

On the Mechanism of the Oxidation of Toluenes in Artificial P450 Model Systems: Formation of Benzyl Alcohols, Benzaldehydes, and Phenols[1]

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Systems with pentafluoroiodosylbenzene (PFIB) and hemin ($FeTPPCl_8Cl$) in dichloromethane were adopted to study the activities of the model system using toluenes as substrates for P450 enzymes. The oxidation products were mainly corresponding benzyl alcohols and benzaldehydes. Previously reported suspension systems were extended to homogeneous mixed solution systems of $CH_2Cl_2/CH_3OH/H_2O$ to study the oxidation of benzyl alcohols to the corresponding benzaldehydes: the Hammett relation with $\rho = -0.86$ against σ^+. As benzaldehydes were scarcely observed in natural P450 systems, the formation of benzaldehyde seemed characteristic only of the "open" model systems. In suspension systems, the product ratios between corresponding benzaldehydes and benzyl alcohols (ald/alc) were about 0.1–0.4, specific to the substituents and conditions applied. Curiously, the ratios (ald/alc) increased with the electronegativity of the substituents on the phenyl rings of the toluene derivatives. Time course experiments in suspension systems indicated that benzyl alcohols and benzaldehydes were formed not stepwise, but simultaneously from toluene. Separate experiments indicated that the reaction of benzyl alcohol to benzaldehyde was four-fold faster than that of toluene to benzyl alcohol. The rate was not enough to elucidate the amount of benzaldehyde. We suggest that the benzyl radical is formed by hydrogen abstraction and is attacked by the second oxidant, PFIB. Rebounding of the hydroxyl radical and the reaction with the oxidant were competitive depending on the conditions. Additionally, small amounts of phenols were formed from toluenes with electron-donating substituents. This was a minor reaction on which the aromatic hydroxylation occurred via epoxidation under the present conditions.

Cytochrome P450 is a family of enzymes which catalyze the oxidation of physiological substrates, including foreign chemicals.[2–4] The mechanistic studies of P450 using artificial model systems have successfully explained[5,6] the nature of the heme protein enzymes.[7,8] The difference between natural and model systems still remains unknown in understanding of the enzymatic mechanism and the chemistry of hemin.[9–12] The distribution of products is the reflection of the structure and the behavior of the active center.[13,14] The multi-character of the intermediate of the P450 model was demonstrated in the case of epoxidation of olefins.[15,16]

Toluenes are reactive and useful for systematic studies[17] and there exist a lot of data in vivo.[18–20] Products in natural systems are benzyl alcohols and a small amount of phenols or cresols (Fig. 1(a)).[21–23] The former group is the result of hydroxylation at the benzylic position, and the latter group is produced by hydroxylation on the aromatic ring.[24] Benzaldehydes are scarcely reported in natural systems,[25,26] while benzoic acid is found in a few cases.[27] There is no report of finding bibenzyl derivatives. On the other hand, in the model systems so far reported, products include benzyl alcohols and benzaldehydes, and no benzoic acid is reported. Similarly, in cases of *n*-alkanes and cyclohexane, no aldehydes, ketones, nor cyclohexanone were reported in natural systems. These were, however, produced, along with the corresponding alcohols, in models.[28,29]

Previously, we examined the product formation rates for benzyl alcohols and benzaldehydes to estimate the reactivity of toluenes.[17] The reaction proceeded having a Hammett relation with $\rho = -1.5$ against σ. Our results supported the hydroxylation mechanism initiated by the hydrogen abstraction and followed by the rebounding of the hydroxyl radical ($\bullet$OH) as shown in Fig. 1(b).[30] The assumption was that benzyl alcohols initially produced were further oxidized to corresponding benzaldehydes (Fig. 1(c)), where k_1 and k_2 were rate constants from toluene to benzyl alcohol and from benzyl alcohol to benzaldehyde, respectively. No benzoic acids were found in the system, indicating no further oxidation of benzaldehyde. The product ratios of benzaldehydes to the corresponding benzyl alcohols were about 0.1–0.4.

It had been assumed that additional benzaldehydes were formed by the faster consecutive oxidation of the resulting benzyl alcohols. However, curiosity remained in these observations as shown in Fig. 2.[17] More benzaldehyde was formed than previously expected, and product ratios (benzaldehyde/benzyl alcohol) were larger with substrates having more electronegative substituents, while total yields were lower.

