors might also complicate the determination of intrinsic kinetic isotope effects, *i.e.* $k_H/k_D = 8.7$ for ethylbenzene-d_{10} hydroxylation catalyzed by a chiral binaphthyl iron porphyrin/iodosylbenzene system, whereas $k_{RH}/k_{RD} = 6.4 = k_{SH}/k_{SD}$ (*pro-R* and *pro-S* hydrogen removal, respectively) when the two enantiomers of ethylbenzene-*1-d* are used.[15] But for ethylbenzene-*1-d* hydroxylation performed by cytochrome P-450$_{LM2}$, a large deuterium isotope effect was observed for *pro-S* hydrogen removal ($k_{SH}/k_{SD} = 19 \pm 10$) and a smaller one for *pro-R* hydrogen removal ($k_{RH}/k_{RD} = 4.0 \pm 1.3$) because cytochrome P-450$_{LM2}$ exhibits *pro-R* hydrogen removal 4-fold less favorably than *pro-S* for ethylbenzene-*1-d*.[14] Finally, introduction of an even slight dissymmetry by isotopic substitution has been shown to influence primary and especially secondary KIE.[22] In alkane hydroxylations catalyzed by cytochrome P-450 models, KIE values were found to be dependent on the nature of (i) the oxidant (with PhIO $k_H/k_D = 6$ to 12, whereas with $KHSO_5$ $k_H/k_D = 2.5$ to 5), (ii) the central atom of the complex (higher KIE values were found with iron complexes compared to those with manganese), and (iii) the ligand itself (lower KIEs were observed with *meso*-tetrakis(2,6-dichlorophenyl)porphyrin compared to *meso*-tetramesitylporphyrin or its derivatives).[4,21] However, most of these data on biomimetic systems have been obtained by using the intermolecular approach (*i.e.* cyclohexane *versus* cyclohexane-d_{12}), and furthermore, these KIE values are a combination of primary and secondary isotope effects, although an approach to separate primary and secondary components of KIEs has been developed for enzyme-catalyzed hydroxylations.[12-15] This approach was based on models with several successive calculations, and consequently with propagation of experimental errors which can easily result in deviations as large as some secondary KIEs.[23] When the KIE studies are performed on secondary C–H bond hydroxylations, simultaneous formation of alcohol and ketone is usually observed. The formation of ketone proceeds *via* the cleavage of two C–H bonds and, therefore, product yields cannot be considered as a direct indication of the C–H or C–D bond activation step.[21] The values of KIE calculated by adding all reaction products could not be considered as reliable.[24] In order to overcome these different problems we decided to investigate KIEs in biomimetic hydroxylations by using a substrate with the following properties: (i) a high chemical reactivity of tertiary C–H (D) bonds to avoid side reactions masking the hydroxylation step and complicating the product analysis, (ii) C–H and C–D bonds with equal steric and stereochemical environment, and (iii) an easy preparation of the starting material to facilitate its use in C–H bond activation studies by different enzymes or biomimetic catalysts. Taking into account all these requirements, adamantane-*1,3-d*$_2$ appears to be highly suitable for intramolecular KIE determinations (see Scheme I). The two tertiary C–D bonds have the same steric and stereochemical environment as the two other tertiary C–H bonds. The resulting tertiary alcohols are stable in the reaction mixture, making possible the determination of KIEs based on product formation.

Here, we report KIE values obtained in the hydroxylation of adamantane-*1,3-d*$_2$ by various P-450 models. We used iron and manganese complexes of two sterically hindered porphyrin ligands: *meso*-tetrakis(2,6-dichlorophenyl)porphyrin [M^{III}(TDCPP)Cl, M = Fe or Mn] and *meso*-tetramesitylporphyrin [M^{III}(TMP)Cl]. Both ligands are known for avoiding the formation of inactive dimeric μ-oxo species.[2] The first ligand exhibits electron-withdrawing substituents on the phenyl groups and the second one electron-donating substituents. PhIO and two water-soluble oxygen atom donors, $KHSO_5$ and NaOCl, have been used. Catalytic hydroxylation reactions were performed in solvents of different polarity, dichloromethane or benzene. The KIE values reported in the literature for cytochrome P-450 and model systems (Table I) show a rather large range of k_H/k_D, from 2 up to 22. Some of these high KIE values are higher than semiclassical isotope effect (7 is usually considered as the maximum value)[25-27] and suggest the occurrence of hydrogen atom tunneling during the attack of the C–H bond by the high-valent metal–oxo species. Temperature dependence of k_H/k_D was studied not only to investigate the possible transition state structure but also to indicate a possible tunneling effect.[28,29] Temperature dependence of k_H/k_D was studied from 10 to 60 °C for the three hydroxylation systems Fe(TMP)Cl/NaOCl, Fe(TMP)Cl/PhIO, and Mn(TMP)Cl/$KHSO_5$ and from 5 to 38 °C for the Mn(TDCPP)Cl/$KHSO_5$ system.

