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Synthesis of Metallo-Deuteroporphyrin Derivatives and the Study of Their Biomimetic Catalytic Properties

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1. Introduction

Selective catalytic oxidations of organic molecules are among the most important technological processes in the synthetic chemistry as well as in the chemical industry for the preparation of many pharmaceuticals, vitamins, fragrances and dyestuffs (Hudlicky, 1990). However, despite great progress in organic synthesis in the last several decades, among varieties of catalysts the ones required in selective catalytic oxidations have the highest cost and the lowest selectivity, which brings the oxidation products tremendous difficulties in separation and purification (Cavani & Trifiro, 1992). On the other hand, alkanes instead of alkenes, which come from natural gas and crude oil, have gradually become the main raw materials of the chemical industry. Due to their intrinsically inert nature, the selective functionalization of alkanes is very difficult and consequently regarded as a key objective in the chemical industry (Sheldon & Kochi, 1981). Although the oxidation of alkanes is a thermodynamically favored process, it is difficult to do so in a controlled and selective fashion, since the oxidation products under the activation of oxygen atoms they involve are more active than the raw materials and prone to causing over-oxidation. Traditional oxidants such as chromates and permanganates can perform reactions of this type but are notoriously nonselective and must be used under forcing conditions. They have been discarded mainly due to their economic and environmental costs in favor of cheap oxidants such as air or peroxides, but these latter processes are extremely inefficient and require constant recycling of substrates (Costas et al., 2000). Thus increasing the efficiency and selectivity of hydrocarbon transformations, especially the activation of $C-H$ bond of saturated hydrocarbons, has been the goal of both academic and industrial research efforts.

Nature has already developed an excellent solution for the problem of the selective oxidation of organic substrates under particularly mild conditions, by utilizing as oxidant the most abundant, cheapest and cleanest one as possible, dioxygen, in the presence of metalloenzymes as catalysts (Wallar & Lipscomb, 1996; Que & Ho, 1996). Indeed, in the biological world, metal-containing proteins are able to perform oxidation reactions at room temperature under atmospheric pressure, even the hydroxylation of hydrocarbons, in spite of the relative inertness of the $C-H$ bond in non-activated substrates. (Ricoux et al., 2007). These include non-heme enzymes, such as methane monooxygenase, which is able to

catalyze the oxidation of methane into methanol, and heme enzymes, such as cytochrome P450-dependent monooxygenases, which use dioxygen and two reducing equivalents to catalyze a great variety of stereospecific and regioselective oxygen insertion processes into organic compounds (Dawson & Sono, 1987; Ortiz de Montellano & De Voss, 2002).

In all the reactions catalyzed by cytochrome P450 enzymes (P450s), an aliphatic C−H bond of the substrate is oxidized to give an alcohol product that is susceptible to further transformation. The selectivity and efficiency of these reactions and the mild reaction conditions indicate a methodology distinct from traditional industrial processes, which usually require higher temperatures and pressures. However, it is not able to directly adapt the rather fragile biological catalyst to tolerate harsher industrial conditions. Thus a great number of biomimetic inorganic catalysts have been developed to mimic the function of P450s that can perform C−H activation (Mansuy, 2007). During the last several decades, a huge amount of work has shown that substituted metallo-porphyrins are efficient catalysts for the direct oxidation of alkanes by air or dioxygen to give alcohols and/or carbonyl compounds at unprecedented rates under very mild conditions without co-reductants or stoichiometric oxidants. However, nearly all the presently used metallo-porphyrin catalysts have centered on synthetic meso-tetraarylporphyrins (TAPs) (Tagliatesta et al., 2006; Haber et al., 2000; Lyons et al., 1995; Połtowicz et al., 2006). With our improved understanding of heme enzyme mechanisms, work on the novel biomimetic heme catalysts, i. e., metallo-deuteroporphyrin and its derivatives, has also made great progress (Hu et al., 2008; Zhou et al., 2009). Here, we focus on these studies of metallo-deuteroporphyrin derivatives [M(DPD)] and mechanistic insights derived therefrom.

2. Monooxygenase cytochrome P450

2.1 Basic structure and function of P450 enzymes

Cytochrome P450 enzymes (P450s) efficiently utilize dioxygen to catalyze oxygenation in various biosyntheses of endogenous organic compounds and in detoxification of exogenous ones (Groves, 2005; Meunier et al., 2004). These enzymes constitute a large family of cysteinato-heme enzymes, are found in almost all forms of life, including bacteria, fungi, plants, insects, and mammals. Thousands of such proteins are now known, such as 57 in the human genome (Guengerich, 2005), 20 in *Mycobacterium tuberculosis* (McLean & Munro, 2008), 272 in *Arabidopsis* (Ehlting et al., 2006), and the surprising number of 457 in rice (Schuler & Werck, 2003), and so on. Molecular oxygen, itself, is unreactive toward organic molecules at low temperatures either due to spin-forbiddenness or to high barriers (Filatov et al., 2000). Consequently, living systems mainly use enzymes that modify dioxygen to a form capable of performing the desired oxidation reaction. This modification can be achieved by metal-dependent oxygenases, like P450s or non-heme metalloenzymes (e.g., methane monooxygenase), or by flavin-containing enzymes that do not possess a metal-based prosthetic group.

P450s were first identified and purified nearly 50 years ago by biochemists and pharmacologists who focused on the early studies of the oxidative metabolism of drugs (Denisov et al., 2005). As a superfamily of electron transfer hemoproteins, P450s are defined by the presence in the proteins of a heme [iron(III) protoporphyrin-IX] prosthetic group coordinated on the proximal side by a cysteinyl thiolate group as an axial ligand to the heme (see Fig. 1) (Ortiz de Montellano, 2010; Dawson & Sono, 1987).
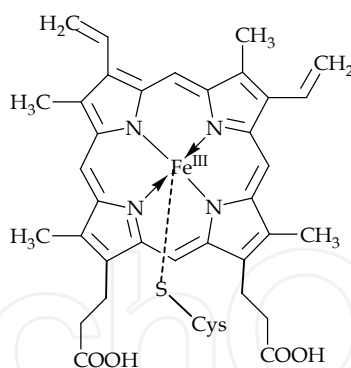
Fig. 1. Prosthetic of cysteinato-heme enzymes: an iron(III) protoporphyrin-IX linked with a proximal cysteine ligand.

This feature gives rise to the spectroscopic signature that defines these enzymes, as the thiolate-ligated ferrous-CO complex is characterized by a Soret absorption maximum at ~450 nm (Omura & Sato, 1964), resulting in a critical structural factor for P450s' unique reactivity (Tani et al., 2002). P450s contain 414 amino-acid residues with a relative molecular weight of about 45000, sharing a common overall fold and topology (Denisov et al., 2005). The basic structure of the P450 protein consists of 12 helices and appears in a triangular form. The conserved P450 structural core is formed by a four-helix bundle, in which the prosthetic heme group is confined between the distal and proximal helix and bound to the adjacent Cys-heme-ligand loop. The absolutely conserved cysteine group is the proximal or "fifth" ligand to the heme iron. Typically, the proximal Cys forms two hydrogen bonds with neighboring backbone amides. Thus, the active site of cytochrome P450 is formed by the wide hydrophobic pocket which contains the prosthetic heme group, which is bound to the apoprotein through a cysteinate axial ligand of the iron, and a binding site for the substrate (Ricoux et al., 2007). P450s are potent catalysts that are able to transfer an oxygen from dioxygen to various organic substrates (Suslick & Reinert, 1985). In mammalian systems, these include cholesterol and other steroids, prostaglandins and a variety of xenobiotics (compounds exogenous to the organism). P450s are also responsible for the carcinogensis of otherwise unreactive molecules such as benzene. The types of reactions catalyzed by P450s are extremely diverse, including aliphatic and arene hydroxylations, alkene epoxidation, N-oxidation, S-oxidation and N-, O- and S-dealkylation (Mansuy, 1998). As the means of oxidation, the P450 uses molecular oxygen, inserts one of its oxygen atoms into a substrate (RH), and reduces the second oxygen to a water molecule, utilizing two electrons that are provided by NAD(P)H via a reductase protein (eq. 1). Since only one of the two oxygen atoms, initially present in O_2, remains in the oxidized substrate, P450s are called monooxygenases (Suslick, 2000).

$$RH \ + \ O_2 \ + \ 2e^- \ + \ 2H^+ \xrightarrow{\text{Cytrochrome P450}} ROH \ + \ H_2O \tag{1}$$
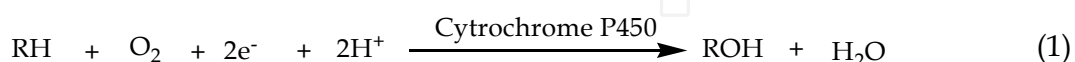
2.2 Enzymatic reaction cycle of cytochrome P450

A common catalytic cycle of the cytochrome P450s proposed in 1968 still provides the core description of the iron, protein, and oxygen roles and is now generally accepted in an updated form (Fig. 2) (Ortiz de Montellano & De Voss, 2002; Groves, 2003). The iron-heme group is shown only for 1, whereas in the rest of the cycle the heme is depicted by two bold horizontal lines, and the cysteinate ligand is abbreviated as CysS. The cycle begins with the resting state (1) in which a water molecule is bound to the ferric ion in the distal side. In this

Fig. 2. Schematic representation of the catalytic cycle of cytochrome P450. RH is a substrate hydrocarbon and ROH the resulting hydroxylated product. The +• over one of the heme lines indicates that the radical cation is located on the porphyrins, whereas its placement beside the brackets indicates that the radical is located somewhere on the protein.

hexacoordinated Fe(III) complex the d-block orbitals of the iron contain five electrons, predominantly in the low-spin doublet configuration. The entrance of the substrate (for example, an alkane, RH) displaces the water molecule, leaving a pentacoordinated ferric-porphyrin (2). With a coordination number of five, the iron moves from a position almost in the plane of the heme to a position below the heme and becomes predominantly a sextet high-spin species. The ferric complex (2) is a slightly better electron acceptor than the resting state and can therefore take up an electron from a reductase protein, leading to a high-spin ferrous complex (3). Subsequent binding of molecular oxygen yields the ferrous dioxygen complex (4), which has a singlet spin state and is a good electron acceptor. This, in turn, triggers a second electron transfer to generate the ferric-peroxo anion species (5). This second electron transfer is usually, but not invariably, the rate-determining step of the catalytic cycle (Davydov et al., 2001). Since the ferric peroxo complex (5) is a good Lewis base, it gets quickly protonated to form the ferric-hydroperoxide species (6) that is also called Cpd 0. The resulting Cpd 0 is still a good Lewis base and abstracts an additional

proton to give a ferryl intermediate that can be formulated, as shown, as a porphyrin radical cation Fe(IV) species (7). Alternative formulations, shown below in Fig. 2, are as a protein radical cation Fe(IV) species (7') or as an Fe(V) species (7''). This ferryl intermediate, also known as Cpd I, is two oxidation states above the resting ferric state. In the common case, Cpd I monooxygenates the substrate; for example, it reacts with the substrate (RH) to produce the hydroxylated metabolite (8) and, after product (ROH) release and reequilibration with water, the resting ferric state of the enzyme.

