Elemental analysis, IR, ^{1}H NMR, Mössbauer and electronic spectroscopic studies as well as magnetic measurements were performed on these crystals.[12]

The molecular structure of **1** is shown in Figure 1. Features of the $\{Fe_2O(O_2CCH_3)_2\}^{2+}$ core geometry in **1** compare favorably with those in the $[Fe_2O(O_2CCH_3)_2(HBpz_3)_2]$ analogue (**2**), in which the terminal ligands are all nitrogen donors (Table I).[8a] Both compounds have distorted octahedral geometry around each iron atom and lengthened Fe–ligand bonds trans to the short Fe–O_{oxo} bridge. The Fe–O_{oxo} bond lengths fall within the known range for $\{Fe_2O(O_2CCH_3)_2\}^{2+}$ complexes. The terminal Fe–O bond lengths in **1** are significantly shorter than the analogous Fe–N distances in **2**. This result supports the geometric criterion previously used to assign oxygen donor terminal ligands in dinuclear iron-oxo proteins.[2] Slightly but significantly weaker antiferromagnetic coupling occurs between the two iron(III) centers in **1** compared to that in **2** (Table I). This difference is reflected in the ambient temperature solution magnetic moments for the two complexes. The observed reduction in the exchange coupling constant (J) for **1** versus **2** is in accord with expectations based upon an empirical correlation of J with molecular geometry parameters;[13] the slightly longer Fe–O bridge bonds lead to weaker magnetic coupling. The electronic spectrum of **1** differs from that of **2** mainly in the visible region, the respective low-energy bands occurring at 569 and 695 nm. This shift is attributed to the weaker ligand field strength of the triphosphite (O_3), compared to the tris(pyrazolyl)borate (N_3), tripod anions coordinated to the high spin iron(III) centers.

Resonance Raman studies of iron-oxo proteins and their model complexes have shown that excitation at or near the UV–vis absorption bands can afford large enhancements of the Fe–O–Fe symmetric stretch.[14] One exception is purple acid phosphatase in which the existence of a binuclear iron-oxo center implied by magnetic and Mössbauer measurements could not be confirmed by a resonance enhanced ν_s(Fe–O–Fe) band in the resonance Raman spectrum.[5] This failure was attributed to the lack of histidine-type unsaturated nitrogen donor ligands in positions trans to the oxo bridge.[5,15] The solution Raman spectrum of **1** reveals, however, that scattering due to the Fe–O–Fe symmetric stretch at 510 cm^{-1} is enhanced to approximately the same extent as in solutions of **2** at their respective enhancement maxima (Table I).[16]

Cyclic voltammograms of **1** in methylene chloride display a quasireversible reduction wave with $E_{p,c}$ = −0.55 V and $E_{p,a}$ = −0.25 V vs Ag/AgCl. The cathodic current of this wave is greatly increased by addition of protons, which presumably stabilize the reduced species. A second irreversible reduction wave appears at E_c = −0.8 V. The electrochemical behavior of **1** is thus significantly different from that of **2**, which decomposes to mononuclear $[Fe(HBpz_3)_2]^+$, under electrochemical conditions.[8a] No evidence was obtained for $[Fe\{CpCo[OP(OEt)_2]_3\}_2]^+$,[16] which has a reversible Fe^{II}/Fe^{III} couple at −0.8 V vs Ag/AgCl. Attempts to isolate and characterize the species obtained upon reduction of **1** are currently in progress.

Acknowledgment. This work was supported by U.S. Public Health Service Grant GM 32134 from the National Institute of General Medical Services. We are grateful to Drs. W. B. Tolman and J. G. Bentsen for helpful discussions, to Dr. G. Papaefthymiou for assistance with Mössbauer experiments, and to Dr. J. Sanders-Loehr for a preprint of ref 15.

Supplementary Material Available: Tables of atomic positional (including a model defining the disordered acetonitrile molecules listed in the table) and thermal parameters for **1**·2CH_3CN (5 pages). Ordering information is given on any current masthead page.

