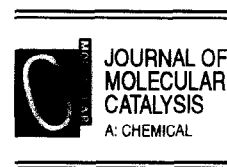




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Hydroxylation of cyclohexane catalyzed by iron(III)–metal-free porphyrin dimer with molecular oxygen: The effect of the steric hindrance and the intramolecular interaction between the two porphyrin rings

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Abstract

Three iron(III)–metal-free porphyrin dimers linked covalently with a flexible butoxy chain at the *para* position of the two phenyl rings have been prepared and characterized. The hydroxylation of cyclohexane catalyzed by these dimers with molecular oxygen under mild condition has been studied preliminarily. The results indicate that the dimers have higher catalytic activity than the corresponding mono-porphyrinatoiron(III), which is related to the steric hindrance caused by the closed conformation of the dimers and the intramolecular interaction between two porphyrin rings.

Keywords: Model of cytochrome P450; Iron(III)–metal-free porphyrin dimer; Hydroxylation; Cyclohexane

1. Introduction

It is well known that a hydrophobic environment produced by a protein chain folded about the binding site of cytochrome P450 play an important part in the process of the hydroxylation of substrate. The lack of the feature of this hydrophobic environment may be one of the reasons that the model of cytochrome P450 has a limited hydroxylation catalytic capability under mild condition. It has been shown that some

porphyrin dimer linked covalently with a flexible alkoxy chain at the *para* position of the two phenyl rings exist in a closed conformation in which the two porphyrin rings come into close contact [1,2]. When this kind of porphyrin dimer is tested as a model of cytochrome P450, the one porphyrin ring can be regarded as an environmental model for another porphyrin ring of the porphyrin dimer and some information about the effect of the environment of steric hindrance on the catalytic activity may be obtained. Zinc–metal-free porphyrin dimer as a model of energy and electron transfer about primary events of green plant and bacterial photosynthesis have been extensively studied [3–5]. There

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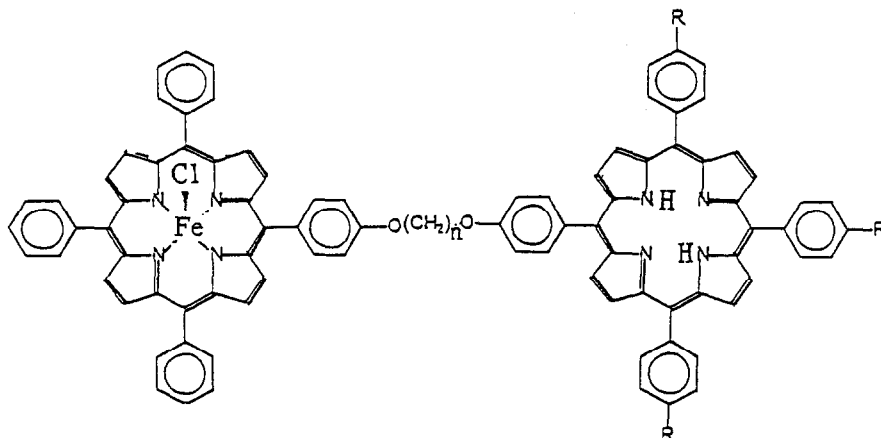


Fig. 1. The structure of iron(III)–metal-free porphyrin dimers.

have been a few studies on the hydroxylation catalyzed by porphyrin dimer. We report here the hydroxylation of cyclohexane with molecular oxygen catalyzed by three iron(III)–metal-free porphyrin dimers linked covalently with flexible butoxy chain at the *para* position of the two phenyl rings (Fig. 1). The effect of the steric hindrance and the intramolecular interaction of the two porphyrin rings on the catalytic activity are examined.

2. Experimental

2.1. Preparation of the dimer

5-(*p*-hydroxy)phenyl-10,15,20-triphenylporphyrin(H_2 HPTPP), 5-(*p*-hydroxy)phenyl-10,15,20-tri(*p*-methyl)phenylporphyrin(H_2 HP-TTP), 5-(*p*-hydroxy)phenyl-10,15,20-tri(*p*-chloro)phenylporphyrin (H_2 HPTCPP) and 5-[*p*-(4-bromo)butoxy]phenyl-10,15,20-triphenylporphyrin (H_2 BrBPPTPP) were synthesized similar to previously methods [6,7]. $Fe(BrBPTPP)Cl$ was prepared as follows: 1.00 g $H_2BrBPTPP$ was dissolved in chloroform/glacial acetic acid (1:1, 100 cm³) in a reaction vessel, then excess $Fe(II)Ac$ (freshly prepared) was added. The mixture was refluxed for 5 h. The mixture was poured into water. The residue in chloroform phase was