After this catalytic reaction the alcohol (ROH) exits the pocket, water molecules enter in, and the enzyme restores the resting state by binding a water molecule. There is uncertainty about the details of the cycle starting from 5 and onward back to 1; Cpd I is elusive, its protonation mechanism is still not fully characterized, and the mechanism of substrate oxidation is still highly debated. Thus, theory has an important role here as a partner of experiment.

In addition to having multiple distinct intermediate states, each of which can display its own rich chemistry, the P450 reaction cycle contains at least three branch points, where multiple side reactions are possible and often occur under physiological conditions (Bernhardt, 1996). The three major abortive reactions are (i) autoxidation of the oxy-ferrous enzyme (4) with concomitant production of a superoxide anion and return of the enzyme to its resting state (2), (ii) a peroxide shunt, where the coordinated peroxide or hydroperoxide anion (5, 6) dissociates from the iron forming hydrogen peroxide, thus completing the unproductive (in terms of substrate turnover) two-electron reduction of oxygen, and (iii) an oxidase uncoupling wherein the ferryl-oxo intermediate (7) is oxidized to water instead of oxygenation of the substrate, which results effectively in four-electron reduction of dioxygen molecule with the net formation of two molecules of water. These processes are often categorized together and referred to as uncoupling (Shaik et al., 2005; Denisov et al., 2005).

3. Metallo-porphyrins and their imitation of cytochrome P450

3.1 Synthetic metallo-porphyrins

Quantities of investigations have demonstrated that cytochrome P450 catalyzes the mono-oxygenation of various organic substrates with high stereo- and regioselectivity under mild conditions, relying mainly on its prosthetic group, an iron-porphyrin complex, as the active site (Groves & Han, 1995). Accordingly, a lot of metallo-porphyrins have been synthesized as models for cytochrome P450 and used for various oxo transfer reactions, which affords important insights into the nature of the enzymatic processes. Indeed, each of the intermediates shown in Fig. 2 has been independently identified by model studies using synthetic analogs, especially meso-tetraarylporphyrins (TAPs) (Ozawa et al., 1994).

The first report of a simple iron porphyrin system that effected stereospecific alkane hydroxylation and olefin epoxidation was reported in 1979. This system introduced the use of Fe[III](TPP)Cl [meso-tetraphenylporphyrinato-iron(III) chloride] and iodosobenzene as the catalyst and oxygen-transfer reagent, respectively, to mimic the chemistry of cytochrome P450 (Groves et al., 1979). Since then, many metallo-porphyrins have been synthesized to catalyze a variety of hydrocarbon oxidations with various oxygen donors (Groves & Nemo, 1983; Bruice, 1991). Metallo-porphyrin-catalyzed oxidations include hydroxylation, epoxidation, N- & S-oxidation and cleavage of 1,2-diols. The largest bulk of reports have been with Mn(III), Fe(III), Ru(III), Co(III) and Cr(III) porphyrins, in that order. Among them, Mn(III), Fe(III), Ru(III) and Co(III) porphyrins have been found to be efficient catalysts for

the mono-oxygenation of alkanes, the epoxidation of simple olefins and the oxidation of sulphides, while Cr(III) porphyrins be competent only for epoxidation (Połtowicz & Haber, 2004; Zhou et al., 2007).

An enormous range of oxidants have been used as oxygen donors to the metallo-porphyrins, including iodosobenzene, peroxyacids, hypochlorite, chlorite, hydroperoxides, N-oxides, hydrogen peroxide, monoperoxyphthalate, potassium monopersulfate and molecular oxygen (or air). Iodosobenzene is one of the very first oxidants and remains in use because it has excellent oxygen-transfer behavior and mechanistic cleanliness (Hill & Schardt, 1980; Rezaeifard et al., 2007; Połtowicz et al., 2006). However, the main trend of the hydrocarbon oxidation is adopting environmentally-friendly reagents, such as hydrogen peroxide, molecular oxygen or air, and so on (Li et al., 2007). Some work has also been accomplished employing various reductants with molecular oxygen to effect substrate oxidation, including borohydrides, aldehydes, H_2, and ascorbic acid (Tagliatesta et al., 2006; Ji et al., 2007).

An essential prerequisite to any successful fulfillment of the hydrocarbon oxidation rests with the oxidative robustness of the catalyst compared to the substrate. Unfortunately, simple metallo-porphyrins are readily decomposed under oxidizing conditions. This oxidative degradation occurs easily at the meso-ring position (the methine carbons), which is actually the route used for the catabolism of heme in *vivo* (Rawn, 1989). Both electronic and steric factors can be manipulated to improve the oxidative robustness of metallo-porphyrins. The introduction of electron-withdrawing substituents on the porphyrin periphery, especially halogenated and perhalogenated phenyl porphyrins, has proved very successful in creating robust catalysts (Traylor et al., 1991). Steric protection of the meso-position of the porphyrin has also been used effectively (Silva et al., 1999). In practice, however, these are not entirely separate approaches, because almost all of the electron-withdrawing substituents will also contribute significant steric protection to the metallo-porphyrin (Suslick, 2000).

In regard to the mechanism of hydrocarbon oxidations catalyzed by synthetic metallo-porphyrins, there exist two nonidentical viewpoints. The first considers instructively the mechanism by which iron porphyrin systems are thought to catalyze $C-H$ bond oxidations in biological systems (Fig. 2) (White & Coon, 1980; Woodland & Dalton, 1984). The representative one has been proposed by Groves and coworkers (Groves & Watanabe, 1986; Groves & Han, 1995) that hydrocarbon hydroxylation with metallo-porphyrin catalysts proceeds via a radical pathway in a "rebound" mechanism, in which an oxygen atom is transferred from an oxidant (for example, iodosobenzene, peroxyacids, etc.) to a metal(III) porphyrin complex to form an active high-valent metal-oxo species (for example, an oxy-ferryl (Fe=O) intermediate, analogous to the Cpd I in the catalytic cycle of cytochrome P450). Hydroxylation has generally been assumed to occur from radical abstraction of a hydrogen from the substrate by the active species, which forms a metal hydroxide complex and substrate radical. The metal hydroxide complex then rapidly transfers the hydroxyl group back to the substrate.

In enzymatic pathways, electrons and protons are available to the heme system throughout the process. However, in the case of artificial metallo-porphyrin systems, without co-reductants (Hill & Schardt, 1980; Suslick & Reinert, 1985) or photochemical (Maldotti et al., 1991) or electrochemical (Leduc et al., 1988) assistance, monooxygenase activity of the type known to occur in vivo is not possible. Consequently, the second mechanism, proposed by

Lyons et al. (Ellis & Lyons, 1989; Ellis & Lyons, 1990), utilizes a hypothetical catalytic cycle for elucidating the behavior of halogenated tetraarylporphyrinato iron(III) complexes in catalyzing alkane hydroxylations (see Fig. 3). It has been found that electron-withdrawing groups (fluoride, chloride and bromide) on the tetraarylporphyrinato ligand of iron(III) complexes are capable of enhancing the rate of alkane hydroxylation with molecular oxygen as the oxidant (Lyons & Ellis, 1991). Therefore, in these reactions a high oxidation state iron oxo complex, analogous to the Cpd I, has been conjectured as the key intermediate, which occurs from a μ-peroxo-bridged iron(III) porphyrin dimer by using the electrons involved in the μ-peroxo dimer system (Ozawa et al., 1994).
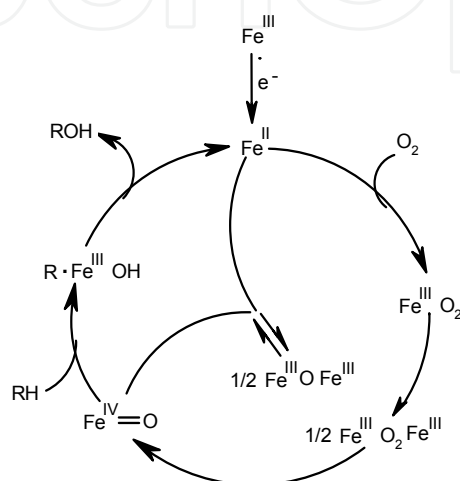
Fig. 3. Conceptual scheme for a hypothetical catalytic cycle for alkane hydroxylations catalyzed by halogenated tetraarylporphyrinato iron(III) complexes (the porphyrin ring is omitted).

Electron-withdrawing halogen substituents may activate the μ-peroxo dimer intermediate and increase its reactivity toward alkanes (Mansuy, 1993; Połtowicz et al., 2005). Two reasons were advanced for the increase in catalyst activity with porphyrin halogenation in the O_2-oxidation of alkanes. On the one hand, halogenation could shift the position of equilibrium away from the μ-oxo diiron(III) species in favor of a low oxidation state iron(II) complex and a high oxidation state iron(IV) ferryl complex. Both steric and electronic factors could destabilize the diiron μ-oxo complex toward disproportionation (Haber et al., 2000; Haber et al., 2004). On the other hand, Electron withdrawal from the porphyrinato ligand should make it more difficult for oxidation of the ligand by electron transfer to the iron center. Thus, perhaps an iron(IV) ferryl species generated from symmetrical cleavage of a μ-peroxo dimmer of a halogenated TPP could survive and be effective in alkane hydroxylation. The reductant, which initially converts Fe(III) to Fe(II) need only be present in small amounts, and might either be an adventitious impurity or, perhaps, the alkane itself (Lyons et al., 1995; Lü et al., 2003).

3.2 Metallo-deuteroporphyrin derivatives
From recent progress in the study on hydrocarbon oxidations catalyzed by metallo-porphyrins, it is found that metallo-porphyrins, as a class of environmentally-friendly oxidation catalysts, will certainly become the lead in the research of biomimetic catalysts and technology and play an increasingly important role in green chemistry (Song et al.,

2007; Tagliatesta et al., 2006). During the last several decades, a vast amount of work has shown that substituted metallo-porphyrins are efficient catalysts for alkane oxidations by molecular oxygen or air without co-catalysts or stoichiometric oxidants to give alcohols and/or carbonyl compounds at unprecedented rates under very mild conditions (Guo et al., 2003). However, there still exists a great distance from the industrial application of metallo-porphyrin catalysts because of their defects, including low catalytic activity, poor stability and troublesome recoverability. Furthermore, the selectivity and mechanism of metallo-porphyrin catalyzed oxidations remain to be further improved and clarified, respectively (Hu et al., 2008; Ma et al., 2009).