If these reactions occurred consecutively, two conditions must be satisfied to elucidate the feature; 1) benzaldehyde formation from benzyl alcohol derivatives with electronegative groups is faster than those with electron-donating groups, and 2) benzyl alcohol oxidation is much faster than toluene hydroxylation. We report here whether the two oxidations,

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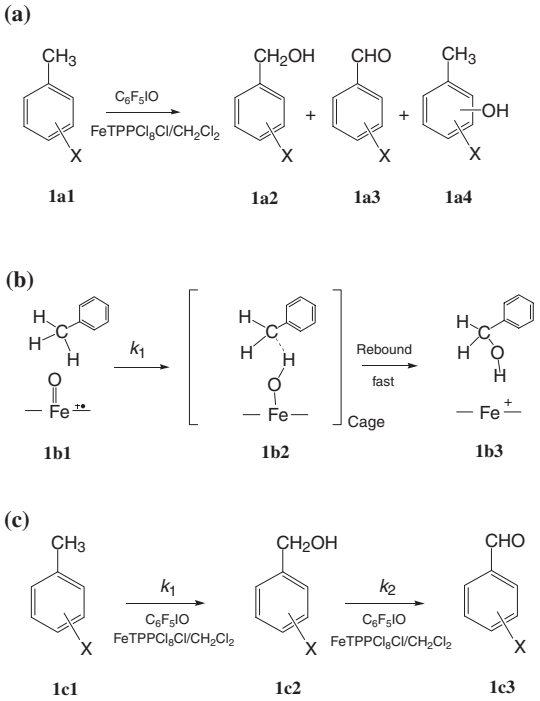

Fig. 1. Reaction of toluenes in P450 model system with $FeTPPCl_8Cl/PFIB/CH_2Cl_2$. (**a**) Product distribution. (**b**) Hydroxylation mechanism. (**c**) Previously proposed stepwise formation of benzaldehydes.

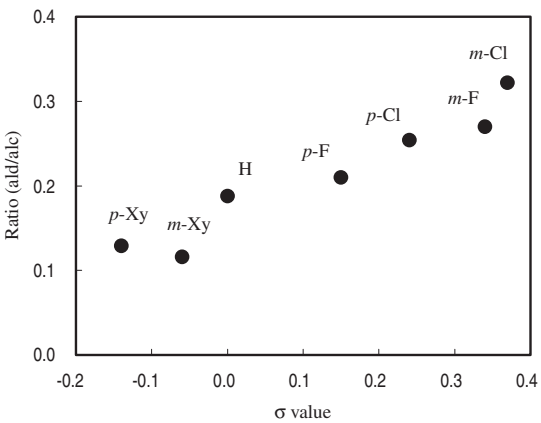

Fig. 2. Plotting of the product ratio (ald/alc) against σ value in suspension systems. The final concentrations of catalyst and oxidant were arranged to be 1.0 and 64 mmol/dm^3. There is no direct thermodynamic relation in the figure.

the formation of benzyl alcohol and benzaldehyde, occurs simultaneously or in steps, and propose a reaction mechanism in "open" (without surroundings but solvent) model systems.

It should be noted that the oxidation by PFIB was considered to occur quickly close to the surface of a solid before each oxidant species migrated away. The possible dependence of the rate on the surface structure of solidified PFIB could not be ruled out at this stage.

In the case of the benzyl alcohol oxidation, we needed to employ homogeneous solution systems containing methanol and water which dissolved PFIB in the form of adduct, MeO(HO)-IC_6F_5.[31] Methanol prohibited the formation of a similar adduct with benzyl alcohol, which disturbed to react with the catalyst, and which resulted in the formation of benzaldehyde when heated on the GLC machine. The homogeneous solution system had been introduced previously in olefin epoxidations.[32,33]

Experimental

Materials. Tetrakis(2,6-dichlorophenyl)porphinatoiron(Ⅲ) chloride ($FeTPPCl_8Cl$) and pentafluoroiodosylbenzene (PFIB) were prepared as reported before.[17] Toluenes were purified by passing through small SiO_2 columns just before use. In case substrates were solid, they were dissolved in dichloromethane and passed through the columns. Other chemicals were reagent grade.

Apparatus. For recording spectra, a JASCO V-530 Spectrometer and a Hitachi 220A Spectrometer were used. Products were measured using a Shimadzu GC-12A Gas Chromatograph: DB-WAX (J&W Scientific), 0.25 μm (width), 0.25 mm (i.d.) × 30 m (length).

