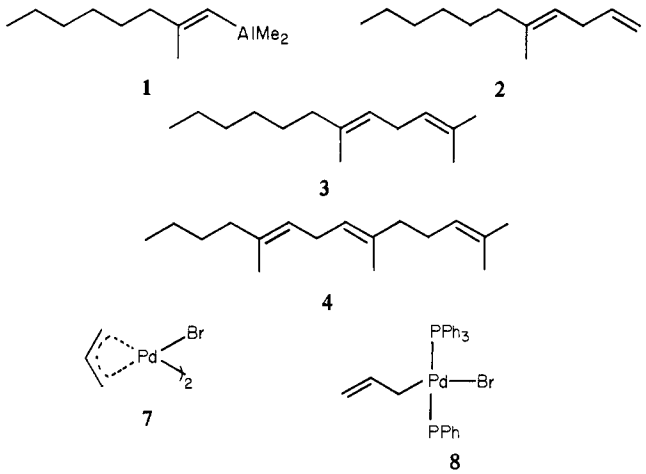

is therefore entirely possible that, unlike Trost's reaction of π-allylpalladium derivatives with "soft" carbanions which has been shown to involve the backside attack of π-allylpalladium cations by the carbanionic species,[8] our reaction might involve attack of σ-allylpalladium derivatives by organometals via transmetalation which is followed by reductive elimination, as we have suggested for various other Pd-catalyzed cross-coupling reactions.[2]

Acknowledgment. We thank the National Institutes of Health and the Japan Tobacco & Salt Public Corp. for support of this research.

(18) The reaction of **7** with the same alkenylalane also produces **2** in 42% yield. The reaction, however, is accompanied by competitive isomerization of **2** into a conjugated diene which is complete in 10 h as well as by formation of 2-methyl-1-octene (~40%). Addition of a small aliquot (~5 mol %) of the above reaction mixture to pure **2** does include the same isomerization but that of **7** to **2** does not.

High-Valent Iron–Porphyrin Complexes Related to Peroxidase and Cytochrome P-450

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The higher valent iron porphyrin intermediates which play an important role in the mechanisms of hemoproteins such as the peroxidases[1] and cytochromes P-450[2] are poorly understood. The enigmatic spectral characteristics of the oxidized states of the peroxidases and the lack of simple model compounds of similar structure and oxidation state have elicited much conjecture regarding the structure of such species. For example, the properties of compounds I of horseradish peroxidase[3] (HRP) and chloroperoxidase[4] are consistent with an iron(IV)–porphyrin π-cation radical formulation,[5] whereas the two-electron oxidized intermediate of cytochrome c peroxidase appears to have unpaired electron density on a protein functional group.[6] No reactive iron–oxygen species has ever been observed for cytochrome P-450. This fact has been used to support recent suggestions[2a] that a protein-derived radical may be responsible for the C–H bond cleavage of cytochrome P-450 mediated aliphatic hydroxylation reactions. We report here the preparation and characterization of a new high-valent iron–porphyrin complex with spectral properties similar to those reported for horseradish peroxidase compound I and reactivity toward olefins indicative of cytochrome P-450 activity.

The oxidation of chloro-5,10,15,20-tetramesitylporphinatoiron(III)[7] [TMPFeCl] with 1.5 equiv of *m*-chloroperoxybenzoic acid in methylene chloride–methanol (4:1) at −78 °C produced a green intermediate A. This change was detected by the disappearance of the β-pyrrole hydrogen resonance at δ 120 in the ^{1}H NMR spectrum of TMPFeCl and the appearance of a new resonance of equivalent intensity at δ −27. Similarly, the EPR signals of high-spin TMPFe(III)Cl were absent in toluene solutions of A.