Up to now, nearly all of the metallo-porphyrins used as oxidation catalysts have been based on the system of synthetic TAPs (Zhou et al., 2008; Rebelo et al., 2005), of which the meso aryl group may reduce the activity of the catalyst and cause degradation of the porphyrin ring in the oxidation (Rawn, 1989). With the similar porphyrinoid structure, the naturally occurring cyclic metallo-tetrapyrroles, present extensively in organisms, are all natural bio-oxidation catalysts which have very high bio-catalytic activity and participate in various oxidation-reduction processes, such as oxygen-transferring, photosynthesis, and so on. However, it is well known that almost all the presently structure-confirmed natural cyclic metallo-tetrapyrroles, such as heme, chlorophyll, bacteriochlorophyll and vitamin B12, are substituted on the β-position of the pyrrole ring other than on the meso-position of the macrocycle (Hu et al., 2004). This suggests that the β-substituted and meso-unsubstituted cyclic metallo-tetrapyrroles might undergo a different mechanism in catalytic oxidations and have better catalytic activity and stability than the meso-substituted ones.

In this regard, it is interesting to note that the prosthetic heme group of cytochrome P-450, which has no substituents on its meso-positions, may be used to construct a new type of metallo-porphyrins as oxidation catalysts, since free heme can be largely obtained from the blood of various livestocks, such as oxen, sheep, pigs, and so on. Generally, the extract of naturally occurring heme, hemin, which is commercially available, is regarded as the substitute of heme. Due to the highly chemical activity of the two vinyl groups in the hemin molecule, hemin cannot be directly employed in catalytic oxidations. However, it stands to reason that metallo-deuteroporphyrin derivatives [M(DPD)], derived from hemin, for example metallo-deuteroporphyrin dimethylester [M(DPDME)], may have efficient catalytic activity values, because they have robust structures as well as close relationships to the naturally occurring heme (Hu et al., 2010).

Recent work by the authors has shown that M(DPDME) are efficient catalysts for the direct reaction of cyclohexane with air in the absence of solvents to give cyclohexanol and/or cyclohexanone with unprecedented rates under mild conditions (Zhou et al., 2009). No coreductants or stoichiometric oxidants are required. Neither is it necessary to employ photochemical or electrochemical techniques in the oxidation (Zhou et al., 2010). On the basis of the above-mentioned investigation, we have designed and synthesized a series of M(DPD) and used them as a catalyst in the oxidation of hydrocarbons with air, in order to study the catalytic mechanism of metallo-porphyrins.

4. Synthesis of metallo-deuteroporphyrin derivatives

In general, the methods for the synthesis of porphyrins may be divided into two types. The one is the total synthesis through condensation either from α-unsubstituted pyrrole derivatives with formaldehyde (or benzaldehyde), or from α-formyl (or methyl, methano, etc) substituted pyrrole derivatives, the other is the modification of naturally occurring

porphyrin derivatives, e.g. heme and chlorophyll, etc. The method of total synthesis is especially suitable for the structurally symmetrical simple porphyrins, while the method of modification is convenient for structure-complicated unsymmetrical ones. Herein, all the metallo-porphyrins used as catalysts are prepared from hemin, the extract of naturally occurring heme. In view of the unstability of the double vinyl groups in the hemin molecule, devinylation is first adopted to synthesize deuterohemin (DH) by heating hemin in a resorcinol melt at 160 ˚C through the so-called Schumm classical reaction (Dinello&Dolphin, 1981). Deuteroporphyrin (DP), as one of the most common porphyirns in organic synthesis, is then synthesized from DH through demetalation. It is from DH or DP that a series of M(DPD) are designed and synthesized. This chapter will focus mainly on the synthetic methods of these compounds.

4.1 Synthesis of deuteroporphyrin

The most convenient pathway for the synthesis of DP is the demetalation of DH, which was reported in as early as 1920s and was performed in the presence of anhydrous $FeSO_4$ and dry gaseous HCl, which is the first and earliest method for the synthesis of DP. Subsequently, a lot of methods, such as Fe/HCOOH, H_2SO_4/CF_3COOH, $HCl/FeSO_4/AcOH/CH_3OH$ and HBr/AcOH were developed in succession for this reaction. However, all the above-mentioned methods are complicated, time-consuming, low-yield producing and inefficient. The development of a simple, highly efficient methodology for the demetalation of metallo-porphyrins remains desired.

For the purpose of preparing DP with high yield and purity, we have systematically studied the demetalation of DH using acetic anhydride as solvent, obtaining two satisfactory results. As shown in Fig. 4, under the conditions of pathway a DH reacts with $FeSO_4 \cdot 7H_2O$ and concentrated hydrochloric acid in acetic anhydride solvent at 100 °C for 2 h to produce DP with a yield of more than 85%. Pathway b indicates another circumstance that the reaction successfully occurs in 82%yield with concentrated hydrobromic acid in the absence of $FeSO_4 \cdot 7H_2O$. On the basis of these results, we have developed a facile and efficient method for the demetalation of metallo-porphyrins by ultrasound irradiation. Thus the solution of DH, concentrated hydrochloric acid and $FeSO_4$ in acetic anhydride was irradiated by ultrasound with a frequency of 40 kHz at room temperature for 30 min to give DP in 95.2% yield (Sun et al., 2011a). Similarly, the demetalations of the complexes ClM(TPP), where M=Fe(III), Co(III), Mn(III) were completed by ultrasound irradiation under very mild conditions with yields of more than 95%. The results have provided a novel methodology for the preparation of porphyins.
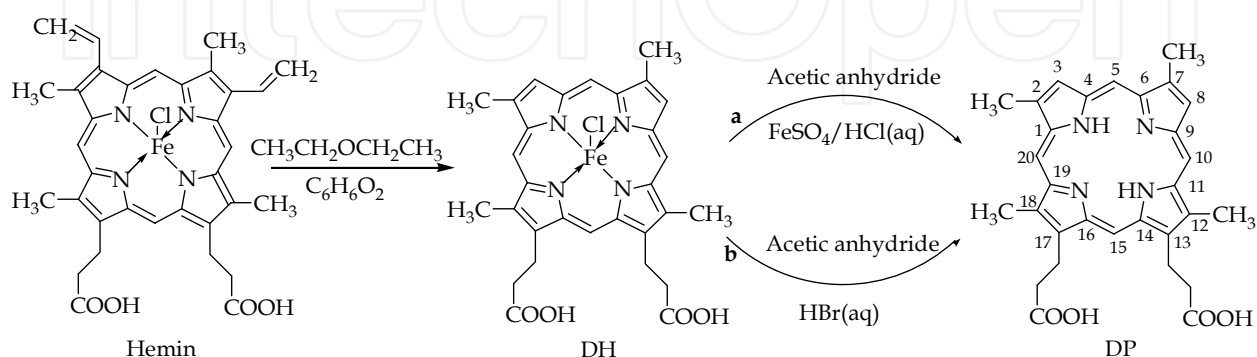

Fig. 4. Synthesis of DP.

4.2 Synthesis of DPDME and its 3,8-substituted derivatives

As seen by the structure of DP's molecule, DP is not suitable for directly using as oxidation catalyst because of the reactivity of carboxylic groups. Moreover, the character of the substituents on the macrocyclic periphery of metallo-porphyrins has great influence on their catalytic properties. The introduction of substituents on the macrocyclic periphery has often been used to regulate the catalytic activity of metallo-porphyrins. For example, Martins (Martins et al., 2001) found that the selectivity and stability of M(TPP) may be considerably enhanced through the introduction of electron withdrawing groups on the β-positions of the M(TPP) macrocycle; Lyons (Lyons et al., 1994) reported that the electron-withdrawing substituents on the macrocyclic periphery can increase the redox potential and improve the catalytic activity of M(TPP) in the oxidation of isobutane. Therefore, we have designed and synthesized DPDME and its 3,8- substituted, i.e., β-substisuted derivatives, including 3,8-dinitro and 3,8-dihalogeno DPDME.

4.2.1 Synthesis of DPDME

DPDME may be synthesized from DP through esterification. But it is more interesting to synthesize DPDME from DH by a "one-pot" reaction. In 1966, Caughey (Caughey et al., 1966) reported the synthesis of DPDME from DH through the cooperative reaction of demetalation and esterification in the presence of anhydrous $FeSO_4$, dry gaseous HCl and CH_3OH, with a total yield of 66%. Dinello (Dinello & Chang, 1978) made an improvement upon the above-mentioned method using the mixed solution of glacial CH_3COOH, concentrated HCl, CH_3OH and concentrated H_2SO_4, with a total yield of 46.5~80%. However, both the methods are complicated, time-consuming, low-yield producing and inefficient. Hence, we have developed a simple and convenient method for the synthesis of DPDME by ultrasound irradiation (Fig. 5, a). As shown in Fig. 5 (a), DH reacted with CH_3OH and concentrated H_2SO_4 under the irradiation of ultrasound with a frequency of 40 kHz at room temperature for 1 h to produce DPDME in 97% yield (Hu et al., 2010).
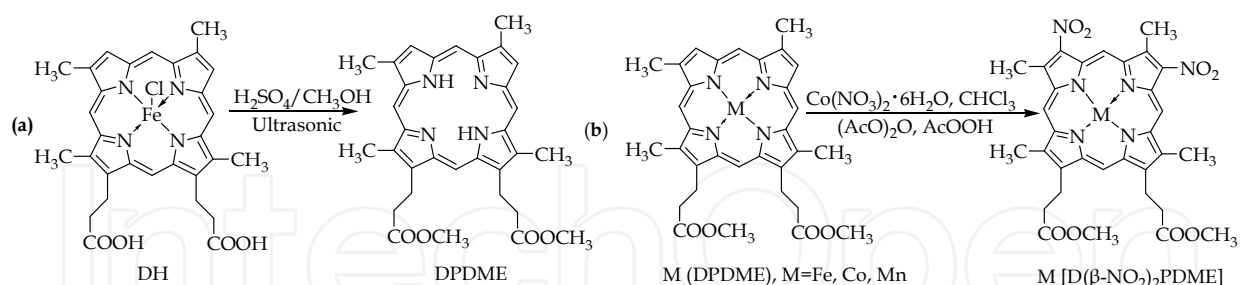

Fig. 5. (a) Synthesis of DPDME from DH under ultrasonic irradiation; (b) Synthesis of M[D(β-NO₂)₂PDME].