Experimental Section

Instrumentation. Gas chromatography analyses were performed with an Intersmat IGC 120 DFL chromatograph equipped with a flame ionization detector and a 30 m × 0.25 mm capillary column bonded FSOT Superox II (Alltech). N_2 was the carrier gas. The internal standard method was employed for absolute quantification (1,4-dibromobenzene being the standard). FT-NMR spectra were recorded on Bruker spectrometers (AC 200 for ^{1}H nucleus and WM 250, working at 62.9 MHz for ^{13}C nucleus). Gas chromatography-mass spectroscopy (GC-MS) was performed on a Hewlett-Packard 5890 instrument using electron-impact ionization at 70 eV. The carrier gas for GC-MS was He, and the following capillary columns were used: a non-polar column A, 12 m × 0.2 mm HL-1 (Crosslinked Methyl Silicone Gum), a polar column B, 25 m × 0.2 mm HL-20M (Carbowax 20M).

Materials. All chemicals used were of reagent grade. Dichloromethane (99.95%, stabilized by 0.3% ethanol) was used without further purification. Benzene was distilled before use. Potassium monopersulfate was a gift from Interox (Curox) and is the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. Sodium hypochlorite was obtained from Prolabo as a 0.52 M aqueous solution, titrated by iodometry; sodium hydroxide was added to keep alkali concentration about 1 M. Iodosylbenzene was prepared from iodobenzene diacetate.[30] Lithium aluminum deuteride was purchased from Fluka (minimum 99 atom % D). *meso*-Tetramesitylporphyrin (H_2-TMP) and *meso*-tetrakis(2,6-dichlorophenyl)porphyrin (H_2TDCPP) were synthesized according to ref 21. Iron and manganese insertions into porphyrins were carried out as previously described.[31] In all cases, the axial ligand of metalloporphyrins used as catalyst precursors was Cl$^-$.

1,3-Dibromoadamantane synthesis was performed in a similar way as previously described.[32] Adamantane (1.36 g, 10.0 mmol) was added portionwise to a stirred mixture of dry bromine (5 mL), $AlBr_3$ (11 mg, 0.04 mmol), and BBr_3 (0.24 mL, 2.5 mmol) under dry nitrogen. The

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reaction mixture was refluxed for 75 min and the stirring continued at room temperature for 45 min. The mixture was then poured on *ca.* 30 mL of crushed ice. Carbon tetrachloride (40 mL) was added and the organic layer was separated and washed with a saturated solution of Na_2SO_3 (3 × 10 mL) in order to remove excess bromine. The original aqueous layer was extracted with CCl_4 (2 × 20 mL), and the combined organic extracts were washed successively with a 5% solution of $NaHCO_3$ and H_2O and then dried over $MgSO_4$. The crude yellow dibromide obtained after removal of solvent was recrystallized from methanol. The yield was 2.21 g (75%) of the expected 1,3-dibromoadamantane (1,3-dibromotricyclo[3.3.1.1^{3,7}]decane), and the product was 99% pure (GC analysis). ^{1}H NMR (δ, $CDCl_3$): 2.88 (bs, 2H, H-2), 2.31 (bs, 8H, H-4,8,9,10), 2.26 (m, 2H, H-5,7 from tertiary carbons), 1.71 (m, 2H, H-6).

Adamantane-*1,3-d*$_2$ synthesis was performed according to a preparation published for adamantane-*1,3,5,7-d*$_4$.[33] To a stirred suspension of $LiAlD_4$ (300 mg, 7 mmol) is 35 mL of dry diethyl ether under nitrogen was added tri-*n*-butyltin chloride (0.9 g, 2.4 mmol) in diethyl ether (5 mL). Then 1,3-dibromoadamantane (2.1 g, 7 mmol) was added in one portion and the resulting mixture was stirred and heated under reflux under nitrogen for 24 h. After the mixture stood at room temperature for an additional 24 h, GC indicated that the reduction was complete. The reaction mixture was cooled at −40 °C and deuterium oxide 99.9% (4 mL) was added slowly. The temperature was raised to 20 °C, and the hydrolysis of the excess $LiAlD_4$ was performed for 30 min. The reaction mixture was poured into 30 mL of water and extracted with pentane (4 × 40 mL). The combined organic extracts were washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by chromatography on a column of basic alumina with hexane as eluent to afford adamantane-*1,3-d*$_2$. This product was recrystallized from a mixture of hexane and methanol: 966 mg (yield: 88%) of 99.2% pure product was obtained (purity measured by GC analysis). Its deuterium enrichment was 98.0 ± 0.2% adamantane-*1,3-d*$_2$ and 2.0% adamantane-*1-d*$_1$. ^{13}C NMR (δ, $CDCl_3$): 37.6 (C-1,3,5,7), 28.3 (C-2,4,6,8,9,10). MS data from GC-MS: *m/z* (rel intensity) 139 (11.1), 138 (100.0), 137 (20.5), 136 (6.0), 123 (7.5), 109 (6.1), 95 (29.9), 94 (28.5).

