Table I. Oxidation Products of Tetralone Derivatives

substrate	oxidation system	product(s) yield,[a] %			total conversion,[b] %
			4-hydroxide	4-one	
11a	$Fe^{III}PFP(Cl)/PhIO$	**12a**	17		
	$Fe^{III}TPP(Cl)/PhIO$	**12a**	1.2		
	P-450*cam*/NADH/O_2	**12a**	(11.5)[c]		
11b	$Fe^{III}PFP(Cl)/PhIO$	**12b**	13	2.2	4.0
		12b	10	5.8	22
		12b	5.7	8.4	36
11c	$Fe^{III}PFP(Cl)/PhIO$	**12c**	11	5.9	25
		12c	8.5	9.3	36
13	$Fe^{III}PFP(Cl)/PhIO$	**14**	7.6		

[a] Yields based on PhIO used were determined by GLC. [b] Total conversion of substrate to products (4-hydroxide + 4-one). [c] Turnover number (product mol/P-450 mol/min).

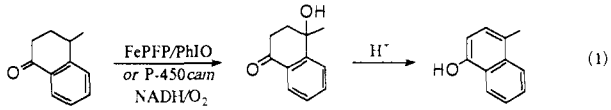
Table II. Oxidation of 1-Tetralone Trimethylsilyl Enol Ethers

substrate	oxidation system	products,[a] %	
15a	$Fe^{III}PFP(Cl)/PhIO$	**16a**, 8.9	**17a**, 27
15b	$Fe^{III}PFP(Cl)/PhIO$	**16b**, 39	**17b**, 13
15b	P-450cam/NADH/O_2	**16b**, 65[c]	**17b**, 35[c] (10)[b]

[a] Yields based on PhIO used were determined by GLC. [b] Overall turnover number (products mol/P-450/min). [c] Ratio between **16b** and **17b**.

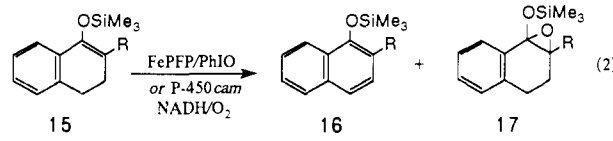
equivalent to **8**, was isolated by column chromatography ($SiO_2/CHCl_3$ and AcOEt) as the sole product. The structure of **12a** was determined by ^1H NMR and mass spectroscopy.[11] Representative results of the oxidation are summarized in Table I.

As shown, only the benzylic position (C-4) of tetralones is reactive for the hydroxylation. The oxidation of **11a** by a reconstituted system with purified cytochrome P-450*cam*[12] (P-450*cam*/*putidaredoxin*/*putidaredoxin reductase*/NADH/O_2) in phosphate buffer (pH 7.4, 0.2 M) at room temperature also afforded **12a** with a turnover number of 11.5 per min. The smaller turnover number[12] suggests that **11a** is not a good substrate for P-450*cam* and binding of **11a** in the active site of the enzyme is not as tight as that for *d*-camphor. While **12**'s are stable upon addition of weak acids such as 6 N HCl (aq) and trifluoroacetic acid, treatment of **12a** in methylene chloride with 12 N HCl gives 4-methyl-1-naphthol in ca. 30% yield with some other unidentified products. When 2-tetralone ethylene ketal (**13**) was oxidized by the model system, the 4-hydroxy derivative (**14**) was obtained (Table I). Hydrolysis of **14** with 1-3 N HCl (aq) readily affords β-naphthol. These results are consistent with the proposed mechanism for the aromatization of **9**.