(12) Anal. ($C_{38}H_{76}P_6O_{23}Co_2Fe_2$) C, H, P, Fe; IR (KBr, cm^{-1}) 2978, 2929, 2905, 2860, 1578, 1425, 1389, 1162, 1123, 1096, 1076, 1036, 933, 832, 761, 729, 592; ^{1}H NMR (250 MHz, 297 K, $CDCl_3$) δ 10.0 (CH_3, acetate), 5.10 (C_5H_5), 4.08 (CH_2), 1.26 (CH_3) ppm.

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(15) Sanders-Loehr, J.; Wheeler, W. D.; Shiemke, A. K.; Averill, B. A.; Loehr, T. M. *J. Am. Chem. Soc.* **1989**, in press.

(16) The Raman spectra of a 0.043 M CH_2Cl_2 solution of **1** exhibited a 510-cm^{-1} band (overtone, 1020 cm^{-1}) assigned as ν_s (Fe–O–Fe) that shifted to 496 cm^{-1} upon ^{18}O substitution into the oxo bridge. A methylene chloride solution of **2** at the same concentration was studied for comparison. Laser lines with wavelengths of 350.7, 356.4, 406.7, 413.1, 457.9, 488.0, and 514.5 nm were employed. Relative Raman scattering intensities were calculated as the ratio of the molar scattering intensities (peak height/concentration) of the ν_s (Fe–O–Fe) at 510 cm^{-1} to the molar scattering intensities of the methylene chloride peak at 704 cm^{-1}. The maximum enhancement was observed at 356.4 nm for **1** and at 406.7 nm for **2**, with the maximum relative Raman scattering intensity for **1** being 1.05 that of **2**.

(17) The mononuclear complex $[Fe\{[OP(OEt)_2]_3Co(C_5H_5)\}_2]BF_4$ was synthesized by a procedure analogous to that previously reported for $[Fe\{[OP(OEt)_2]_3Co(C_5H_5)\}_2]PF_6$: Kläui, W.; Eberspach, W.; Schwarz, R. *J. Organomet. Chem.* **1983**, *252*, 347.

A Model Study on Aromatase Cytochrome P-450 Reaction: Transformation of Androstene-3,17,19-trione to 10β-Hydroxyestr-4-ene-3,17-dione

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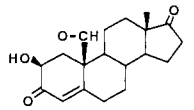
The metabolic transformation of androgens (**1**) to estrogens (**2**) by placental aromatase cytochrome P-450 (P-450*arom*) is known to consist of three consecutive oxidations, each of which requires 1 mol of O_2 and 1 mol of NADPH[1] (Scheme I). The conversion of a formyl cyclohexenone moiety of the 19-aldehyde intermediates (**4**) to the phenol derivatives, the last step in aromatization, is unique in many reactions catalyzed by cytochrome P-450.[2] Among mechanisms proposed for the aromatization reaction, an involvement of 2β-hydroxylation of **4** has received attention as an attractive mechanism.[2c] Fishman and his coworkers showed that nonenzymatic aromatization of 2β-hydroxy-4-androstene-3,17,19-trione (**5**) proceeded with stereo-



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specific 1β hydrogen elimination identical with that in estrogen biosynthesis.[3] However, Caspi et al. showed no incorporation of the oxygen atom of the 2β-hydroxyl of **5** into formic acid in the aromatization reaction.[4] The intermediacy of **5** appears also less favor in view of the following considerations.

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(4) Caspi, E.; Wicha, J.; Arunachalam, T.; Nelson, P.; Spiteller, G. *J. Am. Chem. Soc.* **1984**, *106*, 7282–7283.

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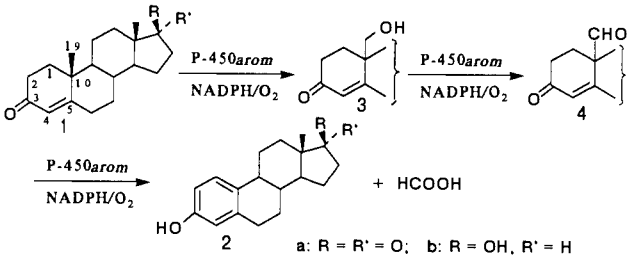
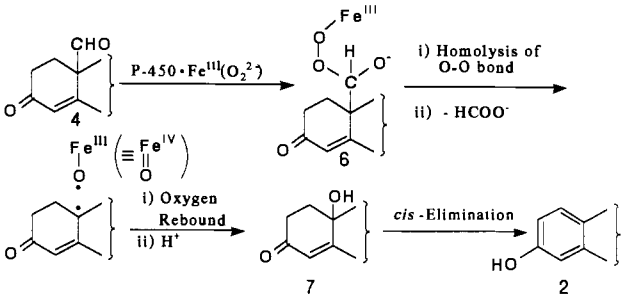
Scheme I