Deuterium Enrichment Measurement. Direct GC-MS analysis of adamantane-d_2 was not suitable for calculating the deuterium content of adamantane-d_2, due to a rather important fragmentation at M − 1, even with a low voltage ionization current. But deuterium content calculations are possible from adamantanone which is the main coproduct in catalytic oxygenation of adamantane-d_2 and gives a strong molecular peak in GC-MS analysis without M − 1 fragmentation. During the formation of this ketone, there is no oxidation of the tertiary C–H or C–D bonds and no change in their proportions. Thus, adamantanone-d_2 should have the same deuterium content as the starting alkane. We calculated the deuterium enrichment of adamantane by GC-MS analysis of adamantanone based on the mean value obtained from 3 to 5 injections of 4 independent catalytic oxidations. The deuterium content of adamantanone, and consequently that of starting adamantane-d_2, was 98.0 ± 0.2%. In the last stage of the present work, this deuterium content was confirmed by analyses of adamantane-d_2 itself performed by GC equipped with an atomic emission detector (found value: 97.9 ± 0.3%).

Experimental Conditions for Alkane Hydroxylations. All reactions were performed in a thermostated reaction tube equipped with a magnetic stirring bar at 20.0 ± 0.5 °C under air. In a typical experiment, the manganese (0.001 mmol) or iron (0.005 mmol) porphyrin complex was dissolved in dichloromethane or benzene with benzyldimethyltetradecylammonium chloride (BDTAC, phase transfer catalyst, 0.038 mmol), 4-*tert*-butylpyridine (0.025 mmol), adamantane (0.250 mmol), and 1,4-dibromobenzene (GC internal standard, 0.100 mmol). The oxidizing agent was then added: 0.4 mmol of $KHSO_5$ in 5 mL of 0.25 M phosphate buffer at pH 7, 0.52 mmol of NaOCl in 1 mL of a 1 M NaOH solution, or 0.25 mmol of PhIO. The following modifications were introduced: (i) no axial nitrogen ligand was used with iron porphyrins, due to the rapid formation of the catalytically inactive bis-adduct Fe(porphyrin)L_2, (ii) there was no need for phase transfer catalyst (BDTAC) for reaction with PhIO. Reactions were monitored by gas chromatography. For KIE determinations, reactions were stopped at an adamantane-d_2 (Ad-d_2) conversion of 10%. In this case, due to the presence of an excess of Ad-d_2 substrate, 1-adamantanol (AdOH) conversion was negligible, avoiding the introduction of any error in the determination of the KIE. The exact isotopic composition of generated 1-adamantanol was determined by GC-MS analysis [data from GC-MS: *m/z* (mode of fragmentation, relative intensity) 153 [(M + 1)$^+$, isotopic ^{13}C peak, 3.3], 152 (M$^+$, 26.5), 109 [(M − C_3H_7)$^+$, 5.9], 96 (8.7), 95 [(M − C_4H_9)$^+$, 100], 94 (14.2), 77 (7.5)]. Because of the discrimination of AdOH-d_2 and AdOH-d_1 on GC columns, all chromatogram peaks were analyzed two or three times by a set of scans (see below for a discussion on this particular point).

Results and Discussion

Adamantane-*1,3-d*$_2$ Synthesis and Methods for KIE Determinations. Adamantane was treated under nitrogen with dry bromine in the presence of $AlBr_3$ and BBr_3 as previously reported.[32] Pure 1,3-dibromoadamantane (99% pure by GC) was isolated in good yield (75%). Its reduction by $LiAlD_4$ (99% D) in association with *n*-Bu_3SnCl provided the expected 1,3-dideuterioadamantane (Ad-*1,3-d*$_2$). The yield was 88% after chromatography on alumina and recrystallization from hexane–methanol. The final compound was found to be 99.2% pure by GC with a deuterium enrichment of 98.0% ± 0.2% for adamantane-*1,3-d*$_2$ and 2.0% for adamantane-*1-d*$_1$.

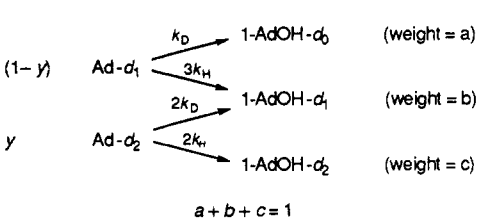
The kinetic isotope effects were measured by quantitative analysis of the deuterium content of tertiary adamantanol, the major primary hydroxylation product of adamantane-*1,3-d*$_2$ catalyzed by the different P-450 models. GC-MS analyses of adamantanols were performed without derivatization due to the rather strong parent peak of 1-adamantanol which was detected at 152 (26.5%) with the ^{13}C contribution at 153 (3.3%). All other fragments were below 110 mass units, leaving a large window for the analysis of parent peaks, 154 and 153 for 1-adamantanol-d_2 and 1-adamantanol-d_1, respectively. These two products correspond to the hydroxylation of a C–H bond or a C–D bond at a tertiary position of the starting adamantane-d_2 and the ratio of these two tertiary alcohols is directly the KIE value of the catalytic hydroxylation reaction (eq 1). Peak intensities at 153 and 154 have been treated according to the following formalism:

$$I_{153} = \text{AdOH-}d_1 \text{ and } I_{154} = \text{AdOH-}d_2 + \text{AdOH-}d_1\ (^{13}\text{C})$$

$$k_H/k_D = \text{AdOH-}d_2/\text{AdOH-}d_1 = (I_{154} - I_{153}/F)/I_{153} = I_{154}/I_{153} - 1/F \quad (1)$$

where I_{153} and I_{154} correspond to the intensities of peaks at 153 and 154 mass units, respectively, and F is the ratio between the parent peak and the isotope peak due to the natural isotopic abundances of ^{13}C and ^{2}H. The value $1/F = 11.0\%$ observed for mass data of 1-adamantanol is in good agreement with theoretical calculation: $1/F = 1.08\%$ (natural abundance of ^{13}C) × 10 atoms of C + 0.016% (natural abundance of ^{2}H) × 16 atoms of H = 11.06%.