11a 12a (1)

Oxidation of 1-tetralone trimethylsilyl enol ethers: We have further prepared 1-tetralone trimethylsilyl enol ethers (**15**)[13] to compare the reactivity of **11** with the corresponding enolates. Oxidation of **15a** by the PhIO/$Fe^{III}PFP$ system directly affords aromatized product, **16a**, along with **17a**.[14] Introduction of methyl group at the C-2 position (**15b**) suppresses epoxide formation[15] (Table II). In these reactions, no hydroxylated products were observed. The oxidation of **15b** was also carried out with the P-450*cam* system and the reaction products were obtained as shown in Table II. Cole and Robinson have recently reported importance of an enolate in the aromatization reaction of 19-alkyl peroxo derivatives of testosterone.[16]



15 16 17 (2)

a: R = H; b: R = Me

Recent X-ray crystal structure of P-450*cam* has shown that the C-5 methylene of *d*-camphor is fixed right above the heme iron by hydrogen bonding interaction between Tyr 96 and carbonyl oxygen of *d*-camphor.[17] The active site structure of P-450*arom* has not been delineated yet; however, similar interaction between the C-3 carbonyl oxygen of **1** and amino acid residues such as Tyr and His in the active site would allow the regiospecific oxidation of the C-19 hydrogens. The hydrogen bonding interaction may favor keto-enol equilibrium toward the enol side of the steroid. Once the C-1 position of **8** becomes allylic, dehydration will proceed smoothly to yield **4** as observed in the model compounds.

Finally, the reaction of **3a** and a model complex of peroxo-iron(III) intermediate of P-450, $Fe^{III}PFP(O_2^{2-})$, was found to produce **9a** and an unidentified product (**10**) as major products accompanied by a small amount of **4a**.[18] The structure of **10** is not clear yet; however, that the treatment of the reaction mixture with 3 N HCl (aq) readily gave **4a** is indicative of the structure of **10** being **8a**.[19] Isolation and characterization of **10** is currently under investigation.

Acknowledgment. We are grateful to Drs. R. Makino, F. Mitani, and T. Ogishima at Keio University for helpful discussions. This work was supported in part by Grant-in-Aid for Scientific Research on Priority Area No. 035 from the Ministry of Education, Science, and Culture, Japan, and by grants from Keio University.

(11) ^1H NMR ($CDCl_3$) for 4-Me 1.63 ppm (3 H, s); *m/e* 176 (M^+), 161 (base), 148, 105. The other products and synthesized compounds in this paper gave satisfactory ^1H NMR and mass spectroscopic data.

(12) Cytochrome P-450*cam*: cytochrome P-450 isolated from the bacterium *Pseudomonas putida*. It catalyzes oxidation of *d*-camphor to the 5-*exo*-hydroxy derivative with a turnover number of ca. 1000/min; Tyson, C. A.; Lipscomb, J. D.; Gunsalus, I. C. *J. Biol. Chem.* **1972**, *247*, 5777-5784.

(13) **11b** and **11c** were treated with LDA in THF at -78 °C followed by the addition of trimethylsilyl chloride to afford **15a** and **15b**.

(14) Authentic samples were synthesized as follows. Oxidation of **15** by mCPBA in the presence of $NaHCO_3$ (powder) was carried out in CH_2Cl_2 at room temperature and **17** was isolated in quantitative yield. **16** was prepared by the reaction of lithium α-naphtholate and trimethylsilyl chloride in THF at -78 °C.

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(16) Cole, P. A.; Robinson, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 1284-1285.

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(18) $Fe^{III}PFP(O_2^{2-})$ [λ_{max}, nm: 445 (Soret), 555, 586] was prepared by the reaction of $Fe^{III}PFP(Cl)$ and KO_2 in the presence of 18-crown-6 (less than 0.8 equiv to FePFP to avoid contamination of free O_2^-) in acetonitrile according to Valentine's method: McCandlish, E.; Miksztal, A. R.; Nappa, M.; Sprenger, A. Q.; Valentine, J. S.; Stong, J. D.; Spiro, T. G. *J. Am. Chem. Soc.* **1980**, *102*, 4268-4271. The ratio of **9a**/**10** is 0.5-2, depending on the reaction condition.

(19) That the retention time of **10** is shorter than that of **3a** on GLC also indicates the loss of 19-oxo group by the reaction.