The ^{1}H NMR spectrum of A at −77 °C in methylene chloride–methanol showed absorbances at δ 68 (*m* H), 26 and 24 (*o*-methyl), 11.1 (*p*-methyl) and −27 (β-pyrrole H).[8] These chemical shifts were highly temperature dependent and obeyed the Curie law between −26 and −89 °C. The magnetic susceptibility of A was determined by the Evans method[9] to be 4.2 μ_B, slightly larger than expected for an $S = {}^3/_2$ system. The visible spectrum of A showed a broad Soret band at 406 nm and another broad band centered at 645 nm. The Mössbauer spectrum of A derived from ^{57}Fe-enriched TMPFeCl showed a quadrupole doublet centered at 0.05 mm/s (ΔE_q = 1.49 mm/s).[10] A showed no strong EPR absorbances above 20 K.[11]

The distinctive visible spectrum suggests that A is a porphyrin π-cation radical.[5] The large downfield shifts of the proton resonances of the pendant mesityl groups indicate that significant spin density resides on the porphyrin meso carbons as would be expected for the loss of an electron from the a_{2u} porphyrin π orbital.[12] The small isomer shift in the Mössbauer spectrum of A is similar to that reported for HRP I (δ = 0.08 mm/s, ΔE_Q = 1.25 mm/s) and is in the range expected for iron(IV).[13] The very high-field position of the β-pyrrole hydrogen resonances in the ^{1}H NMR spectrum of A contrasts sharply with the low-field position of those protons in the spectrum reported[14,20] for a [TPP(cation radical)Fe^{III}]$^{2+}$ or [TPPFe^{IV}]$^{2+}$ and the δ 5.0 position reported by Balch and LaMar for an oxo-TPPFe(IV) complex.[15] High-field proton NMR resonances have been reported for the pyrrole hydrogens of HRP-I[16] and a vinylidene carbene porphinatoiron(III) complex[17] which is, formally, at the same oxidation state.

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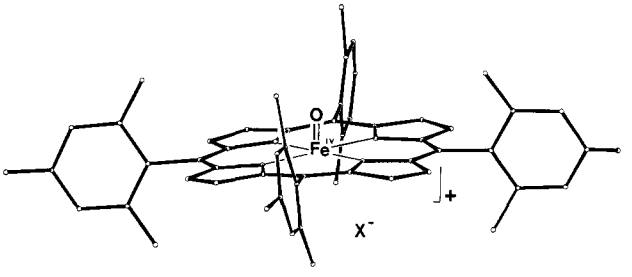
Taken together, the NMR, visible, Mössbauer, and EPR data indicate the A is an iron(IV)–porphyrin π-cation radical structure such as **1** or its conjugate acid. The similarity between the data



1

we have reported here for A and those of HRP I[16,18,19] supports previous suggestions[5,20] that HRP I and related enzymic intermediates are also iron(IV)–porphyrin cation radicals similar to **1**.

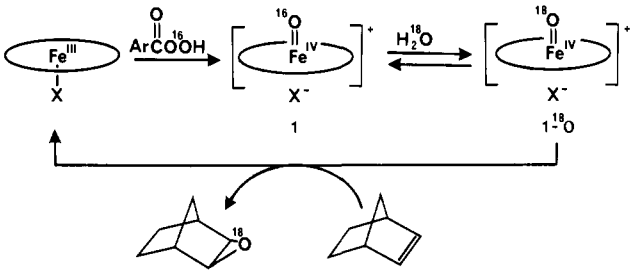
We have recently shown that iodosylbenzene and *m*-chloroperoxybenzoic acid can transfer oxygen to chlorotetraphenylporphinatochromium(III) to give an oxochromium(V) complex.[21] Extended Hückel calculations by Gouterman[12] have indicated that while the lowest lying d orbitals of chromium(III) lie well above the porphyrin a_{2u} orbital, those of iron(III) are similar in energy to the filled porphyrin orbitals. Thus, the differences between the electronic structures of A and its chromium analogue have been correctly predicted by these calculations.

Reaction of TMPFeCl with 1.0 equiv of iodosylbenzene in methylene chloride at −78 °C produced initially a red intermediate B. Addition of acetic acid to solutions of B at −78 °C caused the conversion of B to A. Furthermore, the green species A generated from *m*-chloroperoxybenzoic acid could be converted to B by the addition of tetramethylammonium hydroxide.