However, 1,3-dideuterioadamantane cannot be synthesized with 100% deuterium enrichment because $LiAlD_4$ used for the synthesis has an isotopic enrichment between 99% and 100 atom % D. Hence incompletely labeled substrate must be taken into account according to the following calculations. Considering y as the molar fraction of Ad-d_2 and $(1-y)$ as the molar fraction of Ad-d_1 and assuming that rate constants for the cleavage of C–H and C–D bonds do not depend on the isotopic composition of the remaining part of the substrate, then one can assume that the weighted reaction pathways for the catalytic hydroxylation of 1,3-dideuterioadamantane by the different P-450 models are as follows:



The rate constants are statistically weighted for 1, and a, b, and c correspond to the molar fractions of 1-AdOH-d_0, 1-AdOH-d_1, and 1-AdOH-d_2, respectively, and they can be expressed by eqs 2–4.

Table II. Effect of the Deuterium Enrichment of Adamantane-d_2 on the Calculated Values of the Intrinsic Kinetic Isotope Effect

% deuterium enrichment of adamantane-d_2	intrinsic KIE	
	obsd k_H/k_D = 3.0	obsd k_H/k_D = 7.0
100	3.0	7.0
99	3.1	7.8
98	3.3	8.9
97	3.5	10.4
96	3.7	12.4
95	3.9	15.6

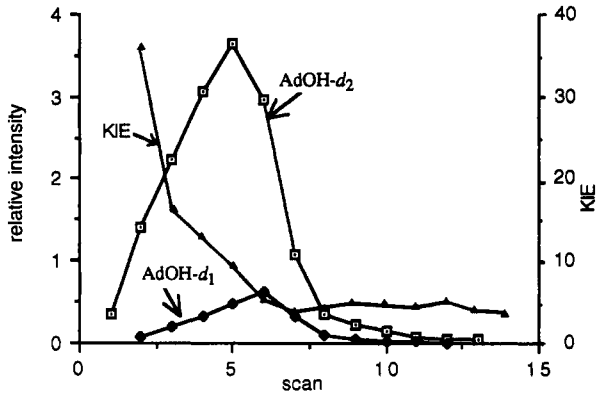


Figure 1. Dependence of k_H/k_D along the eluted peak in GC-MS. Catalytic system: Fe(TMP)Cl/NaOCl(C_6H_6). Integrated k_H/k_D value = 8.71.

$$a = (1-y)k_D \quad (2)$$

$$b = 3(1-y)k_H + 2yk_D \quad (3)$$

$$c = 2yk_H \quad (4)$$

Dividing eq 3 by eq 4 gives

$$b/c = 3(1-y)/2y + k_D/k_H \quad (5)$$

which after transformation into eq 6 allows for the introduction of a correction on the incompletely labeled substrate (*i.e.* the contamination of Ad-d_2 by Ad-d_1).

$$k_H/k_D = 1/[b/c - 3(1-y)/2y] \quad (6)$$

In the limiting case, deuterium enrichment can be equal to 100%, *i.e.* $y = 1$ and then $k_H/k_D = c/b$. What is the influence of this "isotopic purity correction" on calculated k_H/k_D values? As an illustration of the importance of this isotropic purity correction, we have indicated two examples of the dependence of intrinsic isotopic effects on isotopic composition of the substrate for experimental KIE values of 3.0 and 7.0 in Table II. For an experimental value of 3.0, the intrinsic KIE value ranges from 3.0 to 3.9 when the deuterium enrichment of the starting material decreases from 100% to 95%. This effect is even more important for an experimental value of 7.0 (a usual value in C–H bond activation by cytochrome P-450). In this latter case, intrinsic KIE values range from 7.0 to 15.6 when the deuterium enrichment of the starting material decreases from 100% to 95%! Therefore, the correction based on deuterium enrichment of the substrate is essential when intrinsic KIEs are large, and consequently, this factor was taken into account for all KIE determinations in the present study.