β-Hydroxyalkyl σ-Metalloporphyrins: Models for Epoxide and Alkene Generation from Cytochrome P-450

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The mechanism by which cytochrome P-450 mediated alkane hydroxylation occurs is now well understood,[1] but there are still

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divergent views on the way in which epoxidation occurs.[2,3] It has been suggested[3,4] that addition of olefin to the metal-oxo double bond of the active oxidizing agent could give a metallocycle **1** and that subsequent reactions of **1** (Scheme I) could then account for the formation of epoxide, N-alkylation, and substrate rearrangement. On the other hand, an initial electron transfer from olefin to the active oxidizing agent followed by collapse of the alkene cation radical could give an Fe^{III}–O–C–C^+ cation which could also account for the observed chemistry.[5] Recently Castellino and Bruice[2] reported that they have found no evidence for the intermediacy of a metallocycle, and it certainly seems unlikely that bulky alkenes, such as norbornene, could sterically accommodate metallocyclic formation.

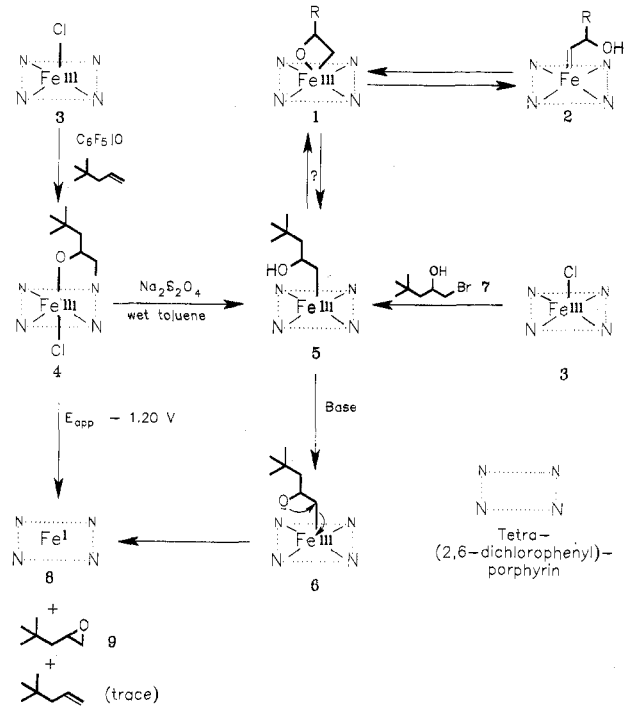
Nevertheless, Groves et al.[4] have shown that epoxidation of small terminal alkenes resulted in stereospecific terminal hydrogen exchange (by D from D_2O) in both recovered olefin and product epoxide when, and *only when*, the enzyme (P-450-$_{LM2}$) was activated by its reductase. Priming the enzyme with iodosyl benzene gave unlabeled epoxide. It was suggested that these exchange reactions proceeded via the reversible deprotonation of the metallocycle **1** to a carbene **2**. It was further reported, and we can confirm, that exchange does not occur during epoxidation with model heme systems. However, model systems, particularly hemins and oxygen atom transfer agents such as iodosyl benzenes, parallel P-450 in much of their chemistry. Indeed, regiospecificity, kinetic isotope effects, alkene epoxidation, alkane hydroxylation, N-alkylation, and even some organometallic chemistry are all closely mimicked by the model systems.[6] Does the absence of deuterium exchange during epoxidation with the model systems mean that the models have finally failed to faithfully mimic the natural systems? We believe not!

