Acknowledgment. This work was supported by a grant from the National Science Foundation (No. CHE-8821588).

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond lengths, and bond angles for the diastereomers of **2** (R = Ph, R′ = $CH(CO_2Me)_2$) (9 pages); observed and calculated structure factors for the diastereomers of **2** (R = Ph, R′ = $CH(CO_2Me)_2$) (20 pages). Ordering information is given on any current masthead page.

Asymmetric Hydroxylation by a Chiral Iron Porphyrin

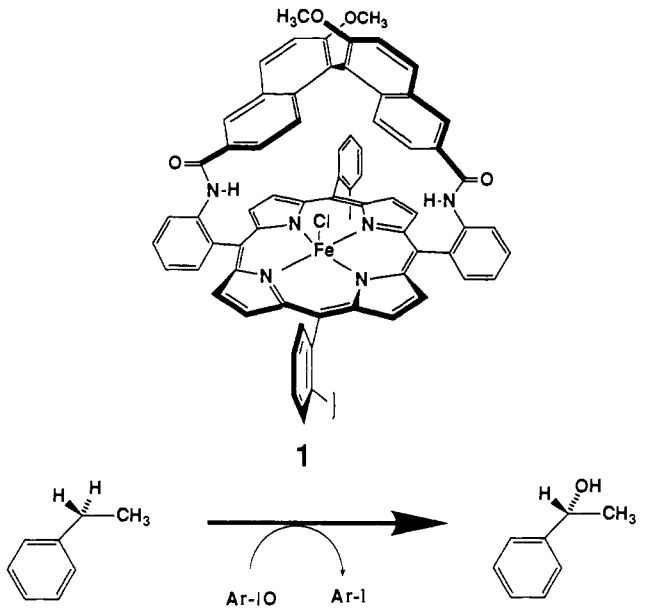
John T. Groves* and Peter Viski†

Department of Chemistry, Princeton University
Princeton, New Jersey 08544
Received June 19, 1989

One of the most interesting features of the cytochrome P-450 family of enzymes is the ability to convert alkanes to alcohols, often with high regioselectivity and stereospecificity.[1-3] There is now abundant evidence that the hydroxylation process is stepwise and that C–H bond scission is an event stereochemically discrete from the subsequent formation of the new C–O bond of the product alcohol. Thus, the hydroxylation of norbornane by cytochrome $P\text{-}450_{LM2}$ was demonstrated in our laboratory to afford both the *exo*- and *endo*-norborneols and that either product could derive from initial removal of either the exo or endo hydrogen.[4a] Likewise, it has been shown that the selective exo-C-5 hydroxylation of camphor by $P\text{-}450_{CAM}$ occurs with a considerable degree of stereochemical indiscrimination for hydrogen removal,[5] that the allylic hydroxylation of olefins occurs with significant allylic scrambling,[4b] and that the benzylic hydroxylation of ethylbenzene is nonstereospecific.[6,7] By contrast, predominant retention[4] of configuration has been reported for the hydroxylation of isotopically chiral methyl groups.[8] The central question becomes whether hydroxylation with retention of configuration at carbon is a mechanistically enforced outcome or whether the enzyme can adequately control the stereochemical outcome of a stepwise, free-radical process.

Many of the essential features of oxygen transfer by cytochrome P-450 have been modeled with synthetic metalloporphyrin catalysts by using iodosylbenzene[9] or other oxygen donors[10-17] as oxidants.

Scheme I



In this paper we describe the stereochemical course of the hydroxylation of ethylbenzene with a chiral iron porphyrin catalyst. The results indicate that the degree of stereospecificity is related to the fit of the substrate into the catalyst and provide insight into how a stepwise free-radical reaction may proceed with apparent retention of configuration at carbon.

