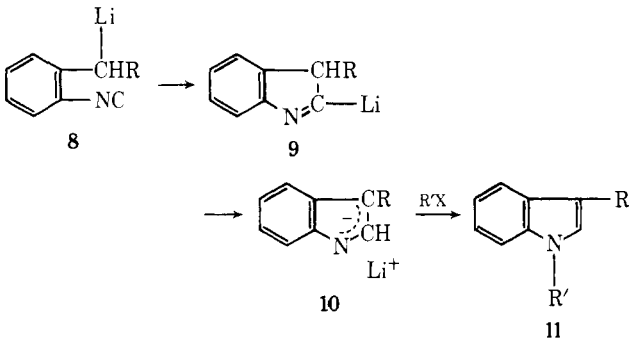
pared independently.[8] Some one-flask syntheses of tryptophol derivatives are listed in Table III.

The present indole synthesis constitutes an interesting example of a "5-endo-digonal" ring closure as classified by Baldwin,[9] in which the carbanion of **8** intramolecularly adds to the adjacent isocyano carbon, resulting in the formation of lithium derivative **9**. However, attempts to trap the lithium



derivative **9** with electrophiles, which could provide an entry to 2-substituted indole, were not successful. When **2** prepared in diglyme at −78 °C was allowed to warm up to −25 °C, the characteristic red color of **2** gradually changed to brown. The brown solution at −25 °C was treated with alkyl halides and with alkylene oxides to afford 1-alkylindoles and 1-(β-hydroxyalkyl)indoles, respectively, in good yields (**11**: R = H, R′ = *n*-C_4H_9, 82%; R = H, R′ = $(CH_3)_3Si$, 87%; R = H; R′ = CH_3CH_2CO, 79%; R = H, R′ = $C_2H_5CH(OH)CH_2$, 84%; R = H, R′ = $(CH_3)_2C(OH)CH_2$, 65%). The finding indicates that the lithium derivative **9** is rapidly converted to **10** even at −25 °C. Consequently this procedure presents a convenient synthesis of 1-substituted indoles starting with *o*-tolyl isocyanide.

In comparison with the previous methods of indole synthesis,[10] the synthesis of 1- and 3-substituted indoles in this study has some advantages: good yields of the products and simple manipulations as well as the ready availability of the starting *o*-tolyl isocyanide.[11]

Work is in progress to investigate a full scope of the present indole synthesis.

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(3) It is noteworthy that 2,4-xylyl isocyanide was treated with 2 equiv of LDA in diglyme at −78 °C to produce 2-lithiomethyl-4-methylphenyl isocyanide selectively. This observation suggests that the lithiation at the ortho methyl group of **1** may be assisted by the neighboring isocyano function.
(4) LDA was prepared by adding dropwise 1 mol of diisopropylamine at −78 °C to 1 mol of *n*-butyllithium (1. 8 M hexane solution).
(5) Cyclization of *o*-*n*-pentylphenyl isocyanide with LDA afforded only 30% of 3-*n*-butylindole along with *N,N*-diisopropyl-*N*′-(*o*-*n*-pentylphenyl)formamidine (60%).
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Active Site Models of Horseradish Peroxidase Compound I and a Cytochrome P-450 Analogue: Electronic Structure and Electric Field Gradients

Sir:

Recent work has been reported with partially purified cytochrome P-450's in which the normal enzymatic pathway is by-passed and an active form produced by the addition of certain peroxides and peracids to the ferric state of the enzyme.[1] More recently, optical spectra have been obtained for an enzymatically active adduct of soluble $P\text{-}450_{cam}$ and peracetic acid.[2] A strong resemblance is suggested between the enzymatically active species of cytochrome P-450 and compound I, an intermediate formed by the reaction of peroxides, peracids and other oxidants with ferric horseradish peroxidase.[3,4]

Unlike the cytochrome P-450 analogue, compound I is stable enough to have been isolated and more fully characterized. One axial ligand appears to be an imidazole group[5] while a single oxygen atom has been shown to be transferred to the iron by peracid and peroxide substrates.[3,6] Magnetic susceptibility studies indicate a $S = 3/2$ state[7] although no ESR has been detected.[8] Mössbauer resonance spectra yield a quadrupole splitting of $\Delta E_Q = 1.20$ mm/s and confirm the presence of unpaired spin.[9] Numerous formal oxidation and spin states of the iron and its ligands have been suggested[4] to account for the unpaired spins and two oxidizing equivalents above the ferric resting state known to be present[10] in this formal $[FeO]^{3+}$ complex. They include: (Fe(V) $S = 3/2$) with a spin paired porphyrin ring;[11] (Fe(IV) $S = 1$) with a porphyrin radical,[12] and (Fe(III) $S = 3/2$ or $S = 1/2$) with the two oxidizing equivalents centered on a singlet or triplet porphyrin ring.[8,12]

