groups to yield a kinetically inert dialkytin–enzyme substitution complex (Scheme II).[13] We have not completed a detailed kinetic analysis of the inhibition of the enzyme by these various organostannanes.

Previous studies have shown that the relative ease of protonolysis of organostannanes by protic acids (e.g., acetic or hydrochloric acid) is dependent on the organic moiety and decreases in the order vinyl > methyl > ethyl > butyl.[14] This pattern is apparently mimicked in the enzymatic cleavage, where tetravinyltin is cleaved more rapidly than tetramethyltin, and the butyl derivatives are not cleaved at all. Electrophilic reactions of unsaturated organometallics are known to be facilitated via stabilization of the developing positive charge by the metal atom (Scheme III).[15] This stabilization, which was invoked to explain the rate acceleration observed with alkenylmercurials,[2b] may also account for the increased rate of enzymatic cleavage of the vinylstannanes relative to the methyl derivatives. We previously suggested that turnover of organomercurials may involve labilization of the carbon–mercury bond via coordination of an active-site nucleophile to the metal, with concomitant S_E2-type protonolytic bond cleavage. In the present examples of protonolytic cleavage of fully substituted tetraorganostannanes this coordinative labilization presumably cannot occur and may account for the decreased rate of carbon–tin bond cleavage relative to that of carbon–mercury bonds. It is nevertheless noteworthy that cleavage of a vinyl–tin bond, which chemically is carried out by using forcing conditions (glacial acetic acid, 100 °C, 1.5 h for triethylvinyltin),[14] can be effected by organomercurial lyase at a lower temperature (37 °C) and pH 7.4.

Electrophilic reactions of tetrasubstituted organotin compounds are well-known and generally proceed via an S_E2 mechanism.[16] On the basis of this known chemistry and our mechanistic findings on the enzymic cleavage of mercurials it is plausible that the enzymic turnover of the organostannanes reported here may also proceed via an S_E2 pathway. Although the possibility of a radical mechanism cannot be discounted, it appears unlikely given the lack of evidence for a radical pathway in the cleavage of organomercurials.

The turnover of certain organotin compounds by organomercurial lyase is significant in light of the environmental presence of organotin compounds.[4,5] Several reports have presented evidence of microbial resistance to organostannanes,[4-10] although no protonolytic enzymes involved in detoxification have yet been isolated. It appears unlikely that organomercurial lyase per se could confer substantial resistance to organostannanes, given the sluggish V_{max} values and limited range of compounds that are substrates. The existence of organomercurial lyase for detoxification of organomercurials and our observations that certain organostannanes are substrates for it suggest, however, that an analogous enzyme optimized for carbon–tin bond cleavage may exist as a detoxification enzyme of organostannanes.

Finally, the potent inhibition observed with dimethyltin dibromide suggests the possibility of using the tin atom as a tool for probing the active site of organomercurial lyase. The inhibition of numerous enzymes by triethyltin compounds is well-known,[17] as is the inhibition of α-keto acid oxidases by diethyltin dichloride, which is proposed to involve binding of diethyltin to an enzyme dithiol.[18] Elucidation of the intimate mechanistic details of the enzymic cleavage of both organomercurials and organostannanes awaits determination of the active-site sequence and geometry of the lyase, an effort in which the use of organotin inhibitors may prove valuable.

Acknowledgment. Partial support for this research from the National Institutes of Health (Grant GM-20011) is gratefully acknowledged. We thank the research group of Professor D. Seyferth (MIT) for generously providing several of the organometallic compounds described herein, as well as for helpful comments and discussions during the course of this work.

Registry No. $Sn(CH{=}CH_2)_4$, 1112-56-7; $Et_3Sn(CH{=}CH_2)$, 2117-47-7; Me_4Sn, 594-27-4; Me_3SnF, 420-60-0; organomercurial lyase, 72560-99-7.

(13) The formation of radicals is expected to be more facile from dimethyltin dibromide than from dimethyltin dichloride. It is thus possible that the differential inhibition observed for the dibromide versus the dichloride is due to a radical mechanism. Experiments to rule out this possibility have not been undertaken.

(14) (a) Seyferth, D. *J. Am. Chem. Soc.* **1957**, *79*, 2133. (b) Ingham, R. K.; Rosenberg, S. D.; Gilman, H. *Chem. Rev.* **1960**, *60*, 459.

(15) Negishi, E.-I. *Organometallics in Organic Synthesis*; Wiley: New York, 1980; Vol. 1, pp 416-447.

(16) Fukuto, J. M.; Jensen, F. R. *Acc. Chem. Res.* **1983**, *16*, 177.

(17) (a) Selwyn, M. J. In *Organotin Compounds: New Chemistry and Applications*; Zuckerman, J. J., Ed.; Advances in Chemistry 157; American Chemical Society; Washington, DC, 1976; p 204. (b) Aldridge, W. N. *Ibid.*; p. 186. (c) Siebenlist, K. R.; Taketa, F. *Biochem. J.* **1986**, *233*, 471.

(18) Aldridge, W. N.; Cremer, J. F. *Biochem. J.* **1955**, *61*, 406.

Model Reactions Related to Cytochrome P-450. Effects of Alkene Structure on the Rates of Epoxide Formation

Teddy G. Traylor* and Feng Xu

Contribution from the Department of Chemistry, D-006, University of California, San Diego, La Jolla, California 92093. *Received June 4, 1987*

Abstract: A kinetic method for measuring the relative rates of epoxidation of various alkenes, based upon the disappearance of the reactive alkenes carotene or 1,4-diphenylbutadiene, has been developed. With this technique a linear relationship between the logarithm of the rates of epoxide formation and the ionization potential of the alkene has been observed. This contrasts the behavior of peracid epoxidation and provides further evidence for the intermediacy of alkene cation radicals in the hemin-catalyzed epoxidation.