Oxidation of Toluenes in Suspension Systems with PFIB.[34] For typical runs, 2 mg of PFIB (final concentration: 64 mmol/dm^3) was placed in a small glass tube (6 mm (i.d.) × 5 mm (length)) with a silicone rubber septum and a calculated amount of dichloromethane was injected. After injecting an appropriate amount of substrate, a calculated volume of hemin solution (CH_2Cl_2) was injected to get the reaction started. The final concentrations of the catalyst and the substrate were arranged to be 1.0 mmol/dm^3 and 2.0 mol/dm^3, respectively. The total volume of the solution was fixed at 0.1 cm^3. The reaction mixture was shaken vigorously until the solution became clear at room temperature (25 °C) and then cooled in ice water to stop further reactions. Products were determined by GLC using the resulting pentafluoroiodobenzene as an internal standard. The calibration of detection in GLC was done using authentic samples.

Oxidations of Benzyl Alcohols in Homogeneous Solution Systems.[34] For checking the oxidation of benzyl alcohol, a homogeneous system was needed. A solution containing methanol and water was used as a solvent ($CH_2Cl_2/CH_3OH/H_2O = 80/18/2$). Methanol formed an adduct with PFIB prior to benzyl alcohol. GLC checking resulted in the negligible formation of benzaldehyde without the catalyst. The other reaction conditions were similar to the suspension systems. The partially formed possible adduct was killed by adding sodium dithionite before GLC detection.

Oxidation of Toluenes in Homogeneous Solution Systems with PFIB. To compare the reactivity of toluenes and benzyl alcohols, the reaction was necessarily carried out in mixed solution systems ($CH_2Cl_2/CH_3OH/H_2O = 80/18/2$). After shaking (or stirring) the reaction mixture for 3 min, 2 mg of sodium dithionite and 0.2 cm^3 of water were added and the mixture was shaken again. The reaction mixture was centrifuged and cooled in ice water. Products in the organic layer were measured by GLC.

Competitive Reactions in Homogeneous Solution Systems. The competitive reactions using two kinds of benzyl alcohol were performed under the similar conditions in order to obtain the ratio, k_X/k_H, where k_X and k_H are rate constants, with X and H standing for substituted and unsubstituted benzyl alcohols. Absolute values of ks were not estimated at this stage, but ratios of them were obtained. The total concentration of the substrates was set at 2.0 mol/dm^3. The substrates were chosen to avoid overlapping of retention times. The competitive reactions between toluenes and benzyl alcohols were also performed in homogeneous systems.

Time Course of the Oxidation in Suspension Systems. Four

mg of PFIB was placed at the bottom of a glass tube (6 mm (i.d.) × 45 mm (length)) with a silicon rubber stopper. Into this tube a calculated amount of dichloromethane and toluene derivative were injected. Then, a catalyst solution (final concentration: 1.0 mmol/dm^3) was injected, and the mixture was shaken vigorously. The total volume was 0.2 cm^3. At the time chosen, 4 mg of sodium dithionite was added after taking off the stopper. Then, 0.1 cm^3 of water was injected, and the stopper was replaced immediately. The tube was shaken vigorously for 10–20 s, and centrifuged for 30 s. The reaction mixture was then ice-cooled to prevent further reaction. Products in the organic layer were determined by GLC. The reactions were repeated for each reaction time of 15, 30, 45, 60, 90, and 120 s.

Product Ratios (Ald/Alc) in Suspension Systems at Various Concentrations of Catalyst and Oxidant. Product ratios of benzaldehydes to corresponding benzyl alcohols were similarly measured in suspension systems at various amounts of the catalyst and the oxidant. Substrates typically selected were toluene, *p*-xylene, and *p*-fluorotoluene. Concentrations were 2.0 mol/dm^3. Oxidations depending on catalyst with experimentally possible concentrations (0.25–1.0 mmol/dm^3) were performed at a constant concentration of the oxidant, PFIB (64 mmol/dm^3). The effects of PFIB (0.003–0.1 mol/dm^3) were examined with a constant concentration of catalyst, FeTPPCl$_8$Cl (1.0 mmol/dm^3).

Results

Reactions in Homogeneous Solution Systems. In Table 1, products in homogeneous solution systems with toluenes are listed. Benzyl alcohols and benzaldehydes were produced but with lower yields than in suspension systems. Phenols were not detected in homogeneous systems. The ratios of these products (ald/alc) depended on the σ values. The similarity of the results allowed us to consider the reaction mechanism to be treated totally in the suspension and the homogeneous systems.

As for the oxidation of benzyl alcohols, the relationship between the log of the relative reaction rate, $\log(k_X/k_H)$, and the σ^+ value is shown in Fig. 3. The linear Hammett plotting gave $\rho = -0.86$.