Scheme II



The remarkable reactivity of cytochrome P-450 is believed to derive from an oxoferryl porphyrin cation radical species, so called oxenoid, equivalent to compound I of peroxidases.[2c,5] If **5** is the intermediate responsible for the aromatization in the enzymatic system, the C-2 position of **4** must be more reactive than the C-19 oxo group. However, oxidation of aldehydes to carboxylic acids by the oxenoid intermediate seems more likely over hydroxylation of alkanes. Furthermore, the two successive and stereospecific oxidations at the C-19 position of **1** by P-450*arom*[6] suggest that the C-19 oxo group of **4** could be close to the active center in the substrate-enzyme complex. Thus, we have recently suggested a different mechanism, i.e., the intermediacy of 10β-hydroxyestr-4-ene-3,17-dione (**7**) in the conversion of **4** to **2**.[7] The same intermediate, **7** was also suggested for an intermediate in the aromatization reaction of 19-norandrogens by a reconstituted system with purified human placental P-450*arom*.[7]

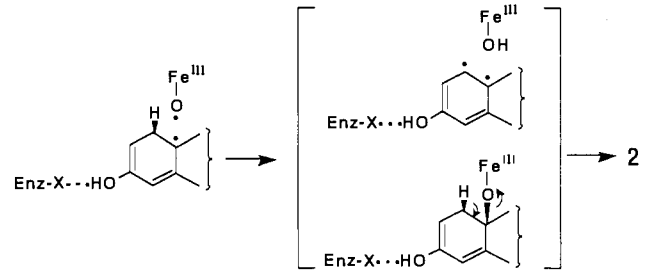
The proposed mechanism is initiated by the reaction of **4** with the peroxo-iron(III) intermediate [$Fe^{III}(O_2^{2-})$] of cytochrome P-450 instead of the oxenoid species. A homolytic O–O bond cleavage reaction of **6** and the release of formate, likewise the decarboxylations of acyloxyl radicals and ester anion radicals,[8] give the C-10 radical intermediate. Then, the oxygen bound to the heme-iron is captured by the radical to yield **7** (Scheme II). Stereospecific cis dehydration and enolization can finally produce **2**.[9] An alternative aromatization process of **6** either by a hydride transfer or proton shift of the C-1 hydrogen was considered by Akhtar et al.[10a,b] and Cole and Robinson.[10c,d] A possible heterolytic

Table I. The Reaction of 4-Androstene-3,17,19-trione with Peroxo-iron(III) Complex

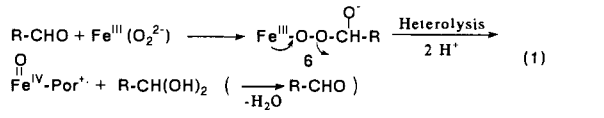
	products[a] (%)		
$Fe^{III}(O_2^{2-})$:18-crown-6	**7**	**9**	**2**
1:0.92	85	14	<5
1:1.80	53	88	trace
0:1.00	0	15[b]	+ unknown products

[a] Yields were determined by GLC and calculated based on FePFP used. [b] Yield was calculated based on 18-crown-6 employed.

Scheme III



O–O bond scission of **6**[11] was ruled out in the mechanism shown in Scheme II since it regenerates **4**-equivalent and the oxenoid species (eq 1).