Electronic spectra seem most consistent with the presence of a π cation radical indicating that one of the three unpaired spins is delocalized on the porphyrin ring in an a_{2u} π orbital centered on the pyrrole nitrogens.[4,13] These results imply that the (Fe(IV) $S = 1$, porphyrin $S = 1/2$) model for compound I is most reasonable. However, in spite of extensive experimental investigations, the ground state electronic structure of compound I and the distribution of the three unpaired electrons among the iron and its ligands have not been totally resolved.

As shown by previous studies,[14,15] the use of iterative extended Hückel theory[16] coupled with calculation of one electron properties can help determine the electronic configuration and spin distribution of transition metal complexes such as the active site of compound I. Given the possible similarity of compound I and the uncharacterized active species of cytochrome P-450, further comparisons can help lead to an understanding of the electronic structure of the oxygen atom which serves as an activated axial ligand for both systems. A model for the active site of compound I shown in Figure 1 was therefore formulated with axial imidazole and atomic oxygen ligands for input to an IEHT program previously parameterized

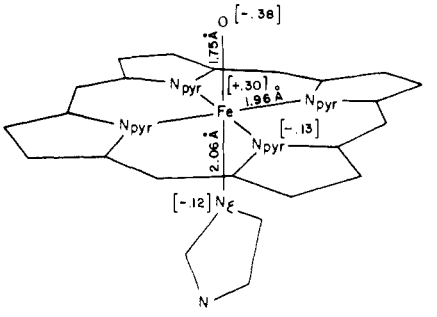

Figure 1. Geometry and calculated net atomic charges [±q] for compound I.

Table I. Electric Field Gradients and Quadrupole Splittings of Compound I and II and of the P-450 Analogues

	V_{xx}[b]	V_{yy}[b]	V_{zz}[b]	η[a]	ΔE_Q[a]	Exptl values of ΔE_Q[d]
HRP:						
Compound I	−0.88	−0.75	1.64	0.08	1.67	1.20 ± 0.02
Compound II[c]	−0.92	−0.79	1.72	0.08	1.75	1.36 ± 0.02
P-450						
Fe(III)-O	−0.66	−0.86	1.52	0.13	1.55	
Fe(II)-O	−0.77	−0.64	1.41	0.09	1.44	

[a] ΔE_Q in mm/s calculated from $\Delta E_Q = 8\langle r^{-3}\rangle(1-R)Qq[1+\eta^2/3]^{1/2}$ where $(1-R)$ = Sternheimer shielding factor = 0.68, $Q = 0.187$ barns, $\langle r^{-3}\rangle = 5.00$ au, and V_{ii} ordered such that $q \equiv$ largest magnitude V_{ii} and $0 < \eta < 1$. Sign of ΔE_Q is sign of largest magnitude V_{ii}. [b] Principal axis values given are very nearly along the chosen molecular axis. The porphyrin plane is xy with pyrrole nitrogens on the x and y axes and ligands on the z axis. [c] Compound II results obtained by adding an electron into the lowest, half filled orbital of compound I keeping all eigenvectors constant. [d] Reference 8.

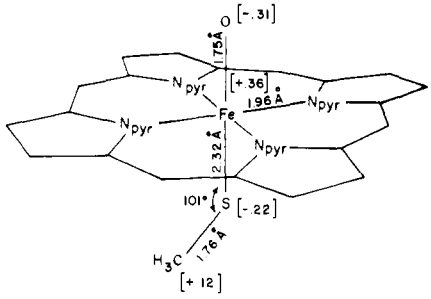

Figure 2. Geometry and calculated net atomic charges [$\pm q$] for cytochrome P-450 analogue.