The ^{1}H NMR spectrum of B at −73 °C showed resonances at δ −33.5 (β-pyrrole H), 2.8 (p-CH_3) and 7.6 (m-H).[8] An extremely broad resonance centered at δ 2.4 at −60 °C in the 360-MHz spectrum of B was assigned to the ortho-methyl hydrogens. The β-pyrrole hydrogen resonance was highly temperature dependent. From −30 to −90 °C the paramagnetic shift obeyed the Curie law indicative of noninteracting paramagnetic sites in B. The magnetic susceptibility of B determined by the Evans method[9] over this temperature range was 2.9 μ_B, close to the spin-only value expected for an $S = 1$ system. The Mössbauer spectrum of B showed a well-resolved quadrupole doublet centered at −0.03 mm/s. (ΔE_q = 2.13 mm/s)[10] and the EPR spectrum of toluene solutions of B showed no strong signals.

The stoichiometry of the reactions that produce B and the interconversion of A and B with acid and base suggest that both are at the same formal oxidation state. Such considerations suggest an oxoiron(V) structure or an Fe(IV) a_{1u} cation radical formulation,[5] but neither appears consistent with all the observed spectral properties of B.[22,23]

Scheme I



Both the green compound A and the red compound B were very reactive toward reducing agents even at temperatures below −85 °C. Treatment of either A or B with tetramethylammonium iodide (2.2 equiv) in methylene chloride at −85 °C caused the appearance of a new, high-spin iron(III) complex which could only be 5,10,15,20-tetramesitylporphinatoiron(III) hydroxide (**2**).[24]

Compound B reacted with cyclooctene in methylene chloride at −40 °C to regenerate TMPFe^{III}Cl. While the half-life of B under these conditions was 15 min, similar treatment of B with *trans*-3-hexene caused negligible reduction. As we have noted,[22a] *cis*-olefins are more reactive than *trans*-olefins in the iron–porphyrin-catalyzed epoxidation of double bonds by iodosylbenzene. The qualitative kinetic behavior observed here is consistent with the intermediacy of B under these catalytic conditions.

Treatment of a solution of A, generated from *m*-chloroperoxybenzoic acid, with norbornene at −80 °C led to the regeneration of TMPFeCl. Gas chromatographic analysis of the solution revealed the presence of norbornene oxide in 78% yield based on peroxyacid. When A was prepared in 6 mL of methylene chloride–methanol (5:1) containing 47 μL of $H_2{}^{18}O$ (99.5%) and treated with norbornene, the mass spectrum of the norbornene oxide produced indicated 99% ^{18}O incorporation into the product epoxide. Thus, the oxygen of the epoxidizing species was exchangeable with added $H_2{}^{18}O$. This result is inconsistent with either free or metal-coordinated peroxyacid as the oxygen-transfer agent but would be expected for an oxoiron intermediate such as **1**[21] (Scheme I).[25]

Compound A is significantly more reactive toward olefins than B. Thus, treatment of a methylene chloride solution containing A and B with methylcyclohexene caused the disappearance of A and the appearance of TMPFeCl within 3 min. Reduction of B to TMPFeCl was complete after 30 min under these conditions. The high reactivity of A toward hydrocarbons supports the view that an oxoiron(IV)–porphyrin π-cation radical intermediate, such as **1**, would be a viable intermediate for the oxyfunctionalization of hydrocarbons mediated by cytochrome P-450.[7] Further, the facile oxygen exchange observed during the epoxidation of norbornene with **1** could explain the ^{18}O incorporation that has been observed in the cytochrome P-450 mediated hydroxylation of cyclohexane.[26]

These compounds now provide the first opportunity to study simple models of peroxidase compounds I and the putative active oxygen species of cytochrome P-450.[27] Such studies are currently under way in our laboratories.