The Reaction from Benzyl Alcohol to Benzaldehyde Was Fourfold Faster Than That from Toluene to Benzyl Alcohol. The ratio of the reaction rates of toluene hydroxylation and benzyl alcohol oxidation was obtained from competitive reactions between *p*-xylene and toluene, and between *p*-xylene and benzyl alcohol in homogeneous solution systems. *p*-Xylene was used as a reference substrate. The results estimated from the product ratios indicated that the benzyl alcohol oxidation was only fourfold faster than the hydroxylation of toluene. However, if benzaldehyde was formed stepwise, as in Fig. 1(c), with $k_1/k_2 = 4.0$, the amount of formed benzyl alcohol at the initial stage was not enough to compete with the excess amount of toluene substrate to approve the stepwise process.

Table 1. Hydroxylation of Toluenes in Homogeneous Mixed Solution Systems[a)]

Substrate	Alcohol yield/%	Aldehyde yield/%
Toluene	1.94	0.43
p-Xylene	11.26	2.24
m-Xylene	4.38	1.02
p-Fluorotoluene	9.67	1.56
m-Fluorotoluene	1.57	0.46
p-Chlorotoluene	8.67	2.03
m-Chlorotoluene	1.67	0.52

a) Mixed solution: $CH_2Cl_2/CH_3OH/H_2O$(80/18/2). Concentration of oxidant, PFIB, was 64 mmol/dm^3 and that of catalyst, FeTPPCl$_8$Cl, was 1.0 mmol/dm^3. Yields were calculated on the added PFIB. Dithionite did not reduce the formed products under the present conditions.

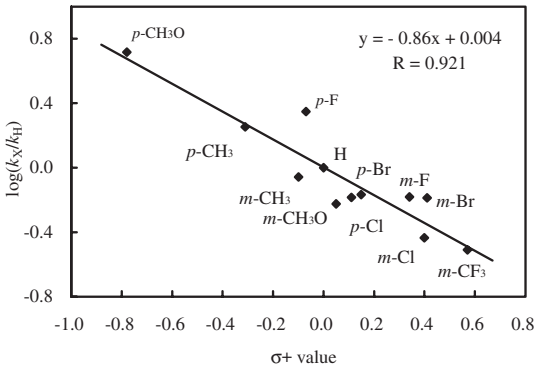

Fig. 3. Relative reaction rates in competitive reactions of benzyl alcohols vs σ^+ values. Oxidations were performed competitively in the homogeneous mixed solution systems ($CH_2Cl_2/CH_3OH/H_2O$). k_H and k_X stood for the rate constants for benzyl alcohol and substituted (X) benzyl alcohols. k_X/k_H were obtained based on product yields. Plotting against σ^+ resulted in better fitting than for σ. If plotted for σ, $\rho = -1.1$ and $R = 0.88$. PFIB did not react directly with benzyl alcohol to form benzaldehyde at room temperature. Possibly formed adducts of PFIB were decomposed by adding reductant before GLC measurements.

Time Course of Oxidation and Product Ratios. The benzaldehyde formation at the initial stage was confirmed through the time course reactions in suspension systems. Some of the results are shown in Figs. 5 and 6. There were some induction periods at early stages observed that were not elucidated at this stage. Nevertheless, in all cases, the formation of benzaldehyde was observed at the very beginning of the reaction, and the product ratios (ald/alc) did not change much from the beginning, as plotted in Fig. 7. The slight changes in the ratios might be caused by the consumption of oxidant, except in the case of *p*-xylene. It was indicated that the amount of benzaldehyde formed secondarily from the resulting benzyl alcohol was small when the amount of substrate was in excess. Again, stepwise reactions were not plausible.

Product Ratio (Ald/Alc) Depends on the Concentration of Oxidant, but not on That of the Catalyst. As the stepwise reactions were ruled out, the oxidant for the second oxidation must be assigned. The examinations with various concentrations of catalyst did not change the ratios (ald/alc) when the amount of oxidant was in excess (data not shown). On the other hand, the effects of PFIB (0.003–0.1 mol/dm^3) were clearly observed at the constant concentration of catalyst (1.0 mmol/dm^3), as shown in Fig. 8. As the amount of oxidant increased, the ratios (ald/alc) increased. The concentrations of oxidant were about 3–100 fold in excess to that of the catalyst. The conditions with a lower amount of oxidant were technically impossible at this stage. The dependence on PFIB was not simple.

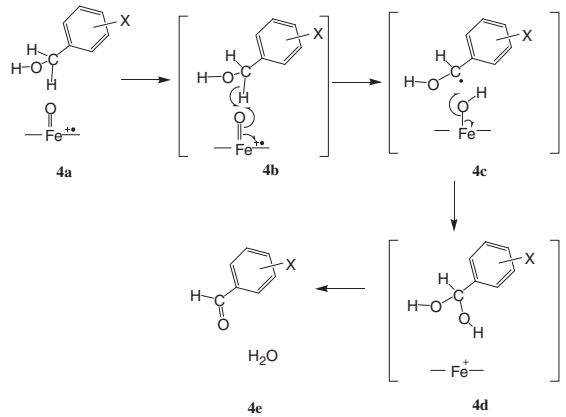

Fig. 4. Proposed mechanism for oxidation of benzyl alcohols in the homogeneous mixed-solution systems. The intermediate (Fe^{+}=O) was supposed to be same as in suspension systems. The step from **4c** to **4d** is the rebound of hydroxyl radical.