The hemin from tetra-(2,6-dichlorophenyl)porphyrin (**3**) is a very robust catalyst,[7] and during alkene epoxidation it can be quantitatively N-alkylated to give **4** by using 4,4-dimethylpentene and perfluoroiodosyl benzene.[6b] Compound **4** was purified by demetalation, chromatography, remetalation ($FeCl_2$/$CH_3OCH_2CH_2OCH_3$ (DME), and crystallization.[8]

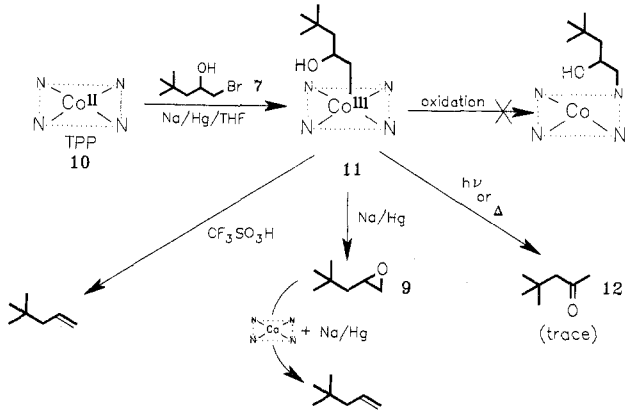
Treatment of the *N*-alkylhemin (**4**) with sodium dithionite in wet toluene[9] converted it to the σ-alkyliron(III) complex **5**.[10] The same complex (**5**) was prepared by the electrochemical reduction of **3** in the presence of the bromohydrin **7** (Scheme I). This electrochemical production of σ-alkyliron(III) porphyrins from hemins in the presence of alkyl halides is well documented[11,12] as is the N→ metal alkyl group migration with both cobalt and iron porphyrins upon a one-electron reduction.[6c,11]

Compound **5** is stable in the presence of a weak noncoordinating base (2,4,6-trimethylpyridine) but when treated with a strong base [10% $(Et)_4NOH$ in CH_3OH] 10–15% of the epoxide **9** was formed.[13] Generation of the alkoxide **6** in the absence of nucleophilic bases was achieved with sodium borohydride. This gave the epoxide in greater than 80% yield along with a trace of the starting alkene. Similarly electrochemical reduction of **4** at −1.2 V (vs Ag/Ag^+) in DME caused migration from N → Fe and reduction of a proton to give a high yield of epoxide, a trace of alkene, and the Fe(I) complex **8**[14] (Scheme I). The fragmentation of **6** to epoxide and the iron(I) complex is a reductive elimination that involves no net redox chemistry.

Scheme I



Scheme II



While the alkyliron complexes described in Scheme I can be handled at room temperature in the absence of oxygen they are, in our hands, too unstable to be isolated, and so we have repeated the chemistry by using cobalt tetraphenylporphyrin **10** as shown in Scheme II.

Reduction of **10** (Na/Hg/THF) followed by treatment with the bromohydrin **7** gave the σ-alkylcobalt(III) complex **11**,[15] (Scheme II). Oxidation of **11** does not result in migration of the

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(7) Traylor, P. S.; Dolphin, D.; Traylor, T. G. *J. Chem. Soc., Chem. Commun.* **1984**, 279.
(8) Compound **4** was identical with that reported previously[6b] λ_{max} (CH_2Cl_2) 361, 439, 573, 639, 686.
(9) Mansuy, D.; Battioni, J.-P.; Dupre, D.; Sartori, E. *J. Am. Chem. Soc.* **1982**, *104*, 6159.
(10) Compound **5** λ_{max} (toluene) 396 (sh), 414, 526, 552 similar to σ-alkylcomplexes described by Mansuy et al.[9] (CH_3-Fe^{III}TPP λ_{max} C_6H_6) 390, 413, 518, 548; Ph-Fe^{III}TPP λ_{max} (C_6H_6) 393, 412, 521, 547 and by Lexa et al.[11]
(11) Lexa, D.; Mispelter, J.; Saveant, J.-M. *J. Am. Chem. Soc.* **1981**, *103*, 6806.
(12) Lexa, D.; Saveant, J.-M.; Wang, D. L. *Organometallics* **1986**, *5*, 1428.
(13) All low molecular weight organics were quantitatively analyzed by GLC with a HP-1 capillary column, a Hewlett Packard 5890 instrument, and authentic reference samples.
(14) Compound **8** λ_{max} (DME) 364, 420, 500, 542, 618, 726 similar to the Fe(I) porphyrins reported by Lexa et al.[11]
(15) Compound **11** λ_{max} (DME) 408, 526 nm; MS, 671 (M-115); ^1H NMR ($CDCl_3$) −4.26 (s, 1 H), −3.73 (t, 1 H), 3.58 (d, 1 H), −2.85 (br m, 1 H), −1.30 (dd, 1 H), −0.87 (dd, 1 H), −0.41 (dd, 9 H), 7.72 (br m, 12 H), 8.09 (br m, 12 H), 8.02 (s, 8 H). Anal. Calcd for $C_{51}H_{43}CoN_4O$: C, 77.9; H, 5.5; N, 7.1. Found: C, 77.7; H, 5.42; N, 6.90.