Recent studies of hemin-catalyzed epoxidation of alkenes, model reactions for the function of cytochrome P-450, have employed iron(III) porphyrins and oxidants such as peracids, hydroperoxides, hypochlorite, and iodosylbenzenes.[1-3] These investigations have established that the reaction proceeds through a two-electron-oxidized iron porphyrin, the oxoiron(IV) porphyrin cation radical,[4,5] and that the epoxidation is usually stereospecific.[3,6]

(1) Ortiz de Montellano, P. *Cytochrome P-450: Structure, Mechanism, and Biochemistry*; Plenum: New York, 1986.

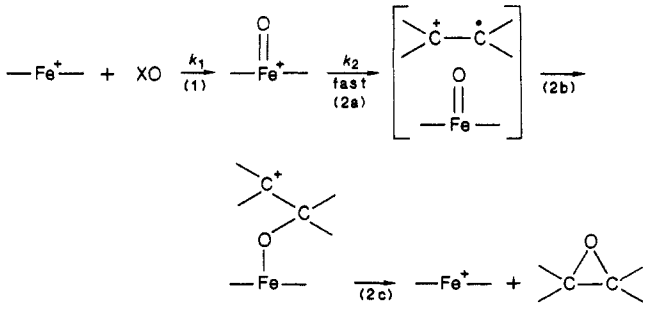
(2) Meunier, B.; Guilmet, E.; De Carvalho, M. E.; Poilblanc, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668.

(3) (a) Lindsay-Smith, J. R.; Sleath, P. R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 621. (b) Lindsay-Smith, J. R.; Sleath, P. R. *Ibid.* **1982**, 1009. (c) Lindsay-Smith, J. R.; Sleath, P. R. *Ibid.* **1983**, 1165.

(4) Groves, J. T.; Haushalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1983**, *103*, 2884.

0002-7863/88/1510-1953$01.50/0

However, in some cases rearranged products and alkenes were obtained.[7-10] On the basis of these rearrangements and the fact that norbornene affords substantial *endo*-epoxide,[8] an electron-transfer process has been suggested (reactions 1 and 2).[1,7-9]



An alternative electrocyclic reaction proceeding through a metallacycle has also been proposed (reaction 3).[11] The relative

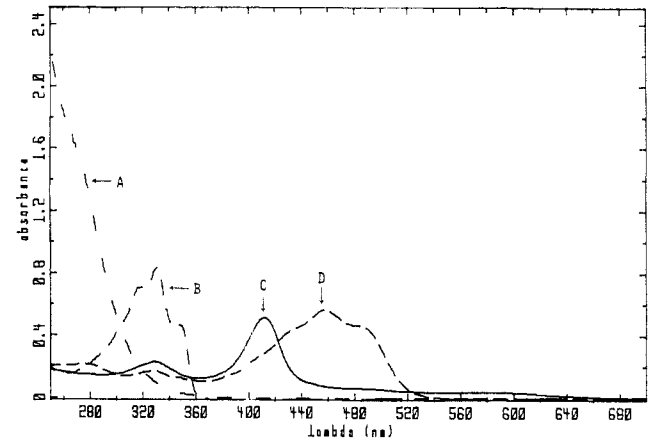


Figure 1. Spectra taken in $CH_2Cl_2/CH_3OH/H_2O$ (80/18/2): pentafluoroiodosylbenzene (5×10^{-4} M) (A); *trans,trans*-1,4-diphenylbutadiene (10^{-5} M) (B); [tetrakis(2,6-dichlorophenyl)porphyrin]iron(III) chloride (4×10^{-6} M) (C); β-carotene (3×10^{-6} M) (D).

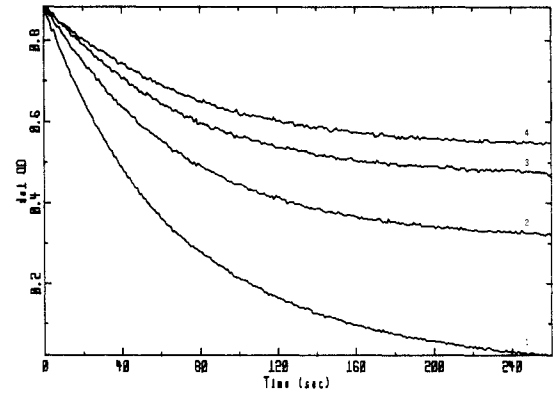


Figure 2. Plots of absorbance (ΔOD at 348 nm) vs time for competitive epoxidation of 1,4-diphenylbutadiene (C_1) and *cis*-2-*trans*-4-hexadiene (C_2) with PFIB (C_3) at 10^{-6} M in hemin I. Concentrations (M $\times 10^5$): 1, $[C_1] = 3.03$, $[C_2] = 0$, $[C_3] = 2.7$; 2, $[C_1] = 2.95$, $[C_2] = 17.1$, $[C_3] = 2.63$; 3, $[C_1] = 2.94$, $[C_2] = 22.1$, $[C_3] = 2.62$; 4, $[C_1] = 2.92$, $[C_2] = 25.4$, $[C_3] = 2.61$.

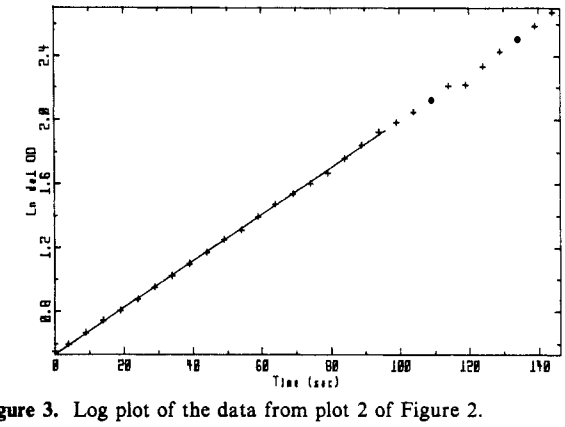
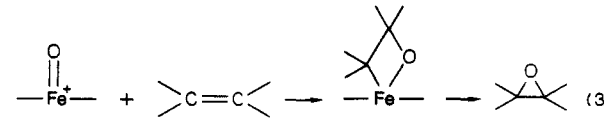


Figure 3. Log plot of the data from plot 2 of Figure 2.

rates of reaction of alkenes have been suggested to depend more upon steric than electronic effects, in support of the electrocyclic mechanism, although correlations of epoxidations of styrenes with σ^+ values of substituents have been reported.[3]



The electron-transfer mechanism for oxygen transfer (reactions 2a–c) suggests a dependence of rate upon ionization potential of the alkene.