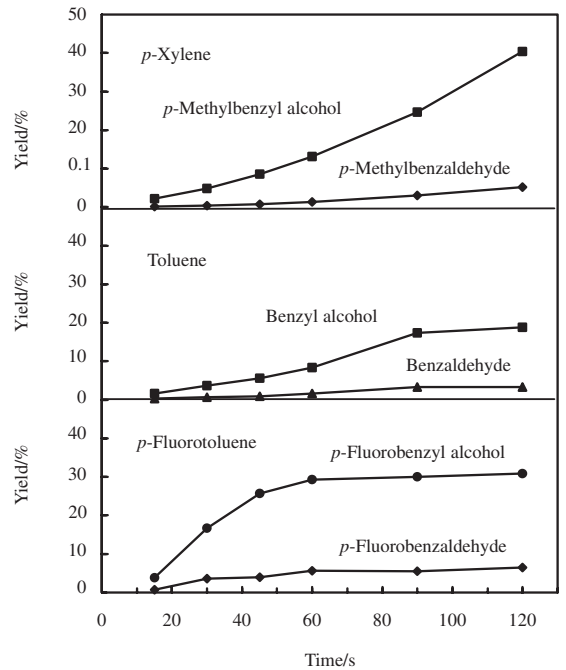

Fig. 5. Time courses of the oxidations of toluenes in suspension reaction system-1. Substrates were *p*-xylene, toluene, and *p*-fluorotoluene. Additions of reducing reagent, dithionite, at the time stopped further oxidations. The final concentrations of catalyst and oxidant were arranged to be 1.0 and 64 mmol/dm^3. Products were corresponding benzyl alcohols and benzaldehydes. There seemed some induction period in the reactions, though the reason was not clear at this stage.

In the case of *p*-fluorotoluene, as the oxidant concentration increased up to about 0.02 mol/dm^3, the aldehyde formation increased steeply, and then slowed down. In other cases, the amount of aldehyde increased slowly. There might be a steep increase under the conditions of less oxidant, in which case the ratio could be extrapolated to zero.

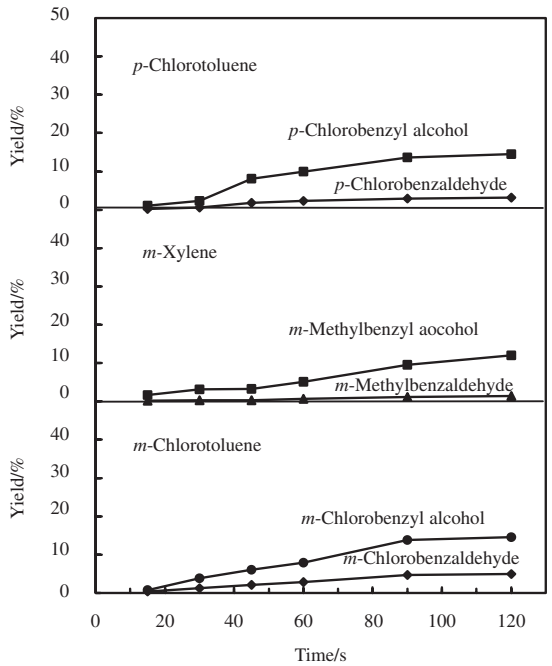

Fig. 6. Time courses of the oxidations of toluenes in suspension reaction system-2. Substrates were *p*-chlorotoluene, *m*-xylene, and *m*-chlorotoluene. Additions of reducing reagent, dithionite, at the time stopped further oxidations. The final concentrations of catalyst and oxidant were arranged to be 1.0 and 64 mmol/dm^3. Products were corresponding benzyl alcohols and benzaldehyde. There seemed some induction periods in the reactions, though the reason was not clear at this stage.