washed with 10% HCl and distilled water several times, respectively, dried over Na_2SO_4 and evaporated in vacuum to a low volume. Elution on a silica gel column with chloroform until the unreacted $H_2BrBPTPP$ was removed and then with chloroform/methanol (70:1) to remove purified $Fe(BrBPTPP)Cl$. After removal of solvent, the product was recrystallized in chloroform/methanol. Iron(III)–metal-free porphyrin dimer p - $FeTPP$ Cl/ p - H_2TTP was prepared by stirring an equimolar mixture of $Fe(BrBPTPP)Cl$ and H_2HPTPP in DMF/acetone(4:1) at 100°C for 24 h. The solution was then cooled, washed with 3 M HCl and distilled water several times, respectively, and dried over Na_2SO_4 . Solvent was removed and the residue was separated by chromatography on a column packed with silica gel. Elution with chloroform removed unreacted H_2HPTPP , chloroform/methanol (80:1) was then used to remove the dimer. The dimer obtained was finally recrystallized in chloroform/methanol. Dimer p - $Fe(TPP)Cl$ / p - H_2TTP and p - $Fe(TPP)Cl$ / p - H_2TTP were also prepared by the method described as above.

2.2. Physical measurements

Elemental analysis was performed on a Perkin–Elmer 240 elemental analyzer. UV–Vis spectra were recorded on a Shimadzu MPS-2000 spectrophotometer. IR spectra were determined

on a Bruker IFS 120 HR spectrometer ($4000\text{--}150\text{ cm}^{-1}$), using CsI pellets. $^1\text{H-NMR}$ spectra were determined on a Bruker Am-400. The EPR investigation was carried out with a Varian E-115 X-band spectrometer (77 K, 10^{-2} mol/l in CH_2Cl_2). XPS spectra were measured on a Fisons ESCALAB 210 spectrometer using Mg K α X-ray radiation ($E_x = 1253.6\text{ eV}$) and accurate binding energies were determined by charge referencing with the C 1s line at 284.6 eV.

The equilibrium constants for addition of imidazole to these porphyrin dimers were measured by spectral technique [8,9] on CHCl_3 at 30.0°C .

2.3. Procedure of catalytic hydroxylation

The hydroxylation reaction using these porphyrin dimers as catalysts were carried out in a specially constructed reaction vessel at $30.0 \pm 0.5^\circ\text{C}$ for 24 h. The catalytic system consists of porphyrin dimer (0.0100 mmol), coreducing agent (1.0 mmol ascorbic acid, 5.0 mmol thioalicyclic acid), substrate (5.55 mmol cyclohexane) and acetone/water (9:1, 10 cm^3). Pure oxygen (101.325 kPa) was passed into the solution through the inlet valve of the vessel with magnetic stirring. The products were detected and analyzed by GC (Shimadzu GC-9A) using n-pentanol as an internal standard.

3. Results and discussion

3.1. Characterization of the porphyrin dimers

The results of elemental analysis for these three porphyrin dimers are close to the calculated values². The UV-Vis spectra of the por-

² The data of elemental analysis for the porphyrin dimers, *p*-FeTPPCl/*p*-H₂TTP: calc., C 78.66; H 4.56; N 7.98; found, C 77.83; H 4.44; N 8.02. *p*-FeTPPCl/*p*-H₂TTP: calc., C 78.87; H 4.84; N 7.75; found, C 78.08; H 4.88; N 7.60. *p*-FeTPPCl/*p*-H₂TCPP: calc., C 73.26; H 4.05; N 7.43; found, C 73.55; H 4.12; N 7.37.