4.2.2 Synthesis of 3,8-dinitro substituted DPDME complexes

There are several ways, as reported in the literature, for the introduction of the nitro group on the porphyrin periphery. For example, Caughey (Caughey et al., 1966) found that the main product of the nitration of DPDME in the mixed acid HNO_3/H_2SO_4 was the meso-nitro substituted DPDME; Catalano (Catalano et al., 1984) put forward the synthesis of β-nitro substituted TAP with the mixture of N_2O_4, acetyl nitric ether and nitrate; Huang and coworkers (Huang et al., 2001) reported the method of using the system of nitrate/(AcO)₂O/AcOOH as nitrating agent to nitrify TPP, etc.

Among all the reported methods, the use of nitrate/(AcO)$_2$O/AcOOH as nitrating agent is the mildest and simplest one. Consequently, we have adopted this kind of nitrating agents in the synthesis of M[D(β-NO$_2$)$_2$PDME] from M(DPDME), finding that the system of Co(NO$_3$)$_2$/(AcO)$_2$O/AcOOH is the best one for this reaction (Fig. 5, b). In the typical procedure, the mixture of (AcO)$_2$O/AcOOH/Co(NO$_3$)$_2$·6H$_2$O/M(DPDME), where M=Fe(III), Co(II), Mn(III) with a molar ratio of 15/10/2/1 in chloroform was stirred at 62 ℃ for 1 h to give M[D(β-NO$_2$)$_2$PDME] in about 55% yield.

4.2.3 Synthesis of 3,8-dihalogeno substituted DPDME

Here, 3,8-dihalogeno substituted DPDME refers to D(β-X)$_2$PDME, where X=Br, I. The introduction of halogen on the β-position of DPDME can be found in the literature. In 1928, Fischer (Fischer, 1928) reported the synthesis of D(β-Br)$_2$PDME using Br$_2$/AcOOH as brominating agent in 36% yield. Caughey and coworkers (Caughey et al., 1966) used the salt of pyridine/HBr to brominate DPDME, obtaining D(β-Br)$_2$PDME with a total yield of 45%. However, both the above-mentioned methods are inefficient and complicated. An improved process for this reaction was advanced by Bonnett (Bonnett et al., 1990) using NBS (N-bromo-succinimide) as brominating agent with a yield of 76%. Therefore, we have exploited NBS as brominating agent in the synthesis of D(β-Br)$_2$PDME from M(DPDME), finding that the yield reached 87% after the mixture of DPDME and NBS in chloroform was refluxed for 3 h (Fig. 6).

The iodination of DPDME needs a method different from its bromination, for iodination is usually a reversible reaction. According to Shigeoka's (Shigeoka et al., 2000) synthesis of D(β-I)$_2$PDME, we have used I$_2$/K$_2$CO$_3$ as iodinating agent to treat DPDME in CH$_2$Cl$_2$ and gained D(β-I)$_2$PDME with a yield of over 95% (Fig. 6).
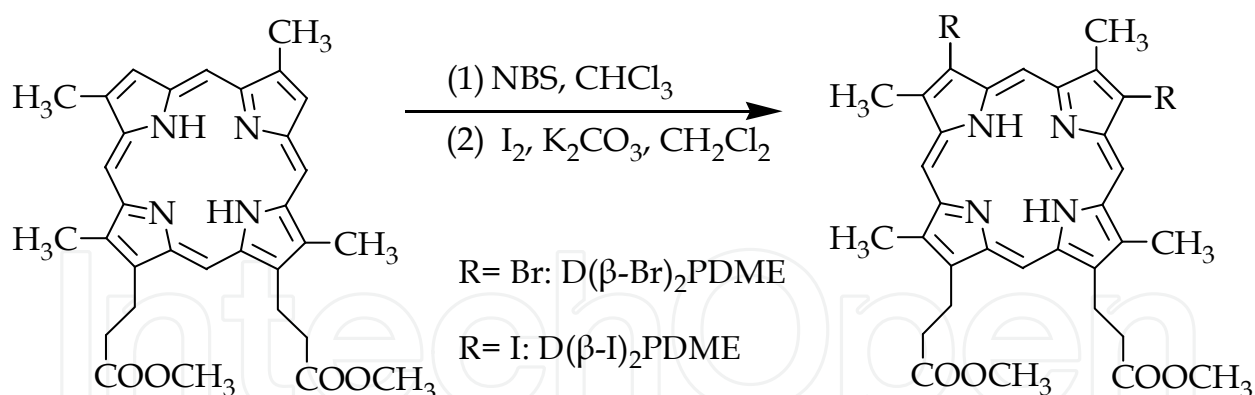

Fig. 6. Synthesis of D(β-X)$_2$PDME.

4.3 Synthesis of 13,17-modified deuteroporphyrin derivatives

The double carboxylic groups in the DP molecule have fairly high reactivity and can be easily converted into other functional groups, which implies that a short-cut for the introduction of substituents on the macrocyclic periphery of DP may be obtained through the modification of the double carboxylic groups. Thus, we have designed and synthesized several 13,17-modified deuteroporphyrin derivates, including deuterporphyrin 13,17-diesters and 13,17-dihalogeno- propyl porphyrins.

4.3.1 Synthesis of deuterporphyrin diesters

Due to the steric influence, it is difficult for DP to react with bulky alcohols. In order to improve the reactivity of DP in the esterification, the carboxylic groups reacted with the alcohol under ultrasound irradiation. Fig. 7 shows the synthetic route for various deuterporphyrin diesters. In the typical procedure, the solution of DP and alcohol was irradiated by ultrasound at room temperature for 2 h. Then, the reaction gave the diester product in more than 86% yield.
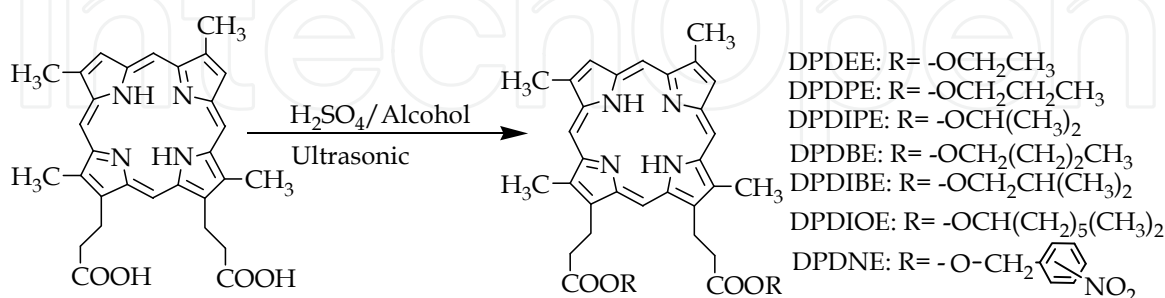
Fig. 7. Synthesis of deuterporphyrin diesters.

4.3.2 Synthesis of 13,17-dihalogeno-propyl porphyrins

Compared with a carboxylic group, an ester group is commonly easier to be reduced. So DPDME instead of DP has been used to prepare the 13,17-dihydroxylpropyl porphyrin (DHPP) by the reduction of $NaBH_4/LiCl$. This reaction was carried out in THF under reflux for 6 h to produce DHPP with a yield of 75%. It is well known that aliphatic alcohols are readily converted into corresponding halogeno-aliphatic compounds in the presence of strong halogenating agents, such as $SOCl_2$, PCl_5, PBr_3, etc. Thus, a solution of DHPP in CH_2Cl_2 was treated with $SOCl_2$ (or PBr_3) under reflux for 4 h to afford 13,17-dichloropropyl porphyrin (DCPP) with a yield of 78% or 13,17-dibromopropyl porphyrin (DBPP) with a yield of 80% (Fig. 8).
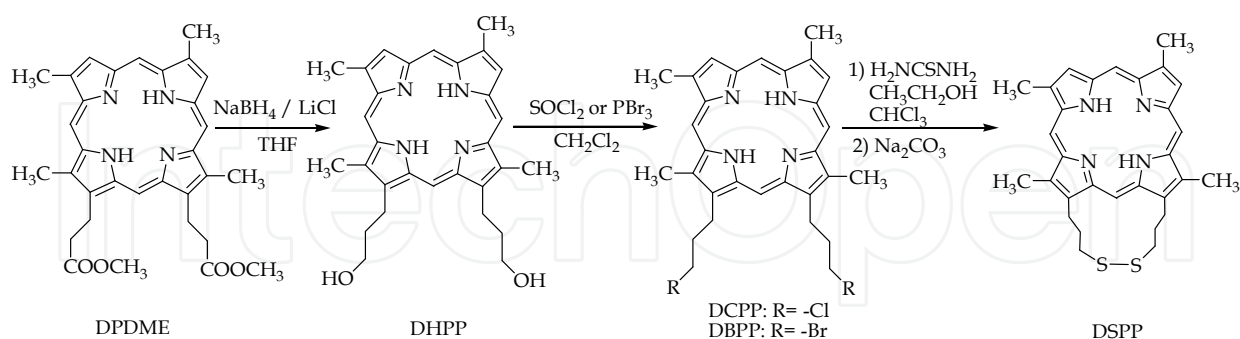

Fig. 8. Synthesis of 13,17-dihalogeno-propyl porphyrins.

4.4 Synthesis of disulphide-derivatised deuteroporphyrins

In all the cysteinato-heme P450 enzymes, the prosthetic group is constituted of an heme covalently linked to the protein by the sulfur atom of a proximal cysteinyl thiolate ligand. Although it is up to now not fully clarified what role the cysteinyl thiolate ligand plays in the catalytic action of P450, it is well known that cysteine has the nature of redox by use of the thiohydroxy group in its molecule. On the one hand, two cysteine molecules can be

oxidized through dehydrogenation to form one cystine molecule with a disulphide bond, and on the other hand, one cystine molecule can also be reduced through the hydrogenolytic cleavage of its disulphide bond to produce two cysteine molecules. This suggests that a disulphide bond may be introduced into the DP molecule to construct a novel type of bifunctionally biomimetic oxidation catalysts, which involve one "oxidation center" and one "dehydrogenation center" by use of the centrally complex metal ion and the disulphide bond, respectively. Due to the facile interconversion between the disulphide bond and the thiohydroxy group, these disulphide-derivatised compounds are provided with the condition to regenerate by itself.