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High Asymmetric Induction during Organometallic β Addition to α,β-Ethylenic Sulfoxides. Synthesis of Optically Active β-Alkylcarboxylic Acids, β-Substituted Cyclopentanones, and Steroidal 11-Oxoequilenin Methyl Ether

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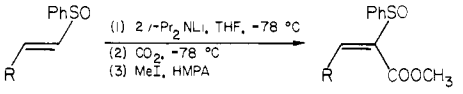
Pursuing our interest in the chemistry of α,β-unsaturated sulfur compounds,[1] we have discovered that several types of optically pure α-carbonyl α,β-ethylenic sulfoxides undergo facile conjugate addition of organometallic reagents with good to excellent amounts of asymmetric induction.[2-4] This transfer of chirality from the sulfoxide sulfur atom to the β-carbon atom during organometallic β addition, followed by reductive removal of sulfur, produces β-alkylcarboxylic esters in 59–65% optical purity and β-substituted cyclopentanones in 79–>98% optical purity. Virtually complete control of absolute stereochemistry is achieved in preparation of 2,2,3-trisubstituted cyclopentanone **11**, the racemate of which we have recently converted into steroidal (±)-11-oxoequilenin methyl ether.[5]

α-Lithiation[1b] and then protonation of optically pure (*E*)-1-undecenyl phenylsulfoxide (**1**) [R = n-C_9H_{19}, $[\alpha]^{22}_D$ = +95.66° (*c* 0.76, $CHCl_3$)][6,7] caused virtually no loss of optical activity ($[\alpha]^{22}_D$ +95.22°) and no *E* → *Z* isomerization. One-pot α-lithiation followed by carboxylation and esterification produced optically pure α-(methoxycarbonyl)alkenyl sulfoxides (*S*)-**2a** and (*S*)-**2b** in 80 and 40% overall yields, respectively (eq 1).[6]



(1)

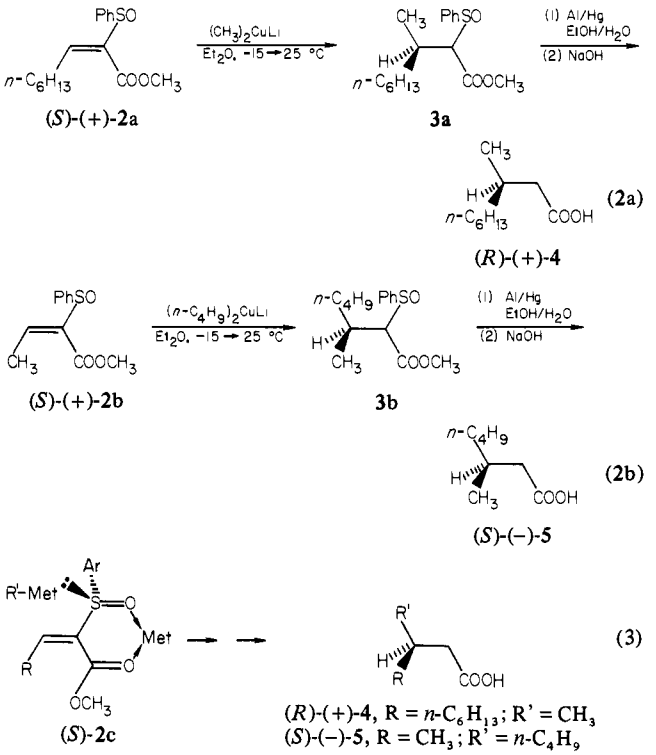
(+)-**1** (*S*)-(+)-**2**

2a, R = n-C_6H_{13}	$[\alpha]^{22}_D$ +200°	(*c* 2.98, acetone)
b, R = CH_3	$[\alpha]^{22}_D$ +216°	(*c* 1.82, acetone)