alkyl group to nitrogen as is observed with simple alkyl complexes. The fragmentation of cobalt β-oxygen substituted σ-alkyl complexes has been reported to occur in preference to migration.[16] Similarly, oxidation of **5** does not generate any N-alkyl complex **4**. Treatment of **11** with heat or light gave traces of the ketone **12** consistent with homolytic cleavage of the Co–C bond.[17] In the presence of triflic acid **11** gave a high yield of the alkene but no oxygen-containing products.

In parallel with the iron system described above, reduction of **11** (Na/Hg/DME) gave epoxide **9** (>90%) with a trace of alkene. However, the yield of alkene increased with time since under the reductive conditions the cobalt(I) porphyrin can be alkylated by the epoxide[18] to give **11** which can then be reductively cleaved generating alkene at the expense of epoxide (Scheme II).

The metallocycle **1** is an alternative way of representing the σ-alkyliron porphyrin **5**. Metal alkyls can be deprotonated to carbene complexes,[19] and we suggest that the novel chemistry described by Groves et al.[4] can be alternatively explained by the chemistry described above for σ-alkyl metal complexes.

We suggest that the first step in the deuterium exchange reactions[4] could involve electron transfer from the olefin and N-alkylation of the subsequent cation to give a β-hydroxy-*N*-alkylporphyrin.[6c] We note, again, that deuterium exchange during the enzymic reaction occurs *only under reducing conditions*, a condition where N→Fe alkyl migration can occur.[11,12,20] Castellino and Bruice[2] describe the transition states needed for N-alkylation; this and the subsequent migration of the alkyl group to iron will be more favorable with very small substrates (this may explain why even butene-1 shows little and hexene-1 no deuterium exchange[4]). Cleavage of the Fe–C bond could then give epoxide and alkene, both labeled if exchange occurs with the σ-alkyl complex.

Acknowledgment. This work was supported by the United States National Institutes of Health, GM 29198, and the Natural and Engineering Research Council of Canada.

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Book Reviews *

Electroanalytical Measurements in Flowing Liquids. By K. Štulík and V. Pacáková (Charles University, Prague). John Wiley & Sons: New York. 1987. 290 pp. $77.95. ISBN 0470-20875-9.

The stated intention of this text is to bridge the gap between analytical flow measurements and pertinent electroanalytical methodologies, with emphasis largely on laboratory practice rather than industrial monitoring. However, it should prove useful both to those with interests in lab analysis and separations, e.g., the growing use of LC-ED (liquid chromatography–electrochemical detection), and to industrial practitioners with flow detection/measurement problems. The contents are organized in six chapters with copious references to up-to-date electroanalytical flow techniques and developments.