In a typical reaction, the hydroxylation of ethylbenzene was carried out under anaerobic conditions in dichloromethane at 0 °C by using the chiral binaphthyl iron porphyrin **1** (Scheme I) we have described elsewhere[18] as the catalyst. Reactions were initiated by the addition of iodosylbenzene (100 equiv based on **1**) to a dichloromethane solution of **1** (1.5 mg in 2 mL) and ethylbenzene (1000 equiv). The product alcohols were isolated by chromatography on silica and esterified with (*R*)-(−)-2-phenylpropionyl chloride. Yields, enantiomeric excesses, and alcohol:ketone ratios were determined by GC, and the deuterium content of each diastereomeric ester was measured by GC–MS (Table I).

Ethylbenzene afforded a 40% yield of 1-phenylethanol with a 71:29 ratio of the *R* and *S* enantiomers, respectively (41% ee). Some acetophenone was also detected but was shown not to be due to further oxidation of the alcohol product. Samples of optically pure (*R*)- and (*S*)-(1-deuterioethyl)benzene were prepared by the method of Mosher.[19] (*R*)-(1-deuterioethyl)benzene provided the *S* alcohol in excess (16% ee) while (*S*)-(1-deuterioethyl)benzene afforded the *R* alcohol but with a much higher, isotopically enhanced stereoselectivity (77% ee). Multiple determinations of at least three oxidations indicated that the enantiomeric excesses were reproducible and accurate to ±2%.

The deuterium content of the enantiomeric alcohols derived from (*R*)- and (*S*)-(1-deuterioethyl)benzene was determined from the mass spectra of the diastereomeric 1-phenylpropionyl esters. The base-line separation of the GC peaks and the uncomplicated parent region for these compounds (no m-1 peak) allowed an unambiguous determination. Tabulations of the mass spectra of the diastereomeric esters and the deuterium content of each diastereomer derived from the data are shown in Table I. The primary data provide a measure of the stereoselectivity of these hydroxylations and the proton/deuterium inventory for each stereoisomeric product. Two things are immediately apparent: (1) the major hydroxylation product was determined by the stereochemistry of the deuteration and (2) *the extent of deuteration of the major product was indistinguishable from 100% whereas the minor product in each case contained nearly equal*

† Current address: Central Research Institute for Chemistry, Hungarian Academy of Sciences, P.O. Box 17, H-1515 Budapest, Hungary.

(1) For an extensive review, see: *Cytochrome P-450: Structure, Mechanism, and Biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum: New York, 1986.
(2) Orme-Johnson, N. R.; Light, D. R.; White-Stevens, R. W.; Orme-Johnson, W. H. *J. Biol. Chem.* **1979**, *254*, 2103.
(3) Nakajin, S.; Shinoda, M.; Haniu, M.; Shively, J. E.; Hall, P. F. *J. Biol. Chem.* **1984**, *259*, 3971.
(4) (a) Groves, J. T.; McClusky, G. A.; White, R. E.; Coon, M. J. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 154. (b) Groves, J. T.; Subramanian, D. V. *J. Am. Chem. Soc.* **1984**, *106*, 2177.
(5) Gelb, M. H.; Heimbrook, D. C.; Sligar, S. G. *Biochemistry* **1982**, *21*, 370.
(6) (a) White, R. E.; Miller, J. P.; Favreau, L. V.; Bhattacharyya, A. *J. Am. Chem. Soc.* **1986**, *108*, 6024. (b) Holland, H. L.; Carter, I. M.; Chenchaiah, P.; Shaheer, H. K.; Munoz, B.; Ninnis, R. W.; Richards, D. *Tetrahedron Lett.* **1985**, *26*(52), 6409.
(7) McMahon, R. E.; Sullivan, H. R.; Craig, J. C.; Pereira, W. E., Jr. *Arch. Biochem. Biophys.* **1969**, *132*, 575.
(8) Shaphiro, S.; Piper, J. V.; Caspi, E. *J. Am. Chem. Soc.* **1982**, *104*, 2301.
(9) (a) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032. (b) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243.
(10) Nee, M. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6123.
(11) Meunier, B.; Guilmet, E.; DeCarvalho, M. E.; Pailblanc, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668.
(12) Groves, J. T.; Haushalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1981**, *103*, 2884.
(13) Mansuy, D.; Bartioli, J. F.; Chottard, J. C.; Lange, M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 909.
(14) Mansuy, D.; Fontecave, M.; Bartioli, J. F. *J. Chem. Soc.* **1983**, 253.
(15) Battioni, P.; Renaud, J. P.; Bartioli, J. F.; Mansuy, D. *J. Chem. Soc.* **1986**, 341.
(16) De Pooter, B.; Meunier, B. *Nouv. J. Chim.* **1985**, *9*, 939.
(17) Groves, J. T.; Neumann, R. *J. Am. Chem. Soc.* **1989**, *111*, 2900.
(18) Groves, J. T.; Viski, P. *J. Org. Chem.* In press.
(19) Elsenbaumer, R. L.; Mosher, H. S. *J. Org. Chem.* **1979**, *44*, 600.