(*E*)-1-Octenyl sulfoxide (*S*)-**2a**[7] reacted with dimethylcopperlithium to afford β-adduct **3a** in 86% chemical yield (Scheme I). Reduction of α-sulfinylcarboxylic ester **3a** with aluminum amalgam in ethanol[1a] and saponification gave (*R*)-(+)-3-methylnonanoic acid (**4**), $[\alpha]^{22}_D$ +4.68° (*c* 1.1, acetone), in 53% chemical yield and 65% optical purity.[8] Reversing the order of introducing the larger and the smaller alkyl groups at the prochiral β-carbon atom afforded mainly that enantiomer having opposite absolute stereochemistry. (*E*)-1-Propenyl sulfoxide (*S*)-**2b**[6] reacted with di-n-butylcopperlithium to produce conjugate adduct **3b**; reductive removal of the sulfinyl group and saponification gave (*S*)-(−)-3-methylheptanoic acid (**5**), $[\alpha]^{22}_D$ −2.46° (*c* 0.65, acetone), in 59% enantiomeric excess (eq 2b).[8] Comparable levels of asymmetric induction were also obtained by using >2 equiv of various methylcopper species and the carboxylic *acid* corresponding to *ester* (*S*)-**2a**. We tentatively rationalize these results in terms of an approximately planar metal chelate such as (*S*)-**2c** which suffers nucleophilic addition from that side of the plane containing sulfur's nonbonding electron pair and opposite to that side containing the aryl group.

Activation of α,β-ethylenic sulfoxides toward organometallic β addition is not limited to α-carboxyl groups; α-keto groups also are highly effective. For example, optically pure, crystalline (mp 121–122 °C), stable cyclopentenone *p*-tolyl sulfoxide (*S*)-**6**, $[\alpha]^{22}_D$ +141.7° (*c* 0.11, $CHCl_3$),[6,9] underwent methyl Grignard (1.5 equiv) *conjugate* addition (*even in the absence of copper salts*).

Scheme I



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(2) For β addition of alkyllithium reagents to α,β-ethylenic sulfoxides, see: Isobe, M.; Kitamura, M.; Goto, T. *Chem. Lett.* **1980**, 331. Sugihara, H.; Tanikaga, R.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 655.

(3) For β addition of enolate ions and heteroatomic nucleophiles to α,β-ethylenic sulfoxides, see: (a) Tsuchihashi, G.; Mitamura, S.; Ione, S.; Ogura, K. *Tetrahedron Lett.* **1973**, 323. (b) Tsuchihashi, G.; Mitamura, S.; Ogura, K. *Ibid.* **1973**, *2469*. (c) Tsuchihashi, G.; Mitamura, S.; Ogura, K. *Ibid.* **1976**, 855. (d) Abott, D. J.; Colonna, S.; Stirling, J. M. *Chem. Commun.* **1971**, 471. (e) Guitet, E.; Julia, S. *Tetrahedron Lett.* **1978**, 1155.

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(6) All new compounds were fully characterized spectroscopically and by combustion and/or high resolution mass spectral analysis.

(7) Prepared according to ref 1c.

(8) (a) Optically pure (*R*)-(+)-**4** is reported to have $[\alpha]^{24}_D$ +7.6° and optically pure (*S*)-(−)-**5** to have $[\alpha]^{27}_D$ −4.2°: Meyers, A. I.; Kamata, K. *J. Am. Chem. Soc.* **1976**, *98*, 2290. (b) For other examples of high asymmetric induction in preparation of β-alkylcarboxylic acids, see: Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250. Hashimoto, S.; Yamada, S.; Koga, K *J. Am. Chem. Soc.* **1976**, *98*, 7450.

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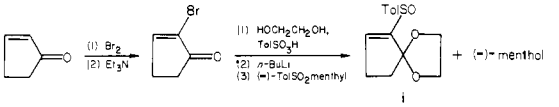

involves liberation of optically pure (−)-menthol which, as the original source of chirality for the entire scheme, can be recycled easily. Ketal sulfoxide i, $[\alpha]^{22}_D$ +49.5° (*c* 1.03, $CHCl_3$), was easily and quantitatively converted into the corresponding ketone (*S*)-**6** by stirring it in acetone at room temperature over copper sulfate (Posner, G. H.; Mallamo, J. P.; Rose, R. K., unpublished results).

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