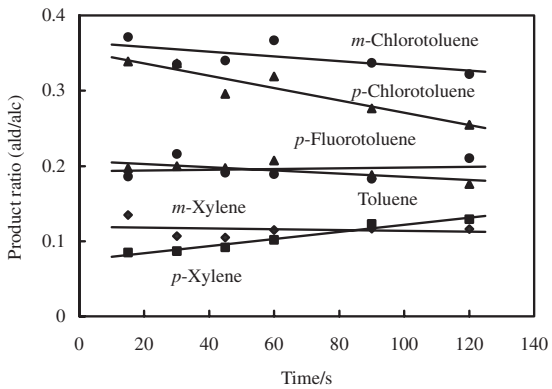

Fig. 7. Time course of product ratios (ald/alc) in oxidation of toluenes in suspension systems. Data were derived from those in Figs. 5 and 6. Product ratios indicated that benzaldehydes were formed even at the initial stages of the reactions.

Discussion

It is generally accepted that an oxoiron(Ⅳ) complex with a cation radical on the peripheral porphyrin ring is the active intermediate in actual P450 enzymes.[35–38] The system with iodosylbenzenes in dichloromethane could be considered to produce only a high-valent oxoiron(Ⅳ) intermediate, **9a**, which simplified the situation. The formation step of the oxoiron(Ⅳ)

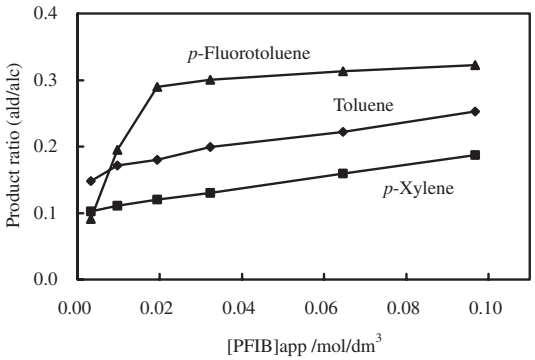

Fig. 8. Dependence of oxidant (PFIB) amount on product ratio (ald/alc). Catalyst was $FeTPPCl_8Cl$ (1.0 mmol/dm^3) in suspension systems. The complicated effect of the oxidant reflected the interactions between substrate and oxidant in this particular system. The effects of PFIB (0.003–0.1 mol/dm^3) were examined at the constant concentration of catalyst, $FeTPPCl_8Cl$ (1.0 mmol/dm^3).

Table 2. Oxidation of Benzyl Alcohols in Homogeneous Mixed Solution Systems

Substrate	Corresponding benzaldehyde/%
Benzyl alcohol	31.8
p-Methylbenzyl alcohol	35.2
m-Methylbenzyl alcohol	22.8
p-Fluorobenzyl alcohol	38.5
m-Fluorobenzyl alcohol	28.2
p-Chlorobenzyl alcohol	27.4
m-Chlorobenzyl alcohol	21.4
p-Bromobenzyl alcohol	26.2
m-Bromobenzyl alcohol	31.3
p-Methoxybenzyl alcohol	22.0
m-Methoxybenzyl alcohol	9.7

intermediate has been considered to be rate-determining, especially with substrates such as 2,4,6-tri-*t*-butylphenol and ABTS.[39,40] On the other hand, in the hydroxylation of toluene derivatives, the rates depended on the substrates to indicate that the steps between the active intermediate and substrates were rate-determining.[41,42] As experiments under nitrogen atmosphere did not affect product yields and distributions (data not shown), the participation of dioxygen was eliminated. Similar relations were reported in other cases in P450 models.[43]

The mechanistic similarity in the suspension and homogeneous systems was demonstrated in the data of the homogeneous systems shown in Table 1, though yields were lower. The oxidation of benzyl alcohol was checked in the homogeneous solution systems (Table 2). The results of the competitive reactions selecting sets of two benzyl alcohols are shown in Fig. 3. The trend in the reactions was quite similar to that in suspension systems. The Hammett plotting indicated again the hydrogen abstraction mechanism. Generally, dissociation energies of benzylic hydrogens were smaller than those of hydrogens in hydroxy groups.[44] So, we proposed that the reaction was initiated by the abstraction of hydrogen from the benzylic position, being followed by the quick rebounding of the hydroxyl radical to give acetals that turned to benzaldehyde and water (Fig. 4).[45]

It should be noted that both of the independent reactions of toluenes to benzyl alcohols and of benzyl alcohols to benzaldehydes had Hammett relations with a negative reaction factor, ρ. If this scheme actually occurred in the case of toluene oxidations, the consecutive formation of benzaldehyde should have simply indicated that the product ratios would have decreased in cases of more negative substrates. Apparently, this was not the case, as shown in Fig. 2. There should be an opposite factor in the formation of benzaldehyde.