In addition to this possible source of errors in KIE determinations, we found that the small number of scans used to analyze the GC-MS peak corresponding to the mixture of 1-AdOH-d_1 and 1-AdOH-d_2 is also a second important source of error in KIE determinations. In fact, these two deuterated adamantanols do not have the same retention time on GC columns. The distribution of the two deuterated 1-adamantanols on the nonpolar column is illustrated by Figure 1. The 1-adamantanol peak was analyzed by a set of scans (usually 16) separated by 0.016 min, allowing a precise determination of the two deuterated product distributions: 1-AdOH-d_2 is eluted before 1-AdOH-d_1. Consequently, experimental KIE values are highly dependent on the scan position as indicated in Figure 1. At the beginning of the 1-adamantanol peak, KIE is as high as 36, and at the end of the alcohol peak it is as low as 3.3! The integrated value based on 16 scans (0.25 min) all along the elution of the present chromatogram peak is 8.71 ± 0.20. This peak integration seems to be correct for measuring the KIE values with the necessary accuracy and reproducibility. In general, it should be noted that the effect of a possible discrimination of labeled and unlabeled products on the chromatographic column during GC-MS product analysis must be considered to avoid a serious distortion of the KIE values obtained. This fact was recently pointed out for 1,2-diphenylethane and 1,2-diphenylethane-d_7 which were partially separated by capillary GC.[34] In the absence of such detailed GC-MS peak analysis, published KIEs on alkane hydroxylations catalyzed by monooxygenases or by metalloporphyrins are not necessarily very reliable.

Table III. Kinetic Isotope Effects Associated with Adamantane-d_2 Oxidation by Various Metalloporphyrin–Oxygen Atom Donor Systems in a Polar or Nonpolar Solvent, at 20 °C

entry	oxidant	metal	porphyrin ligand	k_H/k_D[a] in CH_2Cl_2	k_H/k_D[a] in C_6H_6
1	$KHSO_5$	Mn[b]	TMP	3.83 ± 0.09	4.74 ± 0.08
2			TDCPP	3.17 ± 0.13	3.57 ± 0.05
3		Fe[b]	TMP	2.83 ± 0.06	4.09 ± 0.17
4			TDCPP	3.32 ± 0.04	
5	PhIO	Mn	TMP	3.94 ± 0.07	
6			TDCPP	3.31 ± 0.07	4.64 ± 0.11
7		Fe	TMP	6.28 ± 0.13	7.52 ± 0.21
8			TDCPP	3.83 ± 0.06	
9	NaOCl	Mn	TMP	4.04 ± 0.10	
10			TDCPP	3.25 ± 0.07	3.78 ± 0.04
11		Fe	TMP	6.93 ± 0.17	8.71 ± 0.20
12			TDCPP	4.46 ± 0.08	4.96 ± 0.19
13	H_2O_2	Mn	TDCPP	3.10 ± 0.04	
14			TMP	3.70 ± 0.10	

[a] These data are mean values obtained from 3 to 5 different GC-MS analyses of 2 or 3 independent hydroxylation reactions. [b] In all cases, the axial ligand of the metalloporphyrin catalyst precursor is a chloride ion.

Kinetic Isotope Effects in Adamantane-*1,3*-d_2 Hydroxylation by Various Metalloporphyrins and Oxygen Atom Donors. Taking into consideration the isotopic purity correction and the integrated scan calculation, the determined KIE values in hydroxylations of adamantane-*1,3*-d_2 catalyzed by Mn- or Fe(TMP)Cl and by Mn- or Fe(TDCPP)Cl complexes associated with $KHSO_5$, PhIO, or NaOCl are reported in Table III. All data were determined at 20 °C. The highest primary kinetic isotope effects were obtained with NaOCl as the oxygen atom donor. With this oxidant in a biphasic dichloromethane/water medium, KIEs are 6.93 and 4.46 for Fe(TMP)Cl and Fe(TDCPP)Cl, respectively (entries 11 and 12), higher than the KIEs for the corresponding manganese derivatives, 4.04 and 3.25 for Mn(TMP)Cl and Mn(TDCPP)Cl, respectively (entries 9 and 10). The KIE values obtained with PhIO as oxidant are slightly lower than those obtained with NaOCl, especially when iron porphyrins are used as catalysts: 6.28 for the Fe(TMP)Cl/PhIO system (entry 7) compared to 6.93 with Fe(TMP)Cl/NaOCl (entry 11) and 3.83 for Fe(TDCPP)Cl/PhIO (entry 8) compared with 4.46 with Fe(TDCPP)Cl/NaOCl (entry 12). It has to be noted that the value of 6.28 for Fe(TMP)Cl/PhIO is close to the value of 6.4 found in the hydroxylation of (*R*)- and (*S*)-phenylethane-*1-d* (entry 12, Table I) but definitively lower than the intermolecular KIE value of 12.9 found in the hydroxylation of cyclohexane by Fe(TPP)Cl/PhIO (entry 13, Table I). With $KHSO_5$ as the oxidant

(34) Shaffer, M. W.; Leyva, E.; Soudararajan, N.; Chang, E.; Chang, D. H. S.; Capuano, V.; Platz, M. S. *J. Phys. Chem.* **1991**, *95*, 7273–7277 and references therein.