On the basis of the above-mentioned principle, we have designed and synthesized two types of novel disulphide-derivatised deuteroporphyrins, i.e., 2,7,12,18-tetramethyl-13,17-dithio-propyl porphyrin (DSPP) and 2,7,12,18-tetramethyl-13,17-(propionylaminoethyl-dithio-ethylaminoformylethyl)-29,34-bis-(methoxyformyl)-porphyrin (PDTEP), by introduction of a disulphide bond between the two propionyl-hydroxyl groups in the DP molecule.

4.4.1 Synthesis of DSPP

DSPP was synthesized from DBPP (or DCPP) through two steps by means of "one-pot". As shown in Fig. 8, the suspension of DBPP and thiourea in the mixed solvent of $C_2H_5OH/CHCl_3$ was stirred under reflux for 8 h, and then the mixture was basified with a solution of Na_2CO_3 (20%) until the pH was 9.0. A continuous stirring at 60 ℃ for 30 mins afforded DSPP with a yield of 79.8% (Sun et al., 2011b). A possible mechanism may be used to explain this process that DBPP reacts first with thiourea to produce a salt consisting of an alkyl isothiourea and hydrobromic acid. Then, the salt is hydrolyzed under basic conditions to give a thio-alcohol, which is further oxidized in the course of hydrolysis to form the final product DSPP.

4.4.2 Synthesis of PDTEP

PDTEP was prepared by using DP and cystine as the starting materials. For the protection of the carboxylic groups in the cystine molecule, cystine was first converted into cystinyl dimethyl ester through the esterification with methanol by the action of $SOCl_2$. After removal of the superfluous methanol through evaporation, without purification the resultant was directly transferred to the solution of DP, N, N-dicyclohexyl carbodiimide (DCC) and pyridine in N, N-dimethylformamide (DMF). The mixture was stirred at room temperature for 8 h to afford PDTEP in 67% yield (Fig. 9).
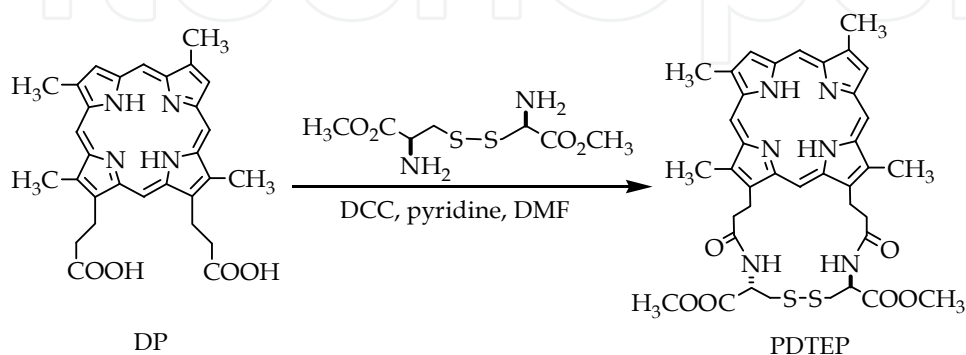

Fig. 9. Synthesis of PDTEP.

4.5 Introduction of the central metal into deuteroporphyrin derivatives

It is reported that metallo-porphyrins may be synthesized from corresponding porphyrins and metallic salts in varied ways. For example, Rothemund (Rothemund & Menotti, 1948) reported the synthesis of M(TPP) from TPP and several types of metallic salts in an acidic medium; Dorough (Dorough, 1951) used various basic mediums, e.g. diethyl amine, pyridine, etc, as solvent in the synthesis of M(TAP); Baum (Baum & Plane, 1966) even advanced the synthesis of M(TAP) from corresponding porphyrin and specific organometallic compound in a neutral medium. The presently most widely used method for the synthesis of metallo-porphyrins was proposed by Adler (Adler et al., 1970), which exploits the reflux reaction of corresponding porphyrin and metallic salt in the solvent of DMF.

In view of the high boiling-point of DMF, we have used the mixed solvent of $CHCl_3/CH_3OH$ instead of DMF for the preparation of the M(DPD) from corresponding deuteroporphyrin derivatives and metallic salts under reflux for about 3 h with a yield of more than 98%.

4.6 Introduction of the axial ligand into M(DPDME)

It is well known that the prosthetic group in all the cysteinato-heme P450 enzymes is formed by the linkage between the sulfur atom of the proximal cysteinyl group and the central iron ion of the heme, i.e., the proximal cysteinyl group acts as an axial ligand of the heme. This arouses the interest of investigations on the axial ligand of the synthetic metallo-porphyrins models. Presently, it has been proved that the character of the axial ligand has great influence on the catalytic property of metallo-porphyrins. For example, Haber (Haber et al., 2000) reported that the yields of the products in the oxidation of cyclooctane catalyzed by manganese porphyrins with molecular oxygen show an almost linear relationship with the electronegativity of the axial ligands.

In this case, for the purpose of examining the effect of the axial ligand of M(DPDME) on their catalytic properties, we have designed and synthesized complexes XM(DPDME) with different axial ligands, where $X=CH_3COO^-$, Cl^-, OH^-, Br^-. According to the method proposed by Ogoshi (Ogoshi et al., 1973), the synthesis of the complex $(CH_3COO^-)Fe(DPDME)$ was performed by the reflux of finely pulverized iron metal and DPDME in glacial acetic acid under nitrogen. Other complexes were prepared by metathesis of $(CH_3COO^-)Fe(DPDME)$ with the corresponding acid, HX (X=Cl, Br) in CH_2Cl_2. The complexes $(OH^-)M(DPDME)$ were prepared by treatment of $(Cl^-)M(DPDME)$ with aqueous KOH in CH_2Cl_2.

5. Investigation on the catalytic property of metallo-deuteroporphyrin derivatives

Metallo-porphyrins are widely used as model compounds simulating the catalytic behavior of P450 in life process. They have been the subject of many investigations as they can be introduced as catalysts in selective oxidation of alkanes with air (or molecular oxygen) to produce alcohol or carbonyl compounds. In contrast to the oxygen atom donors such as iodosobenzene, hydrogen peroxide, organic hydroperoxides, hypochlorites and monopersulphates, air (or molecular oxygen) is an excellent oxidant due to that it is inexpensive, readily available and environmentally-friendly. We have employed M(DPD) as catalysts for cyclohexane oxidation with air in the absence of additives and solvents, finding

that they are efficient catalysts for the selective oxidation of cyclohexane to cyclohexanol and cyclohexanone in the liquid phase under very mild conditions. Moreover, M(DPD) have also shown the similar behavior in the selective oxidation of p-xylene and cyclohexene with air. Herein, we describe the influences of the factors, including reaction temperature, pressure, the substituent on the macrocyclic periphery, the central metal and axial ligand, on the catalytic behavior of M(DPD) in the oxidation of cyclohexane with air, providing a full view of the catalytic property of the catalyst for cyclohexane oxidation.

5.1 Methods of the investigation

The liquid-phase oxidation of cyclohexane was carried out in a 2 L stainless steel autoclave equipped with a mechanical stirrer, an internal thermocouple and cooling coils. In a typical procedure, the experiment was performed for 4.5 h at 150 ℃ under the air pressure of 0.8 MPa. The amount of cyclohexane and catalyst were 1000 mL and 0.02 mmol, respectively. The reaction mixture was sampled by an "on-line" means every 30 min until the yield decreased markedly. The samples and the final products were analyzed by GC-MS.

The results show that all the M(DPD) smoothly catalyze cyclohexane oxidation at the temperature between 110 and 170 ℃ and air pressure between 0.4 and 0.8 MPa in the absence of co-catalysts and solvents. As seen by the GC-MS analysis data, cyclohexanol and cyclohexanone are the predominant products of the reaction, hexanedioic acid and its ester occupying only a very small portion. The result of the comparing experiment shows that cyclohexane can not be converted at the same temperature and pressure in the absence of M(DPD). This proves that M(DPD) act as catalyst during cyclohexane oxidation by air.

Generally, the catalytic property of catalyst is evaluated by some concrete indexes, including the conversion of the substrate, the yield of the designated product, the selectivity of a certain product and the turnover number of the catalyst. They are defined, for example, in the oxidation of cyclohexane as follows:

$$C \% \text{ (conversion)} = \frac{\text{cyclohexane feed} - \text{non reacted cyclohexane}}{\text{cyclohexane feed}} \times 100\%$$

$$Y \% \text{ (yield)} = \frac{\text{cyclohexanol} + \text{cyclohexanone}}{\text{cyclohexane feed}} \times 100\%$$

$$S \% \text{ (selectivity)} = \frac{\text{cyclohexanol} + \text{cyclohexanone}}{\text{cyclohexane feed} - \text{non reacted cyclohexane}} \times 100\%$$

$$TON \text{ (turnover number)} = \frac{\text{cyclohexane feed} - \text{non reacted cyclohexane}}{\text{consumed catalyst}} \times 100\%$$

Furthermore, t/h (time) is defined as the reaction time until the yield reaches the maximum.

5.2 Oxidation of cyclohexane catalyzed by M(DPDME)
5.2.1 Effect of temperature

The effect of reaction temperature on the catalytic property of M(DPDME) was investigated at the range of 110-170 ℃ by using Co(II)(DPDME) as catalyst for cyclohexane oxidation with air in the absence of additives and solvents. The results are shown in Table 1 and Fig.

10. No products were found when the temperature was below 110 ℃. Fig. 10 shows how the yield of cyclohexanol and Cyclohexanone changes with the reaction time in the presence of Co(II)(DPDME) at different reaction temperatures. The reaction rate is evidently influenced by the temperature and the yield increases notably as the temperature rises at the beginning. The higher the temperature is, the shorter is the reaction time that the maximum yield reached. Fig. 10 also indicates that the yield decreases rapidly after reaching the maximum value, especially when the reaction temperature is 170 ℃. This implies that part of the catalyst may be destroyed at high temperature. The group of Chang (Chang & Kuo, 1979) reported the similar result that the meso-unsubstituted metallo-porphyrins are prone to attack at the meso-carbon during oxidation, leading to the degradation of porphyrins. Although the decomposition of catalyst is a problem at somewhat elevated temperatures, well over 11.4% yield has been observed in the oxidation of neat cyclohexane at 170 ℃ catalyzed by Co(II)(DPDME).

T (℃)	C (%)	t (h)	S (%)	$n_{(Alcohol)}/n_{(Ketone)}$	TON
130	15.9	5.5	88.1	1.2	73587
150	18.6	3.5	84.6	1.1	85147
170	18.8	3.0	60.6	1.0	87008

Table 1. Effect of temperature on the oxidation of cyclohexane catalyzed by M(DPDME). Reaction conditions: cyclohexane 1000 mL, Co(II)(DPDME) 0.02 mmol, pressure 0.8 MPa.