The fact that aldehydes were formed at a very early stage of oxidation is shown in Fig. 7, derived from data in the time course experiments (Figs. 5 and 6). If the initial hydrogen abstraction from toluenes was true, the second oxidation must have occurred before the rebounding of the hydroxyl radical and should have been competitive or faster. The intermediate, **9b**, in Fig. 9 has been supposed to be within the solvent cage in which the hydroxyl radical rebounding occurred before liberation. If the "cage" was tight, only benzyl alcohols would be formed. However, if the cage was loose and/or hydroxyl radical rebounding was slow, the intermediate would have a chance to be attacked by the second PFIB. The partially negative-charged oxygen atom of PFIB (iodine is partially positively charged) nucleophilically attacked the benzyl radical, as schematically shown in Fig. 9. Remember that the oxygen atom of PFIB similarly attacked at the iron(Ⅲ) ion of hemin at the initial stage. On the other hand, it was reported that the high-valent oxoiron intermediate electrophilically attacked olefins.[16] As bibenzyl was not found, the secondary attack by PFIB was faster than the dimerization of the benzyl radical under the present conditions. Thus, it was suggested that benzaldehydes were made by the nucleophilic attack of PFIB on the benzyl radicals. The situation should have been reflected on the Hammett plotting with positive ρ values and an increase in the ratio (ald/alc). Though the detail of the rebounding process is not known, if electron-donating groups on the substrate caused the rebounding to occur faster and the electron-withdrawing groups made it slower, such that it was attacked easier by the second oxidant, the situation would be coincident with

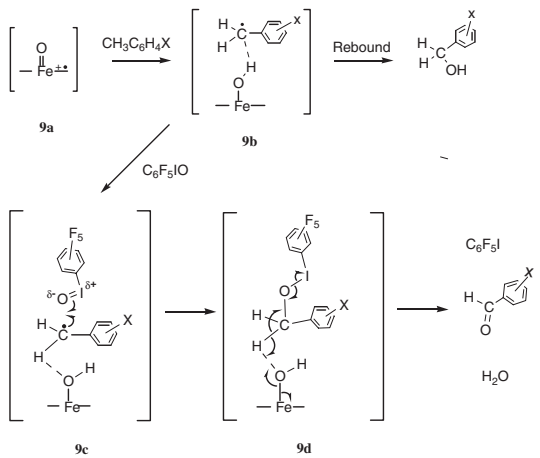

Fig. 9. Proposed mechanism of benzaldehyde formation. Second oxidant PFIB attacked at benzyl radical before rebound of hydroxyl radical. When the life-time of the intermediate is longer and/or the rebound process is slower, aldehyde formation will increase.

the experimental results.

While the rate-determining step is the initial hydrogen abstraction for the overall reaction, the steps to benzyl alcohol and benzaldehyde occurred competitively as faster processes after forming the intermediate, **9b**. Previously reported deuterium isotope effects altered the overall rates, but not the product distributions. The primary deuterium isotope effects on this hydroxylation were clearly observed to be 6.2 for toluene and 5.7 for cumene in the same suspension model systems.[17,46] On the other hand, the product ratio (ald/alc) in deuterated toluene was obtained to be 0.18, similar to the non-deuterated case of 0.15 in the suspension system, though the product yields of the deuterated substrate were only modest.[17] These facts supported that the deuterium transfer process was not involved in the benzaldehyde formation step.

Molecular orbital calculations about the rebounding mechanism were reexamined recently.[47–49] A hydrogen-abstraction followed by a rebounding mechanism in the oxidation of alkanes by permanganate was examined.[48] Only benzaldehyde but benzyl alcohol was formed. In the paper, the authors suggested that the rate-determining step was the hydrogen abstraction, and that an interaction existed between the benzylic carbon and the second oxygen of permanganate in the transition state.

Newcomb and co-workers reported their mechanistic studies for the hydroxylation of hydrocarbons, proposing a concerted mechanism.[50–52] Though we could not exclude the possibility of a concerted mechanism in some of natural enzyme systems, the present model system clearly supports the hydrogen abstraction and hydroxyl radical rebounding mechanism. If the concerted mechanism was involved, the benzaldehyde formed in the model system could not be rationalized unless a different mechanism coexisted.

Modest amount of phenols were observed in the suspension systems. The mechanism should be different from the hydroxylation at the benzylic positions. The hydrogen abstraction mechanism is not plausible, because it requires more energy. It was suggested from the data in Table 3 that an electrophilic attack on the phenyl rings formed unstable epoxides which became phenols. Though yields were small, it is true that under some restricted circumstances in actual heme proteins, phenols can be made.