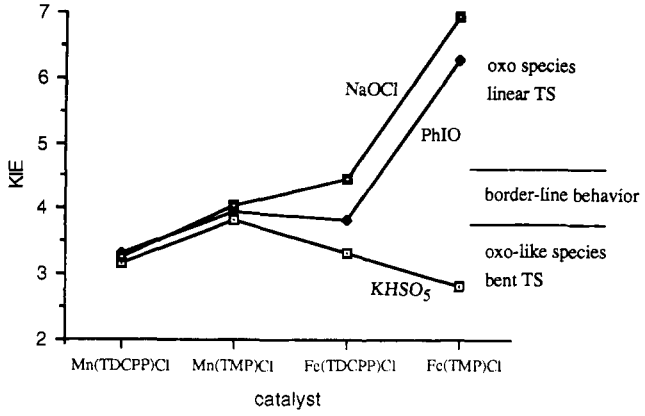


Figure 2. Dependence of k_H/k_D on the oxidant, in CH_2Cl_2 as solvent.

all the KIE values were rather low, between 2.83 with Fe(TMP)Cl (entry 3) and 3.83 with Mn(TMP)Cl (entry 1); Fe(TDCPP)Cl and Mn(TDCPP)Cl gave quite similar values of 3.32 and 3.17, respectively (entries 4 and 2). These low KIE values obtained with this inorganic peroxide suggest that the active oxometalloporphyrin responsible of the hydrogen atom abstraction from the alkane substrate is probably different than with PhIO or NaOCl. The different KIE values depending on the nature of the oxidant are illustrated by Figure 2.

Manganese complexes usually gave lower KIEs than the corresponding iron complexes: 3.94 and 3.31 for Mn(TMP)Cl and Mn(TDCPP)Cl, respectively (entries 5, 6), associated with PhIO, compared to 6.28 and 3.83 for Fe(TMP)Cl and Fe(TDCPP)Cl (entries 7, 8). With NaOCl, the same feature could be observed: entries 9 and 10, compared to 11 and 12.

Finally, it should be pointed out that the influence of the oxidant on KIE values is weak for manganese porphyrins: for example, using Mn(TDCPP)Cl as the catalyst, the observed KIEs were 3.17, 3.31, 3.25, and 3.10 with $KHSO_5$, PhIO, NaOCl, and H_2O_2, respectively (entries 2, 6, 10, 13). With iron porphyrins, the difference according to the oxidant is more significant: if k_H/k_D is always low with $KHSO_5$ (2.83 with Fe(TMP)Cl, entry 3), the value is higher with PhIO (6.28, entry 7) and again higher with NaOCl (6.93, entry 11). The rather high KIE values obtained with the iron porphyrin/PhIO system compared with those obtained with $KHSO_5$ or n-Bu_4NHSO_5 were previously described for intermolecular isotope effects.[21]

The influence of the presence of a pyridine derivative as an axial ligand has also been investigated with the Mn(TDCPP)Cl/PhIO system. No influence of the presence of 4-*tert*-butylpyridine could be detected on the KIE values.

As previously reported by Sorokin and Khenkin,[20] KIEs are higher in a nonpolar solvent like benzene, and the values are increased according to the nature of the catalyst and the oxidant. This result could be explained by the role of polar solvents on factors that decrease the KIE values (*i.e* hydrogen atom transfer is coupled with reorganization of solvent molecules solvating hydrogen atom donor or acceptor). The effect of this phenomenon is an increase of the effective mass along the reaction coordinate, consequently resulting in a decrease of KIE values.[35]

Temperature Dependence of Kinetic Isotope Effect. The temperature dependence of k_H/k_D is based on the Arrhenius relation:

$$\frac{k_H}{k_D} = \frac{A_H}{A_D} \exp(-[\Delta E_a]_H{}^D/RT)$$

The determination of the pre-exponential factor ratio, A_H/A_D, and the isotopic difference of C–H and C–D bond activation energies, $E_a(D) - E_a(H) = [\Delta E_a]_H{}^D$, provides information about the transition state geometry and the possibility of a tunneling mechanism. The importance of tunneling in chemical reactions involving a C–H bond cleavage step has been discussed for many years.[25,28,29,34,36,37] This phenomenon is generally to be expected from molecular quantum mechanics, but it appears that completely unambiguous experimental proof that tunneling occurs in chemical or enzyme-catalyzed reactions is not so easy to obtain. The most direct evidence for tunneling can be obtained from KIE studies since tunneling probability is strongly affected by the reduced mass of the transferred particle. As a rule, KIE values in this case are higher than 7 (the maximum which can be obtained using a semiclassical approach).[25-27] However, KIE values within the range predicted by a semiclassical approach cannot be regarded as unambiguous evidence against tunneling.[26] Recently, Kim and Kreevoy tried to identify all parameters involved in the tunneling effect in hydride transfer reactions.[36] One approach is to examine the temperature dependence of KIE values. It is generally accepted that values of $[\Delta E_a]_H{}^D$ larger than the difference in C–H and C–D bond zero point energies ($\geq$1.2 kcal/mol) and an unusually low pre-exponential ratio of A_H/A_D ($<$0.7) provide strong evidence for the occurrence of tunneling, when both criteria are met.[28,29,34,36,37]

Most KIE values published for P-450 models have been measured at only one temperature. The absence of data on the temperature dependence of KIEs in alkane hydroxylations catalyzed by enzymes or metalloporphyrins is probably related to experimental difficulties in obtaining accurate and precise k_H/k_D data over a sufficient temperature range. To our knowledge the temperature dependence of KIE was studied only for the hydroxylation of cyclohexane by the Fe(TMP)Cl/NaOCl and Fe(T*o*FPP)Cl/NaOCl systems in benzene.[20] In the first case, the low ratio of pre-exponential Arrhenius factors (A_H/A_D = 0.01) suggested a tunneling contribution to the C–H bond cleavage step.[20]