From Table 1, it can be found that the selectivity of cyclohexanol and cyclohexanone decreases as the temperature increases. The selectivity is 88.1% at 130 ℃, but rapidly falls to 60.6% at 170 ℃. This suggests that the high temperature might be beneficial to the convertion of alcohols and ketones to acids and esters.
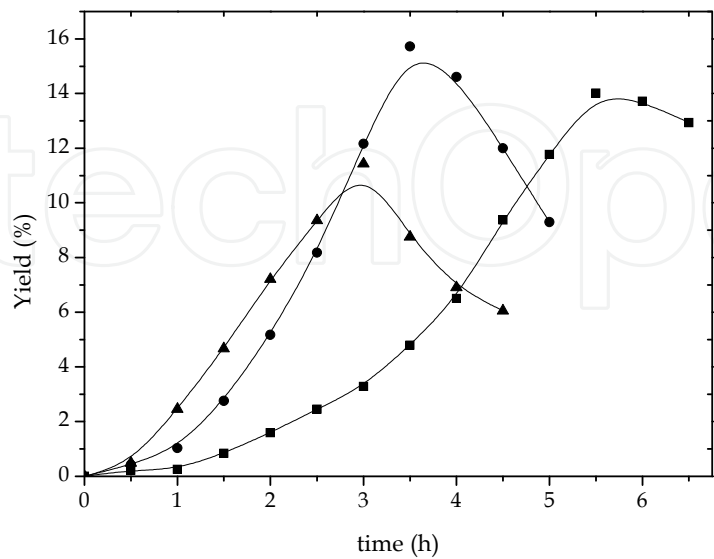

Fig. 10. Effect of temperature on the yield of cyclohexanol and cyclohexanone catalyzed by M(DPDME). temperature 130 ℃ (■), temperature 150 ℃ (●), temperature 170 ℃ (▲).

5.2.2 Effect of pressure

The reaction pressure, which has great influence on the oxidation of cyclohexane, was examined at the range of 0.5-1.0 MPa by using Co(II)(DPDME) as catalyst with air in the absence of additives and solvents, because the oxidation can not occur when the air pressure is below 0.4 MPa. Fig. 11 shows the effect of pressure on the yield of cyclohexanol and cyclohexanone. The pressure has slight influence on the yield and the reaction rate at the beginning of the reaction. The yield increases with the rise of the pressure, and the reaction time that the maximum yield reached is shortened for 2 h when the pressure changes from 0.5 MPa to 0.8 MPa. This implies that the pressure maintains the amount of oxygen in the system; as the pressure rises, the concentration of oxygen increases and favors the oxidation.
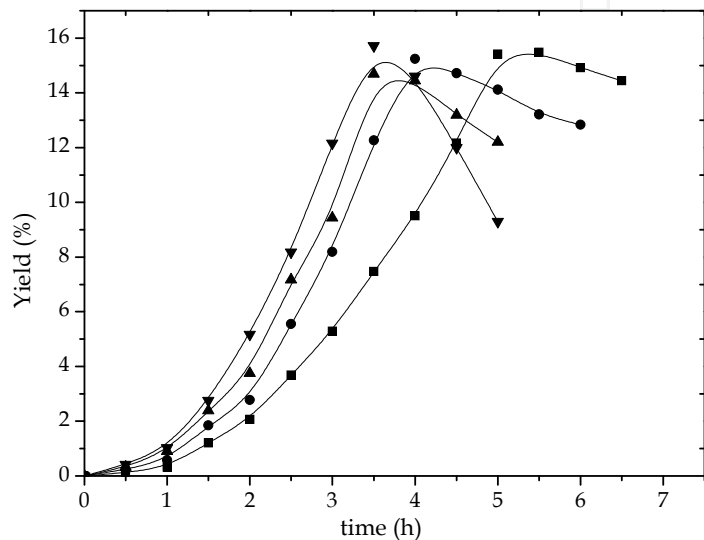
Fig. 11. Effect of pressure on the yield of cyclohexanol and cyclohexanone catalyzed by M(DPDME). Reaction conditions: cyclohexane 1000 mL, Co(II)(DPDME) 0.02 mmol, temperature 150 ℃, pressure 0.5 MPa (■), pressure 0.6 MPa (●), pressure 0.8 MPa (▲), pressure 1.0 MPa (▼).

P (MPa)	C (%)	t (h)	S (%)	$n_{(Alcohol)}/n_{(Ketone)}$	TON
0.5	20.6	5.5	75.1	0.9	95338
0.6	18.9	4.0	80.7	1.0	87471
0.7	17.8	3.5	82.5	1.1	82380
0.8	18.6	3.5	84.6	1.1	85147

Table 2. Effect of pressure on the oxidation of cyclohexane catalyzed by M(DPDME).

As shown in Table 2, the pressure slightly influences the conversion of cyclohexane and the ratio of alcohol to ketone, but the selectivity varies markedly with the pressure. This result is basically associated with the reaction time; as the time is prolonged, some of the produced cyclohexanol and cyclohexanone is over-oxidized to other oxidation products. In this case, part of the alcohol is also oxidized to ketone, resulting in the decrease of the ratio of alcohol to ketone. To sum up, 0.8 Mpa is got as the optimum value of the pressure.

5.2.3 Effect of the central metal

The catalytic properties of Co(II), Ni(II), Cu(II) and Zn(II)-DPDME were studied in order to investigate the effect of the central incorporated metal of DPDME on the oxidation of cyclohexane. Fig. 12 shows how the yield of cyclohexanol and cyclohexanone, the main products of the cyclohexane oxidation catalyzed by the four different complexes, changes with the reaction time and Table 3 indicates the relative catalytic properties of M(DPDME).
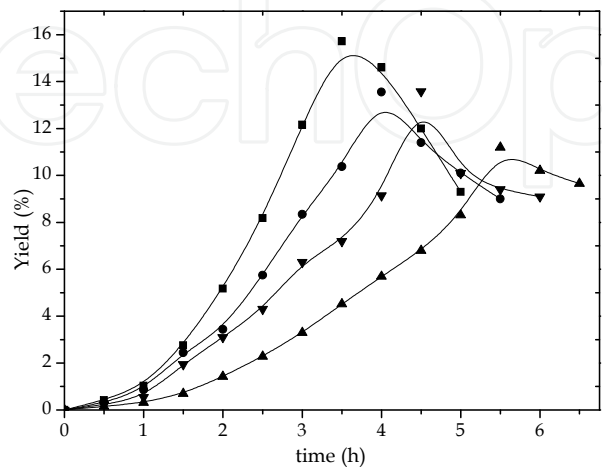

Fig. 12. Effect of the central metal on the yield of cyclohexanol and cyclohexanone catalyzed by M(DPDME). Reaction condition: cyclohexane 1000 mL, catalyst 0.02 mmol, temperature 150 ℃, pressure 0.8 MPa; Co(II)(DPDME) (■), Ni(II) (DPDME) (▼), Cu(II)(DPDME) (●), Zn(II)(DPDME) (▲).

Catalyst	C (%)	T (h)	S (%)	$n_{(Alcohol)}/n_{(Ketone)}$	TON
Co(II)(DPDME)	18.6	3.5	84.6	1.1	85147
Ni(II)(DPDME)	14.5	5.5	77.2	0.8	67107
Cu(II)(DPDME)	16.6	4.0	81.8	1.2	76811
Zn(II)(DPDME)	16.5	4.5	81.3	1.0	76363

Table 3. Effect of the central metal on the oxidation of cyclohexane catalyzed by M(DPDME).

From Fig. 12 one can see that the yield is considerably influenced by the central metal and Co(II)(DPDME) has the highest catalytic activity among the four species. As shown in Table 3, the conversion of cyclohexane and the TON of catalyst vary markedly with the change of the central metal, while the selectivity of the alcohol and ketone changes slightly. Both the conversion and TON reach the maximum values when Co(II)(DPDME) is used as the catalysts for the oxidation. Furthermore, We observed the following order of reactivity: Co(II)>Cu(II)>Zn(II)>Ni(II), identical to that of the series of TMOPP and TCPP (Hu et al., 2008). This phenomenon may be attributed to the fact that the redox potential of Co^{2+}/Co^{3+} is higher than that of other metals, because the catalytic activity of the metallo-pophyrin is influenced by the stability of different valent metal atoms and by the height of electric potential. In agreement with earlier observations (Haber et al., 2003), the catalytic activity of metallo-porphyrins increases as the redox potential goes up. For the cyclohexane oxidation catalyzed by simple Co(II)(DPDME) under the optimum conditions the conversion of cyclohexane, the yield of cyclohexanol and cyclohexanone and the turnover number of the catalyst reach 18.6%, 84.6% and 85147, respectively.

5.2.4 Effect of the axial ligand

For the purpose of examining the effect of the axial ligand of metallo-deuteroporphyrins on the oxidation of cyclohexane, XFe(III)(DPDME) with different axial ligands like Cl⁻, CH₃COO⁻, OH⁻ and Br⁻ were used as catalysts in the oxidation of cyclohexane with air under the pressure of 0.8 Mpa and the temperature of 150 ℃. Table 4 summarizes the data obtained from our catalytic experiments. It can be seen that the conversion of cyclohexane and the ratios of ketone to alcohol vary with the change of the axial ligand, but the values of selectivity are nearly the same. When the axial ligand was acetate, cyclohexane was oxidized with the best conversion of 13.9%. It was observed the following order of reactivity: CH₃COO⁻>OH⁻ >Cl⁻>Br⁻. However, it is interesting to note that in the presence of axial ligand, the conversion of cyclohexane is found to obviously increase. One effect is usually considered in the discussion of the correlation between the catalytic properties of metallo-porphyrins and the electronegativity of axial ligands in oxidation processes. The other has been explained by the assuming that stronger bonds between the metal and the axial ligand make the catalyst more resistant to the oxidative attack.

Axial ligand	C (%)	S (%)	$n_{(Alcohol)}/n_{(Ketone)}$	TON
Cl⁻	12.1	86.7	1.4	55633
CH₃COO⁻	13.9	86.5	0.8	63909
OH⁻	13.3	86.1	1.1	61151
Br⁻	12.6	86.6	1.2	57932

Table 4. Effect of the axial ligand on the oxidation of cyclohexane catalyzed by XFe(III)(DPDME). Reaction conditions: cyclohexane 1000 mL, time 4.0 h, catalyst 0.02 mmol, temperature 150 ℃, pressure 0.8 MPa.