(5) Dolphin, D.; Forman, A.; Borg, D. C.; Fajer, J.; Felton R. H. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 614.

(6) (a) Groves, J. T.; Nemo, T. E.; Meyers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032. (b) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1986**, *108*, 507.

(7) Guengerich, F. P.; Macdonald, T. L. *Acc. Chem. Res.* **1984**, *17*, 9.

(8) Traylor, T. G.; Nakano, T.; Dunlap, B. E.; Traylor, P. S.; Dolphin, D. *J. Am. Chem. Soc.* **1986**, *108*, 2782.

(9) Traylor, T. G.; Iamamoto, Y.; Nakano, T. *J. Am. Chem. Soc.* **1986**, *108*, 3529.

(10) (a) Miller, R. E.; Guengerich, F. P. *Biochemistry* **1982**, *21*, 1090. (b) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791.

(11) (a) Collman, J. P.; Brauman, J. I.; Meunier, B.; Hayashi, T.; Kodadek, T.; Raybuck, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 2000. (b) Collman, J. P.; Kodadek, T.; Brauman, J. I. *Ibid.* **1986**, *108*, 2588.

(12) Kiser, R. W. *Introduction to Mass Spectrometry and Its Applications*; Prentice-Hall: Englewood Cliffs, NJ, 1965; p 308.

(13) (a) Estimated from 1-pentene (9.50 eV[13b]) and 4-methylpent-1-ene (9.45 eV[13c]). (b) Watanabe, K.; Nakayama, T.; Mottle, *J. Quant. Spectrosc. Radiat. Transfer* **1962**, *2*, 369. (c) Morrison, J. D.; Nicholson, A. J. C. *J. Chem. Phys.* **1952**, *20*, 1021.

(14) Kobayashi, T.; Yokata, K.; Nagakura, S. *J. Electron Spectrosc. Relat. Phenom.* **1973**, *3*, 449.

(15) Weidner, U.; Schweig, A. *J. Organomet. Chem.* **1972**, *39*, 261.

(16) Demeo, D. A.; El-Sayed, M. A. *J. Chem. Phys.* **1970**, *52*, 2622.

(17) Dewar, M. S.; Worley, S. D. *J. Chem. Phys.* **1969**, *50*, 654.

(18) Haselbach, E. H.; Schroder, G. *Helv. Chim. Acta* **1971**, *54*, 153.

(19) Masclet, P.; Grosjean, D.; Mauvier, G.; Dubois, J. *J. Electron Spectrosc. Relat. Phenom.* **1973**, *2*, 225.

(20) Estimated from *cis*-3-octene (8.85 eV) and *cis*-4-octene (8.84 eV), taken from ref 19.

(21) Maier, J. P.; Turner, D. W. *J. Chem. Soc., Faraday Trans. 2* **1973**, *69*, 196.

(22) Al-Joboury, M. I.; Turner, D. W. *J. Chem. Soc., Chem. Commun.* **1964**, 4434.

(23) Price, W. C.; Tutte, W. T. *Proc. R. Soc. London A* **1940**, *174*, 207.

(24) Bieri, G.; Burger, F.; Heilbronner, E.; Maier, J. P. *Helv. Chim. Acta* **1977**, *60*, 2213.

(25) Yip, K. L.; Lipari, N. O.; Duke, C. B. *J. Chem. Phys.* **1976**, *64*, 4020.

(26) EI value: Remane, H.; Graeje, J.; Hergschuk, R. *Z. Chem.* **1972**, *12*, 194.

(27) Estimated from $E_{1/2}$(oxidn): Mairanovsky, V. G.; Engovatov, A. A.; Ioffe, N. T.; Samokhvalov, G. I. *J. Electroanal. Chem. Interfacial Electrochem.* **1975**, *66*, 123.

(28) Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*; Springer-Verlag: New York, 1984, p 9.

(29) (a) Corrected to SCE by adding 0.558 V[29c] from the values vs Ag/Ag$^+$ of ref 29b. (b) Kojima, M.; Sakuragi, H.; Tokumaru, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 521. (c) The difference between Ag/Ag$^+$ and SCE references is 0.558 V: *Handbook of Chemistry and Physics*, 56th ed.; CRC: Boca Raton, FL, p D141.

(30) (a) Estimated from E_p[30b] vs Ag/AgCl. (b) Baizer, M. M.; Lund, H. *Organic Electrochemistry*; Marcel Dekker: New York, 1983, p 420.

(31) (a) Corrected to SCE by adding 0.558 V[29c] from the value (vs Ag/Ag$^+$) of ref 31b. (b) Arai, T.; Sakuragi, H.; Tokumaru, K.; Kobayashi, T. *Denki Kagaku oyobi Kogyo Butsuri Kagaku* **1982**, *50*, 201.

(32) Katz, M.; Wendt, H. *Electrochim. Acta* **1976**, *21*, 219.

In order to determine the extent to which steric and electronic effects determine the rates of oxygen transfer to alkenes, we have studied the relative rates of epoxidation of a series of alkenes having widely different ionization potentials. To accomplish the relative rate measurements we have developed new kinetic methods that may be useful in other oxidation studies.

Experimental Section

Instruments. The UV–vis spectra and kinetic measurements were determined on a Kontron 810 spectrophotometer interfaced to a Celerity computer. NMR spectra employed a GE QE-300 300-MHz spectrometer.