Here, the temperature dependence study of *intramolecular* KIE is reported for the hydroxylation of adamantane-*1,3-d*$_2$ with the Fe(TMP)Cl/NaOCl, Fe(TMP)Cl/PhIO, and Mn(TMP)Cl/$KHSO_5$ hydroxylating systems between 10 and 60 °C and with the Mn(TDCPP)Cl/$KHSO_5$ system between 5 and 38 °C. Results are given in Table IV. It should be noted that low A_H/A_D values have been obtained for iron porphyrin catalysts (0.35 and 0.39 for Fe(TMP)Cl/NaOCl and Fe(TMP)Cl/PhIO, respectively) compared to those for manganese porphyrin catalysts (1.11 and 1.10 for Mn(TMP)Cl/$KHSO_5$ and Mn(TDCPP)Cl/$KHSO_5$, respectively). For this latter catalytic system, data were obtained from experiments performed in dichloromethane, not in benzene as for the first three, suggesting that the solvent has no large influence on these values. A significant difference was also observed between iron and manganese catalysts for the difference in activation energy values $[\Delta E_a]_H{}^D$. High values were obtained for iron complexes: 1.83 and 1.76 kcal/mol for Fe(TMP)Cl/NaOCl and Fe(TMP)Cl/PhIO, respectively, and 0.85 and 0.73 for Mn(TMP)Cl/$KHSO_5$ and Mn(TDCPP)Cl/$KHSO_5$, respectively. The k_H/k_D values obtained with the Mn(TDCPP)Cl/$KHSO_5$ system in CH_2Cl_2 are not highly influenced by temperature and are in agreement with a "low primary classical isotope effect" as previously described for the intermolecular isotope effect with this catalytic system.[17] The possible contribution of a tunneling effect in the case of Fe(TMP)Cl/NaOCl and Fe(TMP)Cl/PhIO systems will be discussed below.

One of the main questions about aliphatic hydroxylation by cytochrome P-450 and model systems concerns the nature of the active species: Is the structure of the high-valent metal complex the same in all systems? If not, how are the catalyst structure (porphyrin ligand and metal) and oxidant able to influence the structure of the active species formed or the transition state of the C–H bond cleavage reaction?

(35) Melander, L.; Saunders, J. M. In *Reaction Rates of Isotope Molecules*; Wiley-Interscience: New York, 1980; p 152.

(36) Kim, Y.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 7116–7123 and references therein.

(37) Bosch, E.; Moreno, M.; Lluch, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 2072–2076.

Table IV. Temperature Dependence of KIE in Adamantane-d_2 Hydroxylation by Four Different Metalloporphyrin-Based Catalytic Systems

	k_H/k_D			
temp, °C	Fe(TMP)Cl/NaOCl[a]	Fe(TMP)Cl/PhIO[a]	Mn(TMP)Cl/$KHSO_5$[a]	Mn(TDCPP)Cl/$KHSO_5$[b]
5				3.38 ± 0.04
10	8.96 ± 0.24	8.88 ± 0.14	4.96 ± 0.12	
20	8.71 ± 0.20	7.52 ± 0.21	4.74 ± 0.08	3.17 ± 0.13
30	7.01 ± 0.10	7.10 ± 0.13	4.46 ± 0.10	
38				2.94 ± 0.06
40	6.67 ± 0.08	6.58 ± 0.12	4.43 ± 0.08	
50	6.25 ± 0.10	5.82 ± 0.10	4.13 ± 0.09	
60	5.53 ± 0.14	5.49 ± 0.11	3.93 ± 0.08	
A_H/A_D	0.35 ± 0.04	0.39 ± 0.04	1.11 ± 0.08	1.10 ± 0.10
$[\Delta E_a]_H^{D}$ [c]	1.83 ± 0.07	1.76 ± 0.07	0.85 ± 0.06	0.73 ± 0.04

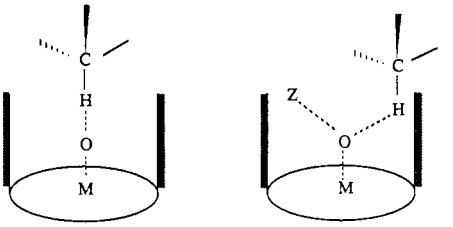
[a] Benzene as solvent. [b] Dichloromethane as solvent. [c] In units of kcal mol^{-1}.