Chapter One introduces general terminology and discusses the advantages/disadvantages of segmented flow analysis (SFA), continuous flow analysis (CFA), and flow-injection analysis (FIA). Electrochemical techniques are categorized without detailed theoretical discussion; however, extensive references are given to books that describe modern electrochemical methods. The chapter concludes with some references to industrial analysis problems and automation. Chapter Two briefly treats the theory of electroanalytical flow measurements, first by outlining detector signal criteria, next by giving a summary of classical hydrodynamic principles and general aspects, and finally by providing a section on analyte zone dispersion. These first two chapters attempt only an introductory treatment to hydrodynamic engineering. In Chapter Three, the design and operational parameters for particular electrochemical flow detectors are covered with greater emphasis on practical aspects. Included are on-line ISEs (ion-selective electrodes, including ISFETS), voltammetric and coulometric detectors and their maintenance in a reproducibly active state, cell design considerations, and conductometric and high-frequency impedance detectors. Chapter Four continues with valuable practical details of pumps, instrumentation for gradient elution HPLC, sample introduction techniques, reservoirs, mixers, reactors, and temperature control. The final two chapters cover general analytical methods and a compilation of selected applications, respectively. Methodology includes calibration, direct measurements, titrations, electrochemical pre-concentration techniques for stripping analyses, spectroelectrochemical methods of photochemical derivative formation (abbreviated to HPLC-hν-ED), the use of enzymes, and a section describing the applications and advantages of electrochemical immunoassays. Finally, broad ranges of applications for biologically important substances, drugs, metals, organometallics, pesticides and environmental pollutants, etc., are categorized by using the various representative flow/electrochemical methods. Overall, although the condensed presentation is not especially readable in parts, the book is jam-packed with information of value to biochemists, chromatographers, electrochemists as well as industrial analytical chemists. Its authors are to be commended for their timely extensive survey and coverage of the literature of these topics.

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Metal–Support Interactions in Catalysis, Sintering, and Redispersion. Edited by Scott A. Stevenson, J. A. Dumesic, R. T. K. Baker, and Eli Ruckenstein. Van Nostrand Reinhold Catalysis Series. Van Nostrand Reinhold Company: New York. 1987. xii + 315 pp. $62.95. ISBN 0-442-21160-0.

This book is introduced as the first in a series that would consider specific topics in catalysis. It treats in detail the phenomenon of strong metal–support interactions (SMSI) and the thermodynamic basis for the sintering and redispersion of supported metal particles. The book is divided into two sections of nine chapters each. Section I (Metal–Support Interactions: Discovery, Characterization, and Implications) is made up of contributions by several authors. However, Stevenson, Baker, Dumesic, G. B. Raupp, and S. J. Tauster contribute to eight chapters. Section II (The Role of Interactions and Surface Phenomena in Sintering and Redispersion of Supported Metal Catalysts) is written in its entirety by E. Ruckenstein. The two sections complement each other, and the entire volume provides a perceptive and balanced account of metal–support interactions.

Section I is written in the coherent fashion of a lengthy review article. Data from the literature up to 1985, on the interaction of group VIII metals with reducible oxides, are summarized in the form of very clear diagrams. The section begins with an historical introduction, followed by a review of how SMSI manifests itself in chemisorption studies. The authors then consider how SMSI complicates the task of catalyst characterization. Data relating to the nature of the reduced support are reviewed, and the interrelationship between the support, the particle size distribution, and particle morphology is discussed. The results of catalytic studies are discussed in detail, with special emphasis on the fact that SMSI often improves activity or selectivity for CO hydrogenation, whereas hydrogenolysis reactions are suppressed. The longest chapter of the section is devoted to a critical analysis of the various models for SMSI. Most emphasis is placed on the decoration model, and the possible role of electronic perturbation at the oxide–metal perimeter. In an 8-page summary of the section the authors emphasize that the dynamic nature of SMSI makes the phenomenon a difficult one to study experimentally, and that critical pieces of information remain unknown. The entire section is written in such a well thought out and balanced style that it transcends the domain of SMSI and will provide many ideas for experiments on metal–support interactions.

In Section II of the book, Ruckenstein considers how metal–support interactions determine the changes in small metal particles that occur on

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