Materials. Iron(III) tetrakis(2,6-dichlorophenyl)porphyrin chloride (I), purified *m*-chloroperbenzoic acid (MCPBA), pentafluoroiodosylbenzene (PFIB), and 1,4,4a,5,8,8a-hexahydro-1,4,5,8-*endo*,*endo*-dimethanonaphthalene (diene 1) were obtained from previous studies.[8,9] Most of the alkenes were the best grade available from Aldrich Chemical Co. and were used as received. 1-Octene (C&B Manufacturing Co., 97%), 4,4-dimethylpent-1-ene (Pfaltz & Bauer, 99%), α-pinene (Baker, passed through an alumina column), and norbornene (Aldrich, distilled before use) were treated as indicated. The solvent used in all these studies was a mixture of methylene chloride (Fisher Scientific, spectra grade, distilled), methanol (Fisher, spectra grade), and glass-distilled water in a respective ratio of 80/18/2 by volume.

Kinetic Measurements. The relative rates of reaction of alkenes were determined by competition with one of two alkenes, β-carotene or *trans*,*trans*-1,4-diphenylbutadiene (Aldrich), whose disappearance could be monitored at the appropriate wavelength, 485 (ϵ 1.3 × 10^5) and 348 nm (ϵ 3.7 × 10^4), respectively. In a typical experiment sufficient solution of 10^{-2} M PFIB was added to a solution of 10^{-5} M reference diene and 10^{-6} M hemin, all in the standard (80/18/2) solvent, to bring the oxidant concentration to 10^{-5} M. The rate of decrease of the diene peak at 348 or 485 nm was then followed. The first-order rate constant obtained was independent of the added second alkene as expected. In the absence of a second diene, methanol was oxidized as indicated by a shift in the hemin Soret to 390 nm due to formate displacing chloride. The rate of methanol oxidation was determined from the difference between oxidant added and diene consumed. Correction for this side reaction was usually very small.

Results

In order to demonstrate that 1,4-diphenylbutadiene is converted to the monoepoxide by our catalytic system, solutions of 0.1 M diene in $CDCl_3/CD_3OD/D_2O$ (80/18/2) were treated with $^1/_2$ equiv (to make 0.05 M) of either MCPBA alone or PFIB containing enough hemin to make the final solution 10^{-4} M in hemin. Both solutions, after the reaction was finished, showed an NMR of 50% diene plus 50% (quantitative yield) monoepoxide (^{1}H NMR δ 3.904 (J = 6 Hz), 3.546 (J = 6 Hz), 3.526 (J = 5 Hz)). The products of catalyzed epoxidation of β-carotene were not determined. The UV–vis spectra of PFIB, the hemin, 1,4-diphenylbutadiene, and carotene are shown in Figure 1. Plots of absorbance of 348 nm vs time for a solution of reference diene in the presence and absence of a second alkene, *cis*-2-*trans*-4-hexadiene, are shown in Figure 2, and one of these plots is displayed as a first-order plot in Figure 3. The use of β-carotene as reference diene afforded very similar plots.

The relative rates of reaction of an alkene and a reference diene can be obtained from either the differential or the integrated forms of the equations describing the plots in Figure 2. Thus, the ratios of initial rates without and with an added second alkene, corrected for the extinction coefficient of the reference alkene and the initial concentrations of both, afford the relative bimolecular rate constants. This method was used in some cases as indicated. However, in most cases the integrated form was used as described below. With H = hemin, O = oxidant, I = the "oxene" (Hm^+-=O), S_a = the reference alkene, S_b = the alkene being compared, P_a and P_b = the products, and O_a^0, S_a^0, and S_b^0 = the initial concentrations, we can write the reaction scheme as in eq 4–6.

$$H + O \xrightarrow{k_1} I \tag{4}$$

$$I + S_a \xrightarrow{k_a} P_a + H \tag{5}$$

$$I + S_b \xrightarrow{k_b} P_b + H \tag{6}$$

Table I. Rates of Alkene Epoxidation with PFIB Catalyzed by Fe^{III}DCPP (I^+Cl^-) Relative to that of 1-Octene

no.	alkene	Δ log k_2	IP, eV	ref	$E_{1/2}$,[a] V	ref
1	1-octene	(0)	9.52	12	2.8	28
2	4,4-dimethylpent-1-ene	0.40	9.45	13		
3	styrene	1.20	8.47	12, 13, 21	2.51	29
4	4-methylstyrene	1.40	8.20	14	1.94	29
5	allyltrimethylsilane	1.72	9.00	15		
6	β-pinene	1.51			1.89	28
7	methylenecyclohexane	1.23	8.97	16		
8	cyclohexene	1.08	9.00	12, 17	2.14	28
9	*cis*-cyclooctene	1.43	8.98	18		
10	norbornene	1.59	8.81	16	2.02	28
11	*cis*-2-pentene	1.36	9.04	19		
12	*cis*-2-octene	1.40	8.84	20	2.3	28
13	*cis*-stilbene	2.08	8.20	21	~1.53	30
14	cyclododecene	0.43	8.70	26		
15	*trans*-2-hexene	−0.72	9.16	12		
16	*trans*-β-methylstyrene	0.48	8.37	21	1.93	31
17	*trans*-stilbene	1.11	8.00	21		
18	α-pinene	1.45	8.07	22	1.41	28
19	2,3-dimethylbut-2-ene	2.30	8.30	13c, 23	1.48	28
20	diene 1[b]	2.28	8.10	18		
21	*trans*-2-*cis*-4-hexadiene	2.24	8.25	24		
22	1,4-diphenylbutadiene	3.36	7.55	25	1.14	32
23	β-carotene	4.48	6.73	27	0.51	27
24	methanol	−1.3	10.83	17		

[a] Versus SCE. [b] See text.