For different active oxygen atom donors, the catalyst being the same, KIEs should have the same value if the leaving group of the oxidant is eliminated before the reaction with the C–H bond. In this case, obviously, the active high valent metal–oxo species should be linear with the same for the different oxidants used. Otherwise, if the leaving group of the oxygen atom donor is still present during the cleavage of the C–H bond, it will induce a transition state (TS) which should be classified as "bent H-transfer TS". According to the classification of Kwart[29] this kind of transition state must be characterized by low values of KIE. These KIE values could be dependent on the nature of the oxidant used, but not necessarily, and the influence of the TS bending of KIE values is probably more important than the nature of the leaving group of the oxygen atom donor. The KIE values obtained in these cases of "bent TS", according to Kwart,[29] must be temperature independent and then their magnitude determined only by the large value of A_H/A_D (>1.4). This is not the case for the Mn(TDCPP)Cl/$KHSO_5$-catalyzed oxidation of adamantane-*1,3*-d_2 (A_H/A_D = 1.10, Table IV). In spite of that, it can be seen that small KIE values have been obtained when $KHSO_5$, PhIO, NaOCl, and H_2O_2 are used as oxidants: see Table III, entries 2, 6, 10, and 13, respectively. All the obtained values are very close, ranging from 3.10 to 3.31. The complete lack of dependence of KIE values on the oxidant used (Table III) and the low-temperature dependence of KIE for the Mn(TDCPP)-Cl/$KHSO_5$ (CH_2Cl_2) system (Table IV) are strong evidence that the Mn(TDCPP)-oxo like active species responsible for C–H bond hydroxylation probably have a very similar bent geometry in all these catalytic systems based on manganese porphyrins.

With iron–porphyrin based systems, the intramolecular k_H/k_D values obtained for the hydroxylation of adamantane-*1,3*-d_2 are more dependent on the oxygen atom donor used: for example, see Table III—with Fe(TMP)Cl as catalyst, k_H/k_D is 2.83 when $KHSO_5$ is used as oxidant (entry 3), 6.28 with C_6H_5IO (entry 7) and 6.93 with NaOCl (entry 11). A possible explanation for the influence of the oxygen atom donor nature on the KIE value is that the leaving group of the oxidant is still present during the C–H bond cleavage step, thus making the geometry of the transition state with $KHSO_5$ nonlinear, whereas for NaOCl- and PhIO-based hydroxylation systems, a linear transition state is more probable because high KIE values were found, especially in benzene: 7.52 and 8.71 for Fe(TMP)Cl/PhIO and Fe(TMP)-Cl/NaOCl, respectively (entries 7 and 11, Table III). These different possible TS structures are illustrated in Chart I. The suggestion of linear H-transfer TS for these two latter Fe(TMP)-Cl-mediated hydroxylation systems is supported by temperature-dependence studies of KIE. In fact, KIE is largely influenced by temperature in the case of Fe(TMP)Cl/NaOCl and Fe(TMP)Cl/PhIO: at 10 °C, k_H/K_D values are 8.96 and 8.88, respectively, compared to 5.53 and 5.49 at 60 °C. In addition, pre-exponential factors A_H/A_D have low values (0.35 and 0.39, respectively) and differences in activation energies are high (1.83 and 1.76 kcal/mol, respectively). These data suggest that one is observing the case of a linear H-transfer with a possible tunneling effect. A similar contribution of quantum mechanical tunneling in a hydrogen atom abstraction reaction mediated by triplet diarylcarbene has also been suggested for k_H/k_D values ranging from 7.0 to 9.0.[34]

Chart I. Possible Transition State Geometries in Hydroxylation Reactions Catalyzed with Different Metalloporphyrin–Oxygen Atom Donor Systems, Z Being the Leaving Group of the Oxidant

"High" KIE	"Low" KIE
linear transition state	bent transition state
Fe(Por)Cl / NaOCl	Fe(Por)Cl / $KHSO_5$
Fe(Por)Cl / PhIO	Mn(Por)Cl / all oxidants



Concerning alkane hydroxylations mediated by cytochrome P-450 it should be noted that rather high KIE values have been found (Table I, entries 1–11) from intramolecular KIE studies. However, these determinations have been performed at a single temperature and it would be interesting to examine, by temperature dependence in intramolecular KIE studies, if there is a possible contribution of the tunneling effect in cytochrome P-450-catalyzed hydroxylations. In this regard adamantane-*1,3*-d_2 will be a suitable substrate.

Conclusion

Taking into account all the KIE values obtained with various metalloporphyrin catalysts in association to different oxidants, it appears to be obvious that the nature of the high-valent metal–oxo species is probably the same for the different iron porphyrins when activated by PhIO or NaOCl. The leaving group of the oxidant is probably not involved in the rather symmetrical H-transfer transition state in these cases (see Chart I). On the other hand, active metal–oxo species generated by $KHSO_5$ (irregardless of the metalloporphyrin) or by PhIO or NaOCl (only for manganese porphyrins) might qualify as metal–oxo *like* species, since the leaving group of the oxidant is probably involved in the transition state which is consequently more bent than with catalytic systems generating a "*pure*" metal–oxo entity, such as Fe(TMP)Cl associated with PhIO or NaOCl.

Acknowledgment. One of us (A.S.) is indebted to the Ministère de la Recherche for a postdoctoral fellowship. We are grateful to Dr. D. Deruaz (Faculty of Pharmacy, Lyon) and Mr. J. Favre-Bonvin (CNRS, Lyon) for the deuterium content analysis of adamantane-*1,3*-d_2 by GC-AED. We thank Pr A. Shilov for fruitful discussions. Dr. C. Jeffrey Lacey is acknowledged for help with the English in this paper.