5.3 Oxidation of cyclohexane catalyzed by β-substituted M(DPDME)

We have synthesized a series of β-substisuted M(DPD) from M(DPDME) and used them as catalysts for cyclohexane oxidation with air in the absence of additives and solvents. Fig. 13 and Table 5 show the results of oxidations of cyclohexane in the presence of M[D(β-X)₂PDME], where X = Br, NO₂, I. From Fig. 13 one can see that the maximum yield of cyclohexanol and cyclohexanone for Co(II)[D(β-Br)₂PDME] as catalyst in the oxidation of cyclohexane under the conditions of 150 ℃ and 0.8 MPa reaches over 20%, while the relative value for Co(II)(DPDME) is only 15.6% (Fig. 13). Other metal complexes also show the similar behavior.

The data in Table 5 indicate that all M[D(β-X)₂PDME] complexes have high catalytic activity and selectivity in the oxidation of cyclohexane with air, which implies that the introduction of electron withdrawing groups on the β-positions of M(DPDME) can improve the catalytic properties of M(DPDME). This phenomenon may be attributed to the fact that the redox potential of M(II)/M(III) is improved after the introduction of electron withdrawing groups on the β-positions of M(DPDME). Simultaneously, electron-withdrawing groups of M(DPDME) are resistant to attack by the strong oxidizing mediums. The dinitro complexes exhibit more active than the mono ones, which further prove the above conclusion. As shown in Table 5, the catalytic activity of M[D(β-X)₂PDME] doesn't show a linear relationship with the electronegativity of the β-substituents. For example, though the nitro group is more negative than the bromo group, the conversion of cyclohexane for Co(II)[D(β-NO₂)₂PDME] is lower than that for Co(II)[D(β-Br)₂PDME]. This suggests that the oxidation of cyclohexane with air catalyzed by M[D(β-X)₂PDME] may undergo a "μ-peroxo dimmer"

mechanism. The steric volume of the β-substituents may hinder the formation of the μ-peroxo dimmer intermediate and reduce the activity of M[D(β-X)₂PDME].
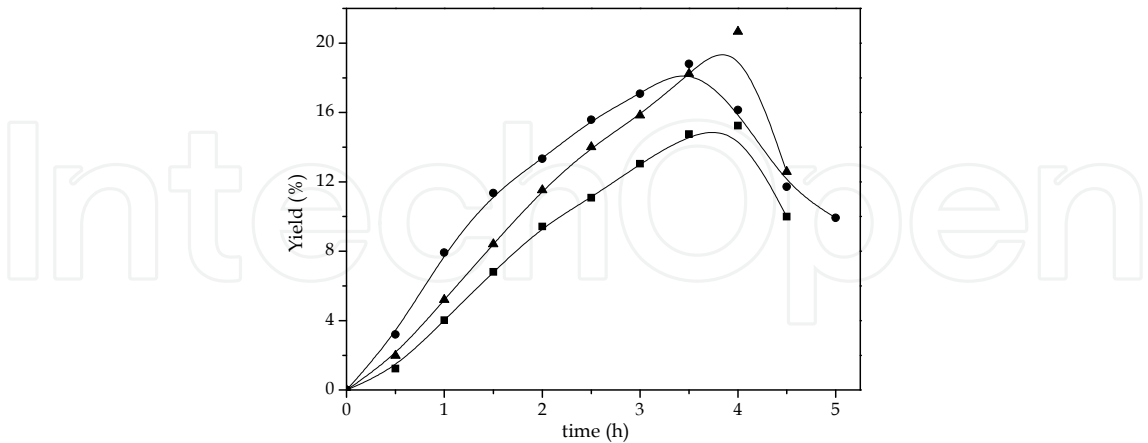

Fig. 13. Yields of cyclohexanol and cyclohexanone in the oxidation of cyclohexane catalyzed by M[D(β-Br)₂PDME]. Reaction conditions: cyclohexene 1000 mL, catalyst 0.02 mmol, temperature 150 ℃, Pressure 0.8 MPa, Co(II)[D(β-Br)₂PDME](▲); ClMn(III)[D(β-Br)₂PDME](●); ClFe(III)[D(β-Br)₂PDME] (■).

Catalyst	t (h)	C (%)	S (%)	$n_{(Alcohol)}/n_{(Ketone)}$	TON
ClFe(III)[D(β-NO₂)PDME]	4.5	12.5	93.4	0.9	57212
ClFe(III)[D(β-NO₂)₂PDME]	4.5	13.9	92.2	1.0	63620
Co(II)[D(β-NO₂)PDME]	3.5	18.8	90.5	1.2	86048
Co(II)[D(β-NO₂)₂PDME]	3.5	19.4	89.6	1.4	88794
ClMn(III)[D(β-NO₂)PDME]	4.0	15.1	91.3	1.2	69113
ClFe(III)[D(β-Br)₂PDME]	4.0	16.60	91.8	1.6	75978
ClMn(III)[D(β-Br)₂PDME]	3.5	23.57	87.6	1.3	107880
Co(II)[D(β-Br)₂PDME]	4.0	21.24	88.5	2.7	97215
Co(II)[D(β-I)₂PDME]	4.0	14.95	91.2	1.8	68426

Table 5. Results of the oxidation of cyclohexane catalyzed by M[D(β-X)₂PDME].

5.4 Oxidation of cyclohexane catalyzed by 13,17-modified metallo-deuteroporphyrin derivates

The oxidation of cyclohexane with air in the absence of additives and solvents was also used as a probe to investigate the catalytic properties of the 13,17-modified M(DPD) complexes, including metallo-deuteroporphyrin diethyl ester [M(DPDEE)], metallo-deuteroporphyrin dipropyl ester [M(DPDPE)], [M(DPDOE)], metallo-13,17-dibromodeuteroporphyrin [M(DBDP)] and metallo-13,17-dichlorodeuteroporphyrin [M(DCDP)]. Table 6 shows the results of oxidations of cyclohexane in the presence of 13,17-modified M(DPD), where M = Co. It may be seen that in the case of cobalt porphyrins, introduction of electron-withdrawing substituents at the 13-/17-position have virtually no effect on the cyclohexane oxide conversion, which is not in agreement with earlier observation for β-substituted M(DPDME)-catalyzed hydrocarbon oxidations. Conversely, the ratio of cyclohexanol to cyclohexanone is extremely sensitive to the influence of electron-withdrawing groups in the

system. It is important to point out that with the same electron-donating substituents, the different activities between the DPDME and other porphyrin diesters may attribute to steric effect, and the bulky groups are not beneficial to form the μ-oxo dimmer.

catalyst	t (h)	C (%)	S (%)	$n_{(Alcohol)}/n_{(Ketone)}$	TON
Co(II)(DPDME)	3.5	18.6	86.4	1.1	85147
Co(II)(DPDEE)	4.0	17.7	83.4	0.9	81026
Co(II)(DPDPE)	4.0	16.1	86.6	1.0	74512
Co(II)(DPDOE)	4.0	15.0	85.8	0.9	69422
Co(II)(DBP)	3.5	17.9	92.1	6.5	82842
Co(II)(DPDNE)	3.0	16.1	86.6	8.0	74512

Table 6. Results of the oxidation of cyclohexane catalyzed by modified 13,17-modified M(DPD). Reaction conditions: cyclohexane 1000 mL, catalyst 0.02 mmol, temperature 150 ℃, pressure 0.8 MPa.

5.5 Oxidation of cyclohexane catalyzed by disulphide-derivatised metallo-deuteroporphyrins

Two types of disulphide-derivatised M(DP) were used as catalysts for the oxidation of cyclohexane with air in the absence of additives and solvents. Fig. 14 shows how the yield of cyclohexanol and cyclohexone changes with time catalyzed by disulphide-derivatised M(DP). Compared with Co(II)DPDME, all the disulphide-derivatised M(DP) complexes exhibit higher catalytic activity. The maximum yield of cyclohexanol and cyclohexanone for Co(II)PDTEP as catalyst in the oxidation of cyclohexane under the conditions of 150 ℃ and 0.8 MPa reaches to 26%. When the centre metal of the disulphide-derivatised M(DP) complexes were different, the yields of alcohol and ketone are dissimilar and the following order of reactivity was observed: Co(II)> ClMn(III)> ClFe(III).
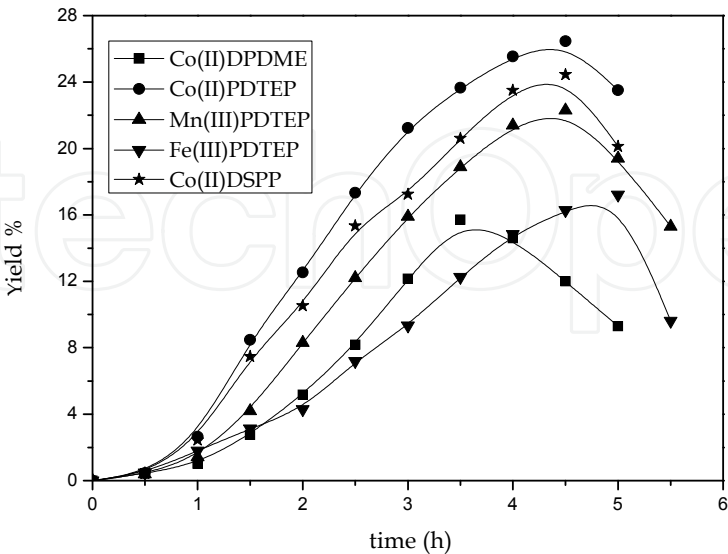

Fig. 14. Yields of cyclohexanol and cyclohexanone in the oxidation of cyclohexane catalyzed by disulphide-derivatised M(DP). Reaction conditions: cyclohexane 1000 mL, catalyst 0.02 mmol, temperature 150 ℃, pressure 0.8 MPa.

The higher catalytic properties of disulphide-derivatised M(DP) complexes suggest that the improvement of the catalytic property should be related to the molecular structure of metallo-porphyrins and the reaction path of the oxidation. On the basis of early research, it's well known that four coordination sites of the iron-ion involved in the active center of cytochrome P-450 is coupled by nitrogen atoms from the porphyrin molecule and the fifth position is occupied by a sulfur atom from the cystine molecule (Fig. 1). In the catalytic cycle proposed for alkane oxidation by dioxygen in the presence of cytochrome P-450, some stages involve the protonation or deprotonation of the sulfur residue. Protonation and deprotonation of the metal-containing species are essential for hydrocarbon oxidations and often constitute the key steps of these processes. For comparing with other experiments in the presence of thiol, thiolate, thioether or disulfide sulfur as donor ligands, the S-S bond in the M(PDTEP) may play a similar role in the oxidation of cyclohexane. The S-S bond is likely to cleave and serves as axial ligand for its central metal ion or other molecules. On the other hand, the disulfide-derivatised metallo-porphyrin may ligate to each other as the ligand by the coordination of S-metal. This is in general agreement with Son and co-workers (Son et al., 1982) studied P-450 adducts with disulfide complexes and found the disulfide·P-450 complex exhibited even closer spectral similarities to the native enzyme; to a certain extent, disulfide coordination to the heme iron of P-450 is significant in its own right.