For analytical purposes we choose the conditions $O^0 \cong S_a^0 \ll S_b^0$. Assuming that

$$\frac{d[I]}{dt} = 0 = k_1[H][O] - (k_a S_a + k_b S_b)I \tag{7}$$

these conditions give ($S_b \cong S_b^0$)

$$I \cong \frac{k_1[H][O]}{k_a S_a + k_b S_b^0} \tag{8}$$

Combining this with the stoichiometry

$$O^0 - O = (S_a^0 - S_a) + (S_b^0 - S_b) \tag{9}$$

we obtain

$$\frac{dS_a}{dt} = -k_a S_a \frac{k_1[H][O]}{k_a S_a + k_b S_b^0} = \frac{k_a S_a}{k_a S_a + k_b S_b^0} \frac{dO}{dt} \tag{10}$$

and

$$\Delta S_a + \frac{k_b}{k_a} S_b^0 \Delta \ln S_a = \Delta O \tag{11}$$

$$\frac{k_b}{k_a} = \frac{(O^0 - O) - (S_a^0 - S_a)}{S_b^0 \ln (S_a^0/S_a)} \tag{12}$$

This treatment was also used to determine the rate constant for methanol oxidation (as S_b), and this rate constant was then used to make a small correction on the rate of consumption of S_b, the second alkene. In the case of styrenes containing enough inhibitor to interfere with the relative rate measurement, the relative rate of the inhibitor (hydroquinone) was determined and it was shown that its effect is very small. In all cases at least three different concentrations of the second alkene were used to determine the relative rates.

Table I lists the relative rates, compared with that of 1-octene, for a number of alkenes, along with published ionization potentials.

Discussion

We have recently shown that the sterically blocked and halogen-substituted hemins such as iron(III) tetrakis(2,6-dichlorophenyl)porphyrin chloride[8] or especially the iron(III) tetrakis(2,6-dichlorophenyl)octabromoporphyrin chloride[33] can be used

Table II. Relative Rates[a] of Oxidation of Olefins with Various Catalysts

	this work	Lindsay-Smith[b]	Mimoun[c]	Collman[d]	Kochi[e]
1-octene	*1.0*	*1.0*			5.3
styrene	16		4.4	19	
4-methylstyrene	25				35
cyclohexene	12	20	17		35
cis-cyclooctene	27			*27*	18
norbornene	39		37		*39*
cis-2-octene	27			27	
cis-stilbene	120				50
trans-β-methylstyrene	3.0			21	35
2,3-dimethylbut-2-ene	200	200	*200*		

[a] Active intermediate + olefin $\xrightarrow{k_2}$ product + parent catalyst. The columns are normalized to the values in italics. [b] Reference 3b (Fe^{III}(TPP)Cl as catalyst). [c] Reference 36, $K_i k_2$ values (peroxyvanadium catalyst). [d] Reference 11a, V_{max}/K_m values (Mn^{III}(TPP)Cl as catalyst). [e] Reference 37 (Mn^{III}salen as catalyst).

in low concentrations to catalyze rapid high-turnover epoxidations or hydroxylations.[34] We have therefore turned to the development of convenient kinetic methods to determine rates of each step in these reactions and structural effects on each ($Hm^+ \equiv$ iron(III) porphyrin chloride) (eq 13 and 14).

$$Hm^+ + RIO \xrightarrow{k_1} Hm^+O \qquad (13)$$

$$Hm^+O + S \xrightarrow{k_2} SO \qquad (14)$$

Although product analysis by gas–liquid chromatography has been employed for these purposes,[2,3,11] it is inconvenient and, in many cases, too slow for the rapid rates observed. We have therefore sought spectroscopic methods of following reactant and catalyst concentrations.[34] It is clear from Figure 1 that the concentrations of oxidant (RIO), substrate (diene or carotene), and hemin can be followed simultaneously. Plots of diene concentration determined at 348 nm vs time reveal the same second-order rate constant (2×10^3 M^{-1} s^{-1}) as do plots of PFIB concentration (at 280 nm).[34] Thus, in this case, the disappearance of diene merely indicates the rate of formation of the intermediate, as we have previously shown.[34]

However, relative rates can be conveniently determined by using mixtures of one substrate that is observable by UV–vis spectroscopy and one that is not. This is illustrated in Figures 2 and 3. By choosing 1,4-diphenylbutadiene as substrate, all relative rates of alkene epoxidation are within a factor of 100 of the rate of reaction of the reference diene. If less reactive substrates are used, the method must be altered. Thus, to determine relative rates of hydroxylations, which are slower, a less reactive reference substrate must be chosen. Nitrostyrenes, which would lose absorbance upon epoxidation, or benzhydrols, which oxidize to benzophenones and gain absorbance, might be used.

The second consideration is the type of hemins to be employed. Thus, benzhydrols, being rather unreactive, would not protect iron tetraphenylporphyrin from oxidation, and poor kinetics would result. However, carotene or the diene protects even iron(III) tetrakis[4-(dimethylamino)phenyl]porphyrin, and we have used these substrates to determine the effect of hemin structure on epoxidation rates.[35] If less reactive reference substrates are used, then the more robust halogenated hemin catalysts are required. By judicious choice of catalyst and reference substrates, the relative rates of any set of substrates can be measured by these techniques.

In those cases where the first and second steps can be isolated either by preforming the oxene before substrate addition (e.g., with iron porphyrins at low temperature) or by the fact that the second step can be made slower with low substrate concentration (e.g., chromium(III) porphyrin catalyzed reactions), the second step can be observed by changes in the spectra of both the hemin and the reference substrate.[6b]

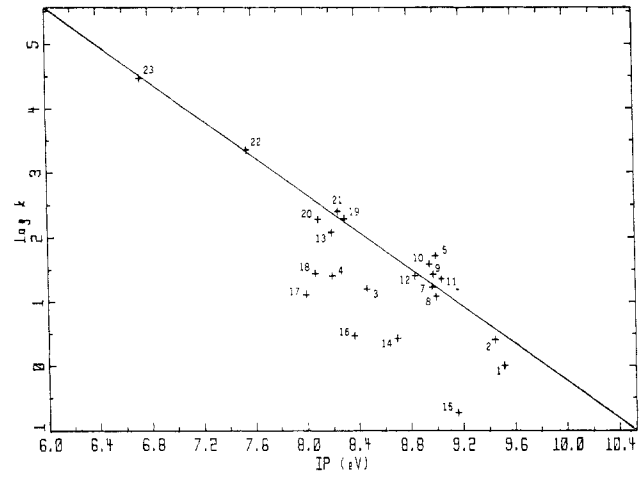
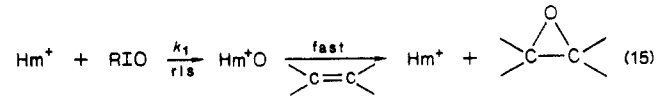


Figure 4. Correlation of log k_{rel} for epoxidation with vertical ionization potentials of the alkene. Numbers identify the alkenes of Table I.