Here we describe the reactions of **4** with model complexes of both the oxenoid species and the peroxo-iron(III) intermediate in the oxygen activation reaction by cytochrome P-450. Synthesis of model complexes of the peroxo-iron(III) intermediate of cytochrome P-450 has been reported by Valentine et al.[12] Further, the oxoferryl porphyrin cation radical complexes [$Fe^{IV}(=O)Por^{\bullet+}$] have been prepared and characterized in the reaction of synthetic iron(III) porphyrin complexes and peracids at low temperature by Groves and co-workers.[11a,c,13]

Reaction of 4 and Peroxoiron(III) Porphyrin Complex. An acetonitrile solution (5 mL) of 5,10,15,20-[tetrakis(pentafluorophenyl)porphyrinato]iron(III) chloride [Fe^{III}PFP(Cl)] (10.6 mg, 10 μmol) containing a large excess amount of KO_2 powder was stirred in the presence of 18-crown-6 (2.6 mg, 9.8 μmol) at room temperature under dry nitrogen atmosphere for several hours. After confirming the formation of $Fe^{III}PFP(O_2^{2-})$ (**8**) with UV–vis spectroscopy,[14] the reaction mixture was centrifuged (2000 rpm) for 20 min to remove unreacted KO_2 powder. Then, **4** was added to the supernatant, and the mixture was stirred at room temperature for 72 h. The products were analyzed by GLC and Al_2O_3–TLC, and **7** was identified as the major product with concomitant formation of 19-norandrostenedione (**9**) (Table I). Independent synthesis of **7** was also carried out in the reaction of estr-5(10)-ene-3,17-dione and mCPBA.[15] Similar hydroxide

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(14) $[Fe^{III}PFP(O_2)]^-K^+$: λ_{max} (CH_3CN) 445 (soret), 555, 586 nm; see ref 7.

Table II. Oxidation of Aldehydes with Oxoferryl Porphyrin Cation Radical

substrate	product(s)[a]	%
4	**10** (as methyl ester)	92[b]
$PhCH_2CHO$	$PhCH_2COOH$	88
$Ph(CH_3)CHCH_2CHO$	$Ph(CH_3)CHCH_2COOH$	87
$Ph(CH_3)_2CHO$	$Ph(CH_3)_2COOH$	92

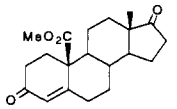
[a] Yields were determined by ^1H NMR and GLC as free acids. [b] Yield was determined as methyl ester by GLC.

formation after the decarboxylation of acylperoxo metalloporphyrins has been observed in the consequence of the homolytic O-O bond cleavage reactions.[11b,c,16] Increased formation of **9** and unknown products either upon the use of an excess amount of 18-crown-6 or in the reaction without $Fe^{III}PFP(Cl)$ might be caused by iron porphyrin-free superoxide ion and/or its decomposed products.[17]

While treatment of **7** with 4-N HCl (aqueous) readily gave an aromatized product, **2**, the enzyme system directly affords **2** at physiological pH.[18] Therefore, if the peroxo intermediate is responsible for the aromatization, the activation of the C-1 hydrogen of **4** by such as enolization due to the hydrogen bond interaction with the active site of the enzyme[7,19] could be involved during the course of oxygen rebound process as shown in Scheme III. A possible participation of the enolate of **4** in the aromatization reaction has been reported.[7,10d]

Then, we carried out the reaction of **4** and a model system of the oxenoid species of P-450*arom* to compare the reactivity of the C-2 hydrogens to that of the C-19 oxo group.

Oxidation of 4 with Oxoferryl Porphyrin Cation Radical. To a methylene chloride solution (3 mL) of **4** (23 mg, 73 μmol) and $Fe^{III}PFP(Cl)$ (2 mg, 1.9 μmol) was added 15 mg of mCPBA (87 μmol) at −78 °C and stirred for 20 min. After confirming the disappearance of **4** on Al_2O_3-TLC, an excess amount of diazomethane was added at 0 °C. Methyl *m*-chlorobenzoate and the oxidation product were separated by column chromatography (Al_2O_3), and the structure of the product was identified to be 4-androsten-19-oic-3,17-dione methyl ester (**10**) by ^1H NMR, IR,



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and mass spectra.[20] No formation of the acid was observed when $Fe^{III}PFP(Cl)$ was absent. Further, oxidation of several alkyl aldehydes, which possess reactive positions for the hydroxylation,[7,21] was examined with the same system by employing 1.1-1.2 equiv of mCPBA. As shown in Table II, the corresponding carboxylic acids were obtained as the sole products. Thus, if the oxenoid species was involved in the final step of the aromatase reaction, the corresponding carboxylic acid (or possibly **9** due to facile decarboxylation) either with or without **5** should be observed. In fact, Suhara et al. have recently reported that when **4** was oxidized by purified adrenal cortex mitochondrial P-45011β,[22] a concurrent formation of **2** and **9** was observed.