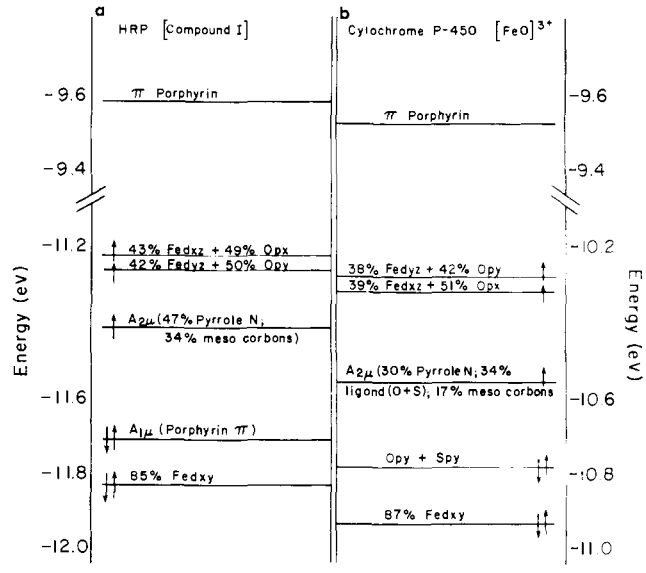

Figure 3. Eigenvalues and electron distribution in highest filled and lowest empty orbitals of (a) HRP-compound I and (b) a P-450 $[FeO]^{3+}$ analogue.

for metal-porphyrin systems.[16] Porphyrin and imidazole geometries were taken from the x-ray structure of a model dioxygen ferrous heme complex.[17] The iron atom was left in the plane of the porphyrin ring and the bound oxygen atom kept at a distance of 1.75 Å. The complex has a net charge of +1 for a formal $[FeO]^{3+}$ odd electron system.

The electron distributions in the five highest filled and the lowest empty molecular orbitals calculated for a $S = \frac{1}{2}$ ground state are shown in Figure 3a. One unpaired electron is in an a_{2u} π type orbital centered on the pyrrole nitrogens and meso carbon atoms and the other two unpaired electrons are in two higher energy, nearly degenerate and extremely delocalized ($d_\pi + O_\pi$) orbitals. The spin distribution corresponds very closely to the porphyrin π cation complex (Fe(IV) $S = 1$, porphyrin $S = \frac{1}{2}$) predicted from the electronic spectra except with a large iron-oxygen covalency which gives substantial unpaired electron density to the oxygen atom as well.

The nine components of the electric field gradient at the iron nucleus were calculated for this configuration by methods described elsewhere[18] and yielded a quadrupole splitting (Table I) of $\Delta E_Q = 1.67$ mm/s, $\eta = 0.08$, in good agreement with experiment ($\Delta E_Q = 1.20$ mm/s). By contrast, a low spin $S = \frac{1}{2}$ configuration gave a much higher value of $\Delta E_Q = 2.67$ mm/s.

Reduction of compound I results in a secondary complex (compound II) with an $S = 1$ ground state[7,10] and a quadrupole splitting similar to compound I. The orbital diagram shown in Figure 3 indicates that the extra electron would be added to the lowest-lying half-filled a_{2u} porphyrin π orbital. Therefore, the electronic environment of the iron in compound II would be basically unchanged from that of compound I. A calculated value of $\Delta E_Q = 1.75$ mm/s, $\eta = 0.08$, verifies the similarity observed in the Mössbauer spectra of compounds I and II. The large covalent effects in the ($d_\pi + O_\pi$) interaction would also remain unaffected upon reduction, consistent with the observed isomer shifts for compound I and II which were previously cited as evidence of highly covalent Fe(IV) complexes.[9] Thus, the calculations on the model for compounds I and II appear to have produced an electronic structure consistent with known electromagnetic properties which supports the (Fe(IV) $S = 1$, porphyrin π cation radical) complex as the most plausible of previously suggested structures for compound I.

Using similar methods, an active state model for cytochrome P-450 analogous to compound I was constructed as shown in Figure 2 by replacing the imidazole ligand with methyl mercaptide. While there is some controversy about whether the axial ligand thought to be retained in all stages of the substrate bound enzyme is a mercaptide[19,20] or a mercaptan,[21] the latest evidence points to the former. In a more extensive investigation the effect of a mercaptan as an axial ligand will be explored. The geometry of the mercaptide ligand was taken from the crystal structure of a high spin ferric P-450 model compound.[22] As shown in Figure 3b, a calculated electronic configuration very similar to that of compound I was obtained. In particular the three half-filled orbitals have the same character: an a_{2u} pyrrole nitrogen π orbital and two higher energy, nearly degenerate, delocalized ($d_\pi + O_\pi$) orbitals. Quadrupole splittings calculated for the P-450 analogues of compounds I and II were found to be very similar (Table I). Again, little difference was found between the oxidized and reduced forms of the analogues.