The advantages of our method is that each run is a complete kinetic determination in a homogeneous system in addition to being a relative rate determination; it is as quick as necessary, convenient, and capable of determining kinetics of reactions of involatile substrates that are not amenable to GLC analysis. If intermediates develop, they are detected by fast spectroscopy.

The relative rates reported here were determined under kinetically controlled conditions in a homogeneous system. In every case the rate constant for the disappearance of the diene or β-carotene was 2×10^3 M^{-1} s^{-1}, independent of concentrations or structures of the alkenes or concentration of, e.g., β-carotene and identical with that determined from oxidant disappearance.[34] This is to be expected from the fact that the rate-limiting step is the formation of the intermediate I (eq 15). This constancy of rate



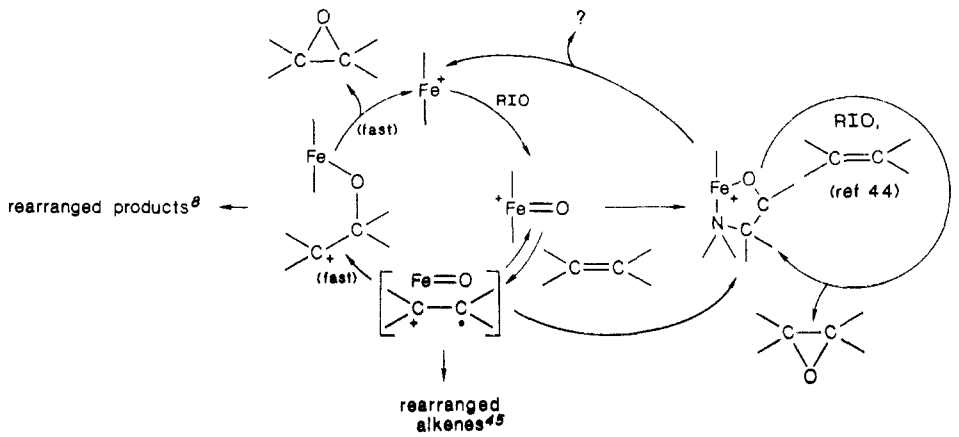
(15)

shows that there is no inhibition of one alkene by even large concentrations of a second alkene. A comparison with the relative rate data for various metal-catalyzed epoxidations reported by others is shown in Table II. The close similarity adds confidence to the use of our analytical method.[38] It should also be noted that with PFIB and the octachlorohemin used here quantitative yields of epoxides are usually obtained.[11b,34] Therefore, our reactions are kinetically well-behaved, high-turnover, quantitative epoxidations.

A plot of log k_{rel} vs gas-phase vertical ionization potentials for all of our data except the styrenes is shown in Figure 4. Groves et al.[6b] and others[11b] established in competitive experiments that *cis*-alkenes are epoxidized faster than are the trans isomers, and we observe that here as well.[38] In fact, the alkenes seem to fall into two groups, both of whose rates correlate with ionization potential with about the same slope. Removing from consideration those alkenes with severe steric constraints, we observe a reasonable linear relationship of log k_{rel} vs IP over 4.5 powers of 10 in rate. This correlation includes the terminal alkene allyltrimethylsilane whose ionization potential is lowered by σ–π conjugation as well as diene 1, which is geometrically equivalent to norbornene. A similar plot of log k_{rel} against the electrode oxidation potential is shown in Figure 5. Except for the hindered compounds α-pinene and *trans*-β-methylstyrene, the rate of epoxidation cor-

(33) Traylor, T. G.; Tsuchiya, S. *Inorg. Chem.* **1987**, *26*, 1338.
(34) Traylor, T. G.; Marsters, J. C., Jr.; Nakano, T.; Dunlap, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 5537.
(35) Traylor, T. G.; Xu, F., unpublished result.
(36) Mimoun, H.; Mignard, M.; Brechot, P.; Saussine, L. *J. Am. Chem. Soc.* **1986**, *108*, 3711.
(37) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.
(38) We also find the ratio of reactivities of *cis*- and *trans*-alkenes to be about 10 by both the UV–vis and GLC methods.
(39) Lynch, B. M.; Pausacher, K. M. *J. Chem. Soc.* **1955**, 1525.

Scheme I



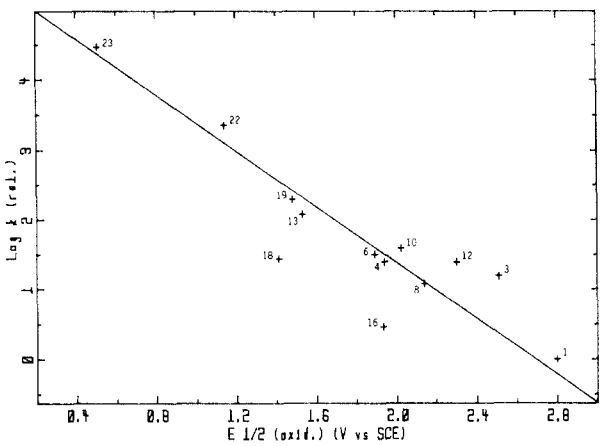


Figure 5. Correlation of log k_{rel} for epoxidation of alkenes with the solution oxidation potentials of the alkenes as in Figure 4.