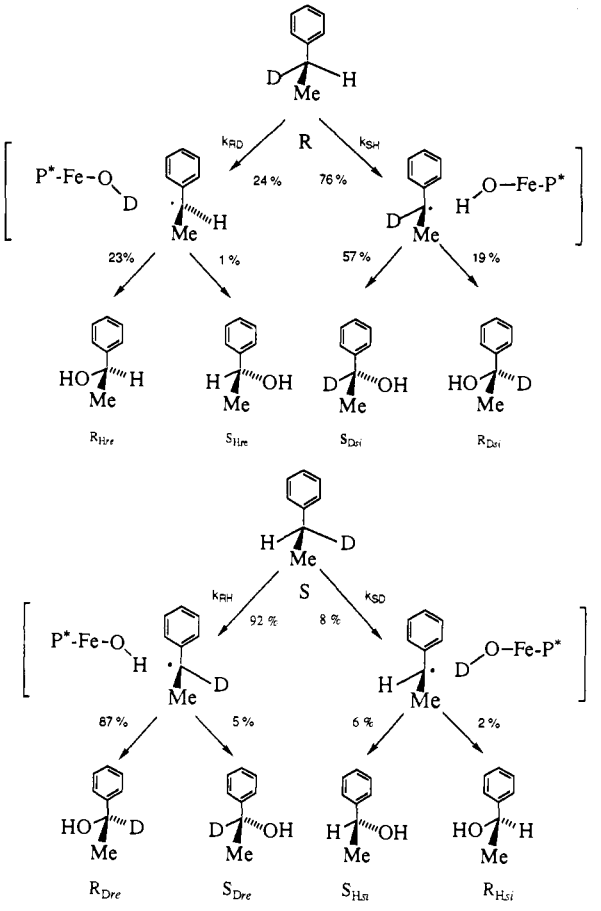
0002-7863/89/1511-8537$01.50/0

Table I. Mass Spectral Data for 1-Phenylethyl Esters Derived from (*R*)- and (*S*)-(1-Deuterioethyl)benzene[a]

	substrate				esters[b] from	
	(*R*)-ethyl-*1-d*-benzene		(*S*)-ethyl-*1-d*-benzene			
m/z	*R,R* ester rel int, %	*R,S* ester rel int, %	*R,R* ester rel int, %	*R,S* ester rel int, %	1-phenylethanol rel int, %	1-phenylethan-*1-d*-ol rel int, %
253	1.75	0.82	0.77	4.72	1.12	0.9
254	98.56	3.51	1.8	85.01	100.0	1.75
255	100.0	100.0	100.0	100.0	19.12	100.0
256	19.3	19.92	19.87	19.78	0.4	16.5
rel yield, %	42	58	88	12		
% deuterated	45.7	98.3	99.0	49.6	0.0	100.0
% ee	16		77			

[a] The relative intensities are averaged over the GC peak and are uncorrected. Deuterium percentages are corrected for ^{13}C natural abundance. Determinations of at least three oxidations were reproducible to ±2%. [b] These authentic phenylethyl esters were made from racemic alcohols.

Scheme II



amounts of hydrogen and deuterium.