phyrin dimers in CHCl_3 are in good agreement with that of a 1:1 mixture of Fe(TPP)Cl and corresponding free-base porphyrin (H_2TTP , H_2TTP , H_2TCPP) except the B band of the dimers is rather broad. Signals attributed to the N-H of free-base porphyrin ($=\text{N-H}$, δ 2.7 ppm) and butoxy chain proton ($-\text{OCH}_2$, δ 4.35 ppm; $-\text{CH}_2\text{CH}_2-$, δ 2.35 ppm) are discernible in the $^1\text{H-NMR}$ spectra of the porphyrin dimers. When porphyrin form complex with a metal ion, the most obvious change in IR spectra is the disappearance of $\nu_{\text{N-H}}$ (about 3360 cm^{-1}). On the other hand, a strong band appears at $900\text{--}1000\text{ cm}^{-1}$ due to the deformation of the porphyrin ring by the interaction of *M-N* bonding [10]. The porphyrin dimers exhibit an absorption band, $\nu_{\text{N-H}}$, at 3315.9 cm^{-1} and a strong band at 1000 cm^{-1} . In addition, they also exhibit two absorption band, $\nu_{\text{C-O-C}}$, at 1175.3 and 1072.1 cm^{-1} . EPR signals at apparent values of $g_{\perp} = 5.74$ and $g_{\parallel} = 2.12$ observed for these porphyrin dimers in CH_2Cl_2 at 77 K reveal the existence of a high spin ferric ion ($S = 5/2$) in these porphyrin dimers. All these indicate that the porphyrin dimers consists of two different porphyrin moieties (porphyrinatoiron(III) and free-base porphyrin) which are covalently linked with a $-\text{O}(\text{CH}_2)_4\text{O}-$ chain.

3.2. Hydroxylation of cyclohexane with molecular oxygen catalyzed by these porphyrin dimers

The preliminary studies were devoted to the hydroxylation of cyclohexane with molecular oxygen catalyzed by these porphyrin dimers and the results are listed in Table 1. The results unambiguously demonstrated that the C-H bond of cyclohexane is activated under mild conditions, cyclohexanol and cyclohexanone were produced in various ratios catalyzed by these porphyrin dimers. It is noteworthy that the catalytic activity in porphyrin dimers appear to be higher than those in the corresponding monoporphyinatoiron(III) system.

We have reported that the steric environment of metalloporphyrin molecule play a predomi-

Table 1

The results of hydroxylation of cyclohexane catalyzed by the iron(III)–metal-free porphyrin dimers

Catalyst number	Product amount (mol $\times 10^{-5}$)		Catalyst turnover	Yield (%)
	Cyclohexanol	Cyclohexanone		
<i>p</i> -FeTPPCL/ <i>p</i> -H ₂ TTP	4.64	2.38	7.02	1.26
<i>p</i> -FeTPPCL/ <i>p</i> -H ₂ TTP	5.05	2.49	7.54	1.36
<i>p</i> -FeTPPCL/ <i>p</i> -H ₂ TCPP	4.78	2.58	7.36	1.33
FeTPPCL	4.14	1.95	6.09	1.09

nant role in view of the catalytic process for some system [11]. It has been shown that equilibrium of two different conformations, open and closed conformation, is exist in *p/p* porphyrin dimers in solution (Fig. 2) [1,2]. The steric environment caused by these characteristic conformation may affect the axial coordination of ligand to porphyrin dimers. Several studies of the axial ligation reaction of Fe(III) porphyrin suggested that the equilibrium constant is very dependent upon the electronic, steric, and solvation factors. The study [8] about the effect of the phenyl substituents on β_2 in Fe(*p*-x)TPPCL system indicated that electron-donating groups favor the addition reaction, that is, the increase of the electron density of iron(III) of nitrogen in porphyrinatoiron(III) favor the addition reaction. The equilibrium constants for the addition of imidazole to these porphyrin dimers are shown in Table 2. It is of interest to note that the values of β_2 observed for these porphyrin dimers are similar and are lower than that observed for Fe(TPP)Cl. The results turned out contrary to the fact that electron density of

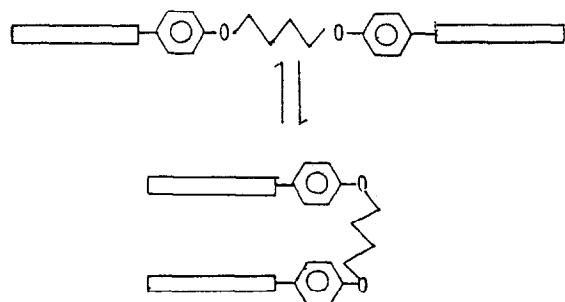


Fig. 2. The equilibrium of two different conformations of *p/p* porphyrin dimers in solution.