While the oxenoid species has been generally considered to be responsible for oxidations catalyzed by cytochrome P-450,[2a,b,5] the results shown above indicate a possible participation of the peroxo-iron(III) intermediate instead of the oxenoid species, if the substrate contains an electrophilic site. Reactions of the peroxo complex of synthetic metalloporphyrins and electrophiles such as acyl halides and CO_2 have been reported to afford the corresponding adducts,[23] consistent with these considerations.

Detection of **7** in the enzymatic oxidation of **4** with purified cytochrome P-450*arom* is now under investigation in this laboratory.

Acknowledgment. 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 (Y.I.) and by grants from Keio University (Y.I. and Y.W.).

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(18) At physiological pH (0.2 M phosphate buffer, pH = 7.2), **7** was not converted to **2**.

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(20) **10**: IR (KBr) 1740, 1730 (sh), 1675 cm^{-1}; mass spectrum, *m/e* 331 (M + 1, 23.7), 330 (M^+, 100), 271 (46.9), 270 (70.4), 253 (38.7); HRMS for $C_{20}H_{26}O_4$ requires 330.1819, found 330.1811; ^1H NMR ($CDCl_3$) δ 5.91 (s, 1 H), 3.76 (s, 3 H, $-CO_2Me$; ^{13}C ($CDCl_3$) δ 220.14 (C-17), 198.73 (C-3), 177.19 (C-19), 162.06 (C-5), 126.85 (C-4), 53.80, 52.16, 50.92 (O-Me), 50.88, 47.5, 35.73, 35.62, 34.94, 33.85, 32.59, 31.38, 30.10, 21.95, 21.66, 13.79.

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Facile Arene C-H Bond Activation by Tantalum Silyl Complexes

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In 1970 Barefield, Parshall, and Tebbe demonstrated the exchange of hydrogen and deuterium between benzene and the hydride ligands on Cp_2TaH_3 (Cp ≡ η^5-C_5H_5).[1] Although a tantalum phenyl complex could not be isolated, this was one of the earliest indications of intermolecular arene C-H activation by a transition-metal complex.[2] Over the past two decades many research groups have investigated the activation of both saturated and unsaturated hydrocarbons by a wide variety of metal complexes.[3] Although several different mechanisms for C-H activation have been identified, the most common pathway, oxidative addition of a C-H bond to an unsaturated, electron-rich metal center, is still believed to proceed as originally postulated in 1970. In this report we show that the addition of benzene to an otherwise unreactive Ta(III) alkyl complex can be catalyzed by di-*tert*-butylsilane and that an isolated silyl complex, $Cp_2Ta(PMe_3)(SiH(t\text{-}Bu)_2)$, will itself activate benzene under extremely mild conditions.

In the presence of 0.7-2.0 equiv of di-*tert*-butylsilane, the 18 e^-, Ta(III) alkyl complex $Cp_2Ta(CH_3)(PMe_3)$ (**1**) reacts with

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(2) The first example of homogeneous intermolecular arene C-H activation by a transition-metal complex was observed by Chatt and Davidson in 1965: Chatt, J., Davidson, J. M. *J. Chem. Soc.* **1965**, 843-855.

(3) For recent reviews, see: (a) Green, M. L. H.; O'Hare, D. *Pure Appl. Chem.* **1985**, *57*, 1897. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (c) Deem, M. L. *Coord. Chem. Rev.* **1986**, *74*, 101. (d) Bergman, R. G. *Science* **1984**, *223*, 902-908. (e) Jones, W. D.; Feher, F. J. *Acc. Chem. Res.* **1989**, *22*, 91-100.

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