Analysis of the results is simplified by consideration of the stepwise hydroxylation process outlined in Scheme II. The C–H bond scission and subsequent C–O bond formation are stereochemically discrete events.[4,9] The intrinsic stereoselectivity for hydrogen removal from ethylbenzene by **1** can be derived from the observed ratio of *R* and *S* alcohols (71:29), and the stereoselectivity of the capture of the intermediate becomes $k_{RH}/k_{SH} = 2.0$, where the subscript RH indicates *hydrogen* removal from the *pro-R* position. The deuterium inventory also allows a direct measure of the ratios $k_{RD}/k_{SH} = 0.311$ and $k_{RH}/k_{SD} = 12.7$ and, as indicated in eq 1, an independent measure of the isotope effects for H(D) removal from the *R* and *S* positions. The equivalence of these two values (6.4) is reassuring and the magnitude in accord with the intramolecular isotope effect for ethylbenzene-d_{10} ($k_H/k_D = 8.7$), which should be inflated by secondary isotope effects and a higher degree of deuteration.

$$k_{RH}/k_{RD} = \frac{k_{RH}/k_{SH}}{k_{RD}/k_{SH}} = 6.4 = \frac{k_{SH}/k_{RH}}{k_{SD}/k_{RH}} = k_{SH}/k_{SD} \quad (1)$$

The results indicate that the chiral porphyrin catalyst **1** has a 2-fold preference for removal of the *pro-R* hydrogen of ethylbenzene. More significantly, however, it is apparent that the radical produced by removal of either H or D from the *pro-R* site is captured with nearly complete *retention* of configuration whereas 20–25% *inversion* (40–50% racemization) results from H(D) removal from the *pro-S* position. Accordingly, by the usual criteria of mechanism, the enantiotopic protons of ethylbenzene are hydroxylated by **1** *by different mechanisms.*

A more satisfying interpretation is that the same mechanism, hydrogen abstraction and subsequent geminate cage recombination,[20] occurs in both cases. Capture of the incipient carbon radical must occur rapidly on the preferred *re* face due to the good fit of the substrate into the binaphthyl cavity. By contrast, the unfavorable nonbonded interactions encountered by the radical on the *si* face afford an opportunity for significant racemization. The results described here for this simple model system provide a clear indication as to how it is possible for asymmetric catalyst–substrate interactions to impose stereoselectivity on a free-radical reaction.

Acknowledgment. Support for this research by the National Institutes of Health (GM-36298) is gratefully acknowledged. The National Science Foundation and the NIH provided funds for the purchase of a high-resolution mass spectrometer.

(20) Greene, F. D. *J. Am. Chem. Soc.* **1955**, *77*, 4869.

Spectroscopic Detection of Organolanthanide Dihydrogen and Olefin Complexes

Steven P. Nolan and Tobin J. Marks*

Department of Chemistry, Northwestern University Evanston, Illinois 60208-3113

Received July 3, 1989

Although dihydrogen complexes[1,2] (**1**) are frequently invoked along the reaction coordinate for lanthanide-centered, actinide-

(1) (a) Kubas, G. J. *Acc. Chem. Res.* **1988**, *21*, 126–128. (b) Crabtree, R. H.; Hamilton, D. G. *Adv. Organomet. Chem.* **1988**, *28*, 299–337 and references therein. (c) Kubas, G. J. *Comments Inorg. Chem.* **1988**, *7*, 17–40 and references therein.

(2) (a) Cotton, F. A.; Luck, R. L. *Inorg. Chem.* **1989**, *28*, 6–8. (b) Gonzalez, A. A.; Zhang, K.; Nolan, S. P.; Lopez de la Vega, R.; Mukerjee, S. L.; Hoff, C. D.; Kubas, G. J. *Organometallics* **1988**, *7*, 2429–2435. (c) Bautista, M. F.; Earl, K. A.; Maltby, P. A.; Morris, R. H.; Schweitzer, C. T.; Sella, A. *J. Am. Chem. Soc.* **1988**, *110*, 7031–7036. (d) Chinn, M. S.; Heinekey, D. M. *J. Am. Chem. Soc.* **1987**, *109*, 5865–5867. (e) Bianchini, C.; Mealli, C.; Peruzzini, M.; Zandini, F. *J. Am. Chem. Soc.* **1987**, *109*, 5548–5549.

0002-7863/89/1511-8538$01.50/0