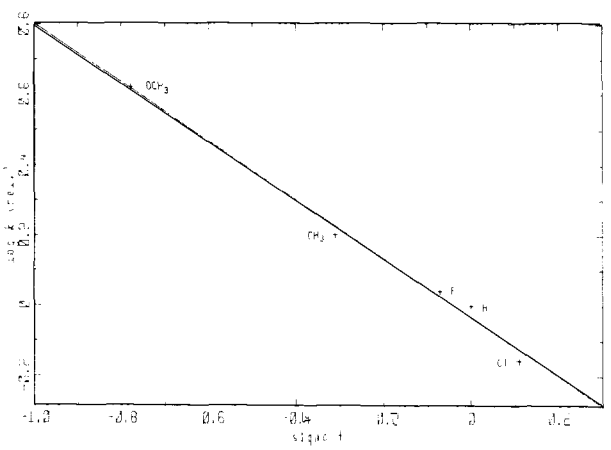


Figure 6. Correlation of log k_{rel} for hemin I catalyzed epoxidation of para-substituted styrenes with σ_p^+ for the substituent.

relates very well with $E_{1/2}$. The data for styrene epoxidation, although giving the same slope in a log k_{rel} vs IP plot as do the other alkenes, are plotted by the Hammett–Brown equation in Figure 6. The correlation with σ^+ is good and the slope, $\rho = -0.84$, is similar to that recorded by Lindsay-Smith ($\rho = -0.93$)[3b] in competitive epoxidations using iron(III) tetraphenylporphyrin in a heterogeneous reaction with iodosylbenzene suspended in methylene chloride. This, and the similar results with other alkenes shown in Table I, indicates that the epoxidation in homogeneous and heterogeneous reactions behave similarly. Groves et al.[6b] report $\rho = -1.9$ at −50 °C for reaction of the intermediate with styrenes.

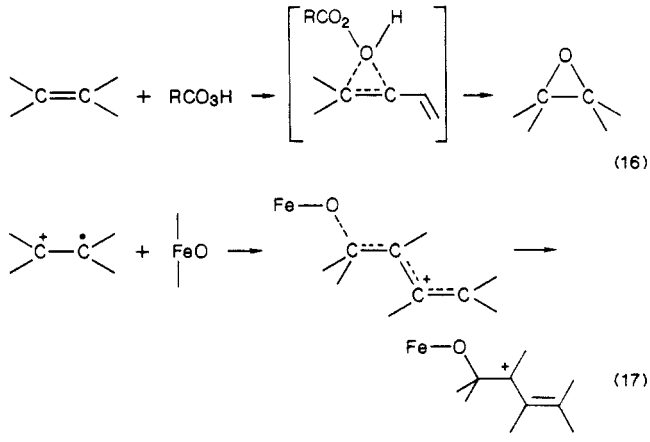
Practically any process in which an electrophilic species reacts with an alkene would respond to electron density. However, one such process, peracid epoxidation, does not show the clear dependency on ionization potential that we observe for hemin-catalyzed epoxidation. Epoxidations with peracids do respond to electron density in that the rate constants increase with alkyl substitution on the alkene. However dienes such as 4-methylpentadiene are reported to be epoxidized more slowly than are similarly substituted alkenes,[40,41] in contrast to our results with hemin catalysts. We have determined the rate constants for reaction of MCPBA in methylene chloride at 25 °C with four of the alkenes used in this work. The bimolecular rate constants are 0.05, 0.16, 0.25, and 10 M^{-1} s^{-1} for compounds **21**, **10**, **22**, and **23** of Table I, further documenting the absence of an effect of delocalization on uncatalyzed epoxidation as well as a lack of correlation of rates with ionization potential. Pausacher[39] reported a ρ value of −0.9 for the Hammett plot of perbenzoic acid epoxidation of 4-substituted stilbenes. This is rather similar to the slope for hemin-catalyzed epoxidations reported here. Therefore, while there are some similarities in the two processes, there is no correlation between the two reactions with regard to alkene structure, even for those alkenes where steric effects are not severe. In particular, 1,4-diphenylbutadiene reacts 60 times faster than does norbornene in the hemin-catalyzed oxidation, but they react at the same rate with perbenzoic acid.

While a higher ρ slope might be anticipated for a mechanism dominated by electron removal from styrenes or stilbenes, it is interesting to note that the photooxidation of 4-substituted stilbenes on a surface, shown to involve the cation radical by Fox et al.,[42] displays a slope of −0.7, similar to that which we observe.

These observations are explicable as differences in delocalization at the transition states. Thus, while both electrophilic direct π orbital association and electron transfer would be favored by the raising of the highest filled orbital by delocalization, the latter process would lose less delocalization at the transition state for bond formation.

The present results, taken alone, are best explained by electron transfer but do not exclude other mechanisms. In particular, we cannot exclude the metallacycle of eq 3. Since no such high-valent iron metallacycle is known,[43] we do not know what chemical or physical properties to assign to it. If, as has been suggested,[11] the metallacycle forms by direct attack on the π bond and if, as we anticipate, such direct electrocyclic reaction responds to structure in the same way as does peracid epoxidation, then the present results are not well accommodated by the metallacycle mechanism. However, the principal evidences against metallacycle

(40) Asahara, T.; Seno, M.; Shimozato, Y.; Otsu, M. *Nippon Kazaku Kaishi* **1972**, *8*, 1251.
(41) Endo, A.; Saito, M.; Yoshida, M.; Fugizaki, Y. *Nippon Kogaku Zasshi* **1967**, *88*, 83.
(42) Fox, M. A.; Chen, C. *Tetrahedron Lett.* **1983**, 547.
(43) Kafafi, Z. H.; Hauge, R. H.; Billups, W. E.; Margrave, J. L. *J. Am. Chem. Soc.* **1987**, *109*, 4775; report an iron(II) oxymetallacycle.



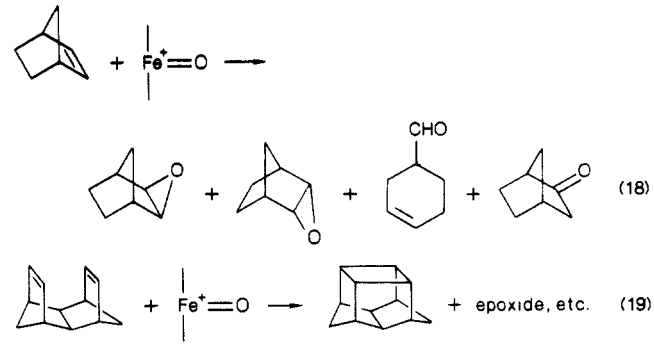
(16)

(17)

intervention are the skeletal rearrangements (eq 18) and cation radical type alkene rearrangements (eq 19) that accompany hemin-catalyzed epoxidation.[8,9,44,45]

The electron-transfer mechanism shown in Scheme I seems to be consistent with these results and with rates of reactions of simple reactive alkenes with high-valent iron porphyrins.