Table 3. Arene Hydroxylation of Toluenes in Suspension Systems

Substrate	Product	Yield/%
Benzene	Phenol	0.96
Fluorobenzene	4-Fluorophenol	0.47
Toluene	*m*-Cresole	0.41
m-Xylene	2,4-Dimethylphenol	2.47
m-Fluorotoluene	4-Fluoro-2-methylphenol	1.28
p-Chlorotoluene	2-Chloro-5-methylphenol	2.28
1,3-Diethylbenzene	2,4-Diethylphenol	3.28
Mesitylene	2,4,6-Trimethylphenol	4.28
1,3-Di-*t*-butylbenzene	2,4-Di-*t*-butylphenol	5.28
1,3-Dimethoxybenzene	2,6-Dimethoxyphenol	6.28

Conclusions

The overall mechanism of the hydroxylation of toluenes in the "open" model system is summarized in Fig. 10. The main route is the hydroxylation at the benzylic position. The mechanism is a hydrogen abstraction by an oxoiron(Ⅳ) intermediate, and a rebounding of the hydroxyl radical. The sub route 1, which is only observed in "open" model systems, allows the attack by the second oxidant on the benzyl radical to form benzaldehyde before the rebounding occurs. The first hydrogen abstraction is rate determining and the consecutive steps are faster. It is suggested the rebounding of the hydroxyl radical and the attack by the second oxidant are competitive, causing the distribution of products. The ratio of the rates depends on the electronic effect of the substituents on the ring. Exper-

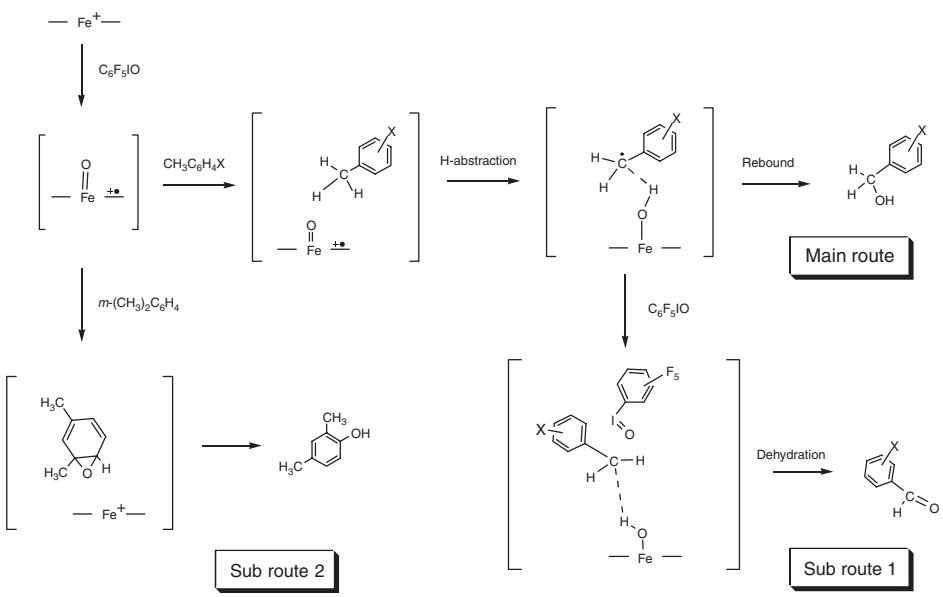

Fig. 10. Overall mechanism of toluene oxidations in "open" model systems. Main route is the ordinary hydroxylation. Sub route 1 is the process resulting in benzaldehyde formation. Additional sub route 2 forming phenols is competitive with other routes.

imental results suggest that electron-donating groups on the substrate cause the hydroxylation and the rebounding to proceed faster, and that electron-withdrawing groups get the situation reverse to make rebounding slower to be easily attacked by the second oxidant. It is reasonable that in natural systems benzaldehyde is not observed if the structure of the protein pocket does not allow the second process during the oxidation. Aromatic hydroxylation occurs through an epoxide, as shown in the sub route 2. Totally, the benzylic and the aromatic hydroxylations are competitive depending on the environment. Previous assumptions made to estimate the kinetics to be $k_X/k_0 = ([alc]_x + [ald]_x)/([alc]_0 + [ald]_0)$ is now verified under the following conditions: $k \ll k_{alc}$ and k_{ald}, where k_{alc} and k_{ald} are competitive. A still unsolved question in the PFIB system is the whereabouts of "oxygen", without reacting with substrates and destroying catalysts. The answer might be dioxygen made through the reaction of the intermediate oxoiron compound with PFIB.

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1 Abbreviations: $FeTPPCl_8Cl$; 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphinatoiron(Ⅲ) chloride, PFIB; pentafluoroiodosylbenzene, ABTS; 2,2′-azinobis(3-ethyl-2,3-dihydrobenzothiazole-6-sulfonic acid).

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