Figures 1 and 2 give the net atomic charges from a Mulliken population analysis of the eigenvectors of compound I and its P-450 analogue. The oxygen atom in both model compounds has a significant negative charge. Thus, if the model for the enzymatically active state of P-450 is correct, the observed electrophilicity of the oxygen atom is not due to a charge

controlled interaction with a nucleophilic substrate. Instead, the electrophilicity of the activated oxygen appears to be covalently controlled. Low energy orbitals which are not completely occupied and yet contain considerable electron density on the oxygen atom can serve as primary electron acceptors in covalent interaction leading to the transfer of the oxygen to a nucleophilic substrate. In previous studies, similar low-lying, oxygen containing orbitals were found to be present in chemical models of cytochrome P-450 such as peroxytrifluoroacetic acid[23] and chromyl chloride.[24] A unifying picture of the electronic nature of the electrophilic oxygen in these systems based on covalent rather than charge controlled substrate interaction thus appears to be emerging from these studies.

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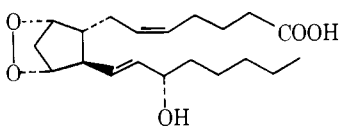
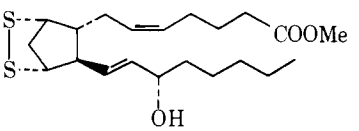
Simple Synthesis of Methyl (5*Z*,9α,11α,13*E*,15*S*)-9,11-Epidithio-15-hydroxyprosta-5,13-dienoate, Endodisulfide Analogue of PGH_2

Sir:

The outstanding biological activity of prostaglandins has stimulated numerous investigations of chemical modifications of the prostanoid structure.[1] Recently, there has been an active interest in the variations of the endoperoxide ring systems of PGG_2 and PGH_2 which possess an interesting spectrum of biological activity.[2] Because of their fairly short half-life in aqueous buffer, the design and synthesis of a stable and active analogue were deemed important.[3] The endodisulfide analogue of PGH_2, methyl (5*Z*,9α,11α,13*E*,15*S*)-9,11-epidithio-15-hydroxyprosta-5,13-dienoate (**1**), is of special interest, since a dithio linkage is more stable chemically than a peroxide unit and the molecular geometry of the rigid endodisulfide ring system approximates that of PGH_2. Herein we report a new and highly effective synthetic approach to **1** and also some biological effects of this readily accessible, stable PGH_2 analogue.

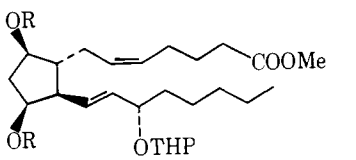


PGH_2

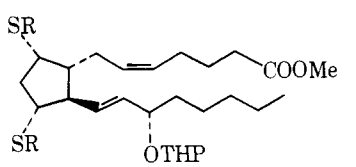


1

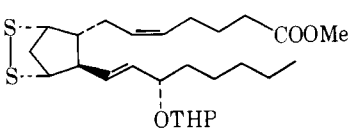
To construct the endodisulfide ring of structure **1**, we required a suitably stereochemically functionalized prostaglandin derivative. For this purpose, we chose dimesylate monotetrahydropyranyl ether **2**, which was obtained by reaction of 9β,11β-diol **3**[4] with mesyl chloride (2.2 equiv) and triethylamine (4 equiv) in methylene chloride at −20 °C for 1 h in 91% yield.[3b] Treatment of dimesylate **2** with excess sodium thioacetate in dimethyl sulfoxide-*N*,*N*-dimethylformamide (1:1) at 50 °C for 20 h afforded the dithio acetate, **4** (60% yield), which was saponified quantitatively with potassium carbonate in methanol at 25 °C for 30 min to provide 9α,11α-dimercapto



2, R = Mes
3, R = H



4, R = Ac
5, R = H



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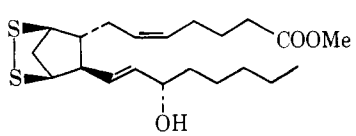

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