iron(III) in the porphyrin dimers is higher than that in Fe(TPP)Cl (the result from XPS, see below). It is obvious that the steric hindrance caused by the closed conformation play a predominant role in the addition process. In the catalytic cycle that cytochrome P450 catalyze hydroxylation of substrates with oxygen as described by Mansuy [12], the high spin ferric complex is first reduced to high spin ferrous complex by one electron coming from NADPH, then O₂ can be bonded to ferrous complex and activated, finally highly reactive [Fe(V)=O] species form. The binding site of cytochrome P450 is a hydrophobic cavity formed in the tridimensional structure of the protein part. The substrate is bonded within this cavity in a specific manner, and it is in close proximity with the reactive [Fe(V)=O] species, thus easily allowing the oxygen transfer step. We believe that the steric hindrance of the hydrophobic environment caused by the closed conformation of the porphyrin dimers may be advantageous to the formation of [Fe(V)=O] and the transfer of oxygen, and is one of the reasons for the higher catalytic activity. In addition, the steric hin-

Table 2

Equilibrium constants for the addition of imidazole to iron(III)–metal-free porphyrin dimers in CHCl₃ at 30°C

Porphyrin dimer	<i>n</i> ^a	β_2 (10 ⁵ M ⁻¹)
<i>p</i> -FeTPPCL/ <i>p</i> -H ₂ TTP	1.87	3.95
<i>p</i> -FeTPPCL/ <i>p</i> -H ₂ TTP	1.90	4.00
<i>p</i> -FeTPPCL/ <i>p</i> -H ₂ TCPP	1.75	1.13
FeTPPCL ^b	2	15.8

^a *n*: molecular number of imidazole added to the porphyrin dimer.

^b Ref. [8].

Table 3
The binding energies (eV) of porphyrin compounds from XPS

Compound	N 1s		Fe 2p _{3/2}	
	=N-H	≡N	Coordinated nitrogen	
	<i>p</i> -FeTPPCL/ <i>p</i> -H ₂ TPP	400.10		
FeTPPCL			398.77	711.45
H ₂ TPP	399.20	397.20		

drance can prevent effectively the formation of the inactive μ -oxo dimer, which may be another reason for their higher catalytic activity.

The intramolecular interaction between the two porphyrin rings in the porphyrin dimers is probably the most important aspect, while these porphyrin dimers have higher catalytic activity to hydroxylate cyclohexane with molecular oxygen in mild conditions. It has been shown that N 1s and metal level binding energies determined by data of XPS are most sensitive for describing the charge distribution in porphyrins and metalloporphyrins [13]. The intramolecular interaction between the two porphyrin rings has been studied by XPS spectra. From the XPS spectra (Table 3), it has been found that the presence of two distinctly different, nonequivalent nitrogen peaks (399.2 and 397.2 eV) which can be attributed to the protonated and unprotonated pyrrol nitrogen in H₂TPP, and that the four pyrrol nitrogen become equivalent with the nitrogen doublet in the free base spectra, collapsing into a single metallo–nitrogen peak (398.77 eV) when Fe(TPP)Cl is formed. The three nitrogen peaks having an area ratio of 4:2:2 (at 398.70, 400.10 and 397.80 eV, respectively) in *p*-FeTPPCL/*p*-H₂TPP can be attributed to the coordinated, protonated and unprotonated nitrogen and clearly indicate the presence of two different porphyrin moieties, including porphyrinatoiron(III) and free-base porphyrin in *p*-FeTPPCL/*p*-H₂TPP. The binding energies of Fe 2p_{3/2} in *p*-FeTPPCL/*p*-H₂TPP and FeTPPCL were obtained from XPS. As is shown in Table 3, the N 1s binding energies of the protonated and unprotonated

nitrogen in *p*-FeTPPCL/*p*-H₂TPP are larger than that in H₂TPP, while the N 1s binding energies of coordinated nitrogen in *p*-FeTPPCL/*p*-H₂TPP is slightly smaller than that in FeTPPCL. On the other hand, the Fe 2p_{3/2} binding energy in *p*-FeTPPCL/*p*-H₂TPP is smaller than that in FeTPPCL. All these indicate that the electron density of iron(III) in one porphyrin ring has increased and the electron density of nitrogen on other porphyrin ring has decreased simultaneously with the form of the porphyrin dimer. This interesting result perhaps arises from the intramolecular interaction between the two porphyrin rings. According to the catalytic cycle of cytochrome P450 described above, it is quite evident that the increase of the ferric electron density in the porphyrin dimers is advantageous to the reduction of ferric which is an important step in the process of the activation of molecular oxygen. This may be also a reason for their higher catalytic activity.

Acknowledgements

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