It is not as yet clear whether such an electron-transfer process extends to other less reactive alkenes such as, e.g., acrylic esters, or to other metalloporphyrin catalysts, e.g., Mn and Cr, where



(18)

(19)

different reactivities are seen.[35,46,47] These questions are under investigation.

Acknowledgment. We are grateful to the National Science Foundation, Grant CHE 84-20612, for support of this research and to Dr. Andrew Miksztal, Beth Dunlap, and Jürg Obrecht for some of the compounds and for helpful advice.

Registry No. 1, 111-66-0; **2**, 762-62-9; **3**, 100-42-5; **4**, 622-97-9; **5**, 762-72-1; **6**, 127-91-3; **7**, 1192-37-6; **8**, 110-83-8; **9**, 931-87-3; **10**, 498-66-8; **11**, 627-20-3; **12**, 7642-04-8; **13**, 645-49-8; **14**, 1501-82-2; **15**, 4050-45-7; **16**, 873-66-5; **17**, 103-30-0; **18**, 80-56-8; **19**, 563-79-1; **20**, 1076-13-7; **21**, 5194-50-3; **22**, 538-81-8; **23**, 7235-40-7; **24**, 67-56-1; I, 91042-27-2; PFIB, 14353-90-3; MCPBA, 937-14-4; cytochrome P-450, 9035-51-2.

(44) Traylor, T. G.; Nakano, T.; Miksztal, A. R.; Dunlap, B. E. *J. Am. Chem. Soc.* **1987**, *109*, 3625.
(45) Traylor, T. G.; Miksztal, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 2770.
(46) Bortolini, O.; Meunier, B. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1967.
(47) Meunier, B.; De Carvalho, M.; Robert, A. *J. Mol. Catal.* **1987**, *41*, 185.

Cyclic Cystine Peptides. Antiparallel β-Sheet Conformation for the 20-Membered Ring in Boc-Cys-Val-Aib-Ala-Leu-Cys-NHMe

Isabella L. Karle,* R. Kishore,† S. Raghothama,‡ and P. Balaram†

Contribution from the Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C. 20375-5000, and Molecular Biophysics Unit and Sophisticated Instruments Facility, Indian Institute of Science, Bangalore 560 012, India. *Received July 20, 1987*

Abstract: Crystal structure analysis of a synthetic cystine peptide, Boc-Cys-Val-Aib-Ala-Leu-Cys-NHMe, containing a 20-membered ring, establishes for the first time in the solid state an antiparallel β-sheet conformation for a peptide molecule with a -S-S- bridge. The antiparallel β-sheet of an individual molecule is extended to the whole crystal by intermolecular hydrogen bonding. A type II′ β-bend reversal is formed at Aib[3]-Ala[4]. This is the first occurrence of an Aib residue at the $i + 1$ position in a type II or II′ β-bend. Three nearly parallel intramolecular hydrogen bonds have N···O distances of 2.85–2.89 Å. In the disulfide bridge $C^{\alpha}(1)$–$C^{\beta}(1)$–S(1)–S(6)–$C^{\beta}(6)$–$C^{\alpha}(1)$, S–S = 2.027 Å, angles $C^{\beta}SS$ = 106.3 and 105.3°, and the torsional angles are −55, −101, +101, −84, and −55°, respectively. The space group is $P2_12_12_1$ with a = 18.674 (3) Å, b = 18.614 (3) Å, and c = 12.652 (3) Å with 1 formula unit $C_{30}H_{53}N_7O_8S_2 \cdot H_2O \cdot (CH_3)_2SO$ per asymmetric unit. Least-squares refinement of 2145 data observed $>3\sigma(F)$ yielded an R factor of 9.6%. Analysis of nuclear Overhauser effect data in $CDCl_3$ and $(CD_3)_2SO$ favors a population of type I′ Aib-Ala β-turn conformation in solution, with the antiparallel β-sheet structure being maintained.

Disulfide cross-links can stabilize specific conformations in model oligopeptides.[1] This report describes the structure of the synthetic cyclic cystine peptide Boc-Cys-Val-Aib-Ala-Leu-Cys-NHMe (**1**),[2] in the crystalline state, providing the first example of disulfide bridging across an antiparallel β-sheet and also the first example of an α-aminoisobutyryl residue (Aib) at the $i + 1$ position of a type II′ β-turn. A chain reversal at Aib-Ala and three intramolecular NH···O=C hydrogen bonds result in a pleated antiparallel β-sheet structure. Surveys of crystal structures of globular proteins have not found any disulfide bridges between neighboring strands of β-sheets.[3]

* Laboratory for the Structure of Matter.
† Molecular Biophysics Unit.
‡ Sophisticated Instruments Facility.

(1) (a) Venkatachalapathi, Y. V.; Prasad, B. V. V.; Balaram, P. *Biochemistry* **1982**, *21*, 5502–5509. (b) Ravi, A.; Balaram, P. *Tetrahedron* **1984**, *40*, 2577–2583. (c) Kishore, R.; Balaram, P. *Biopolymers* **1985**, *24*, 2041–2043. (d) Kishore, R.; Raghothama, S.; Balaram, P. *Int. J. Pept. Protein Res.* **1987**, *29*, 281–391. (e) Kishore, R.; Kumar, A.; Balaram, P. *J. Am. Chem. Soc.* **1985**, *107*, 8019–8023. (f) Kishore, R.; Raghothama, S.; Balaram, P. *Biopolymers* **1987**, *26*, 873–891.
(2) (a) Abbreviations used: Aib, α-aminoisobutyric acid; NOE, nuclear Overhauser effect; Boc, (*tert*-butyloxy)carbonyl. (b) All chiral amino acids are of the L configuration.

0002-7863/88/1510-1958$01.50/0