6. Preliminary exploration on the catalytic mechanism of metallo-deuteroporphyrin derivatives

Currently the main trend of the investigation on hydrocarbon oxidations is the directly selective oxidation of the substrate by molecular oxygen or air under the catalysis of metallo-porphyrin complexes without any co-catalyst or stoichiometric oxidant. To the best of our knowledge, the most reasonably theoretical interpretation for this kind of reactions is the so-called "μ-peroxo dimer intermediate" mechanism, presented by Lyons through the investigation on metallo-TAP complexes as models. As a hypothetical catalytic cycle for the catalytic hydroxylation of alkanes, however, this mechanism finds it difficult to coincide with a lot of experimental phenomena, which gives rise to much controversy.

It is necessary to adopt a new model for the purpose of clarification and improvement of this hypothetical mechanism. Metallo-deuteroporphyrin derivatives, e.g. M(DPDME), with the structure different from metallo-TAP complexes, which have been proved to be efficient catalysts for the directly selective oxidation of cyclohexane by air, become consequently the perfect alternative to the metallo-TAP complex models to attain the above-mentioned goal. Herein, we have taken Co(II)(DPDME) as a model to gain an insight into the catalytic mechanism of M(DPD), by the study on its catalytic property in the oxidation of cyclohexane with air and visible absorption spectral changes by the action of molecular oxygen in the liquid phase.

6.1 Catalytic property of Co(II)(DPDME) in the oxidation of cyclohexane with air

The catalytic oxidation of cyclohexane by air without any co-catalyst or stoichiometric oxidant using Co(II)(TPP), Co(II)[T(p-OCH$_3$)PP], Co(II)[T(p-Cl)PP] and Co(II)(DPDME) is shown in Table 7. Among the three Co(II)-TAP complexes, the conversion of the substrate varied with the character of the substitutent, and Co[T(p-Cl)PP] exhibited the highest

catalytic activity. An order of reactivity were observed as Co(II)[T(p-Cl)PP] > Co(II)(TPP) > Co(II)[T(p-OCH$_3$)PP], which proved that the introduction of electron withdrawing groups on the phene ring of Co(II)(TPP) can improve its catalytic property by reducing the electronic charge on the porphyrin macrocycle and thus enhancing the redox potential of Co(II)/Co(III) (E$_{1/2}$). However, Co(II)(DPDME), which derived from the prosthetic group of cytochrome P450, has no substituents on the meso-position but do has the methyl and propionate groups on the β-position, displayed higher catalytic activity than any of the tested synthetic Co(II)-TAP complexes.

Catalyst	t (h)	C (%)	S (%)	$n_{(Alcohol)}/n_{(Ketone)}$	TON
Co(II)(TPP)	4.5	9.3	90.7	1.1	48100
Co(II) [T(p-OCH$_3$)PP]	4	6.1	90.4	1.3	29676
Co(II) [T(p-Cl)PP]	4	11.0	87.2	1.0	55131
Co(II)(DPDME)	3.5	18.6	84.6	1.1	85147

Table 7. Results of the oxidation catalyzed by different cobalt complexes. Reaction conditions: cyclohexane 1000 mL, catalyst 0.02 mmol, temperature 150 ℃, air pressure 0.8 MPa.

6.2 UV-vis spectroscopic studies of Co(II)(DPDME) by the action of O$_2$ and CH$_3$OH

For elaboration on the catalytic mechanism of metallo-porphyrins in hydrocarbon oxidations, the capture and characterization of the reaction intermediates in the catalytic cycle is undoubtedly the most direct and convincing proof. Because these intermediates are normally very reactive and can be stable only at very low temperature (-30 ℃~-100 ℃), it is difficult to capture them directly. However, as reported in the literature (Ozawa et al., 1994; Mizutani et al., 1990), some analytical approaches by wave spectrum, including UV-vis absorption spectrum, resonance Raman spectroscopy and paramagnetic NMR spectroscopy, may be used to detect and confirm these reactive intermediates indirectly. Hence, we have applied the UV-vis absorption spectroanalysis to the inference of the oxidized intermediates of Co(II)(DPDME) in CHCl$_3$ by the action of O$_2$ and CH$_3$OH.
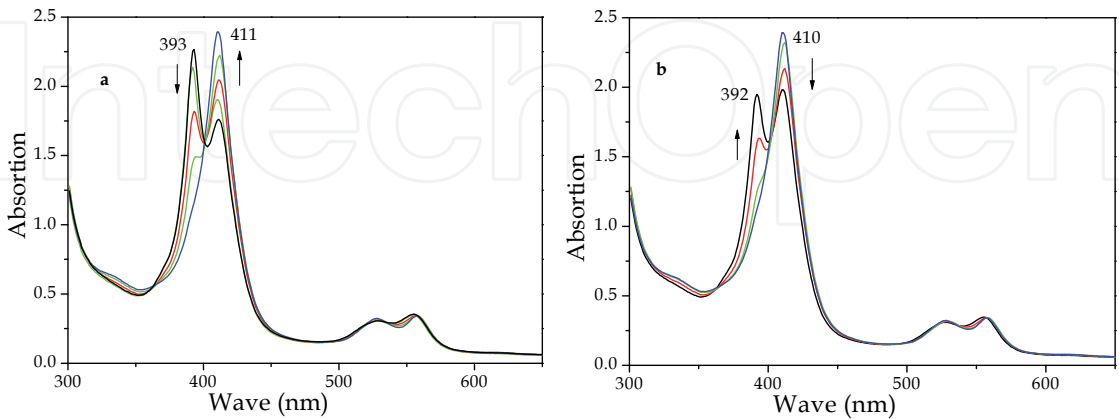

Fig. 15. UV-visible absorption spectral changes of (DPDME)Co^{II} in CHCl$_3$ (0.1 mM) by O$_2$ (a) and by O$_2$ and CH$_3$OH (b). The measurements were made by a UV-vis spectral scanning (300~900 nm) at 25 ℃.

An oxygenated form of (DPDME)Co^{II} (1) was prepared by introduction of O$_2$ into a degassed CHCl$_3$ solution of (DPDME)Co^{II} through a syringe needle at 25 °C. As shown in Fig. 15 (a), the formation of 1 accompanied a decreased intensity of the Soret band and a red shift of the characteristic band for (DPDME)Co^{II}. Upon incorporation of O$_2$ into the (DPDME)Co^{II} solution, the intensity of the 393 nm band decreased and disappeared finally, while in the meantime a new 411 nm band produced, becoming more and more intense. Repetitive evacuation and introduction of N$_2$ did not cause any changes in the spectrum of 1, showing the irreversible formation of 1 under the condition. Thus, 1 is relatively stable at 25 °C under UV concentrations (~10^{-4} M). According to the characteristic features of the μ-oxo-bridged dimer reported (Ozawa et al.; 1994), 1 is considered to be a μ-oxo-bridged dimer, (DPDME)Co^{III}OCo^{III}(DPDME). The formation of 1 suggests a pathway consisting of an adduct [(DPDME)Co^{II}O$_2$, 2] of (DPDME)Co^{II} and O$_2$, a μ-peroxo-bridged dimer [(DPDME)Co^{III}OOCo^{III}(DPDME), 3] and its decomposition product, i.e., an active high-valent cobalt-oxo species [(DPDME)Co^{IV}=O, 4], which reacts with (DPDME)Co^{II} to produce 1.

In order to examine the reactivity of 1, 100 equiv of CH$_3$OH was added to the solution of 1 at 25 °C, resulting in the decrease of the 410 nm band and the increase of the 392 nm band as illustrated in Fig. 15 (b). This phenomenon indicates the formation of (DPDME)Co^{II}. A sample taken from the solution was analyzed by GC/MS, the results confirming that a small amount of HCHO/HCOOH was formed in this transformation. Alternatively, introduction of O$_2$ into the CHCl$_3$ solution of (DPDME)Co^{II} (1 equiv) and CH$_3$OH (100 equiv) at 25 °C yielded the similar results. The formation of (DPDME)Co^{II} and HCHO/HCOOH suggests that 1 might oxidize CH$_3$OH directly. Of course, another possible pathway might be inferred that the oxidation of CH$_3$OH is performed by the active species 4, for the conversion between 1 and 4 is normally reversible.

6.3 Mechanism considerations for the cyclohexane oxidation catalyzed by Co(II)(DPDME)

As indicated above, the β-substituted complex Co(II)(DPDME) has higher catalytic activity than the meso-substituted complex Co(II)(TAP) in the oxidation of cyclohexane by air without any co-catalyst or stoichiometric oxidant.
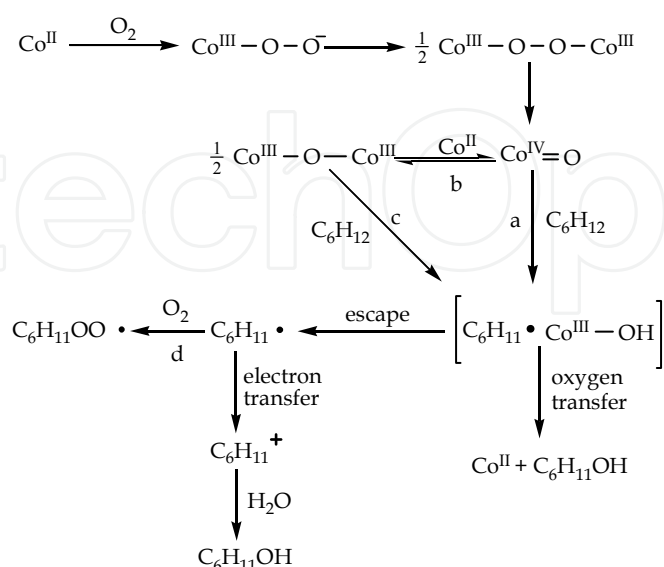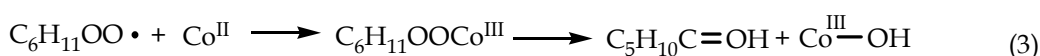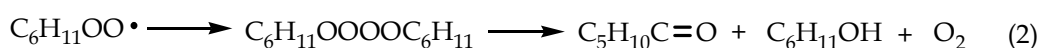

Fig. 16. Scheme for the formation of C$_6$H$_{11}$• in the cyclohexane oxidation catalyzed by Co(II)(DPDME) (the porphyrin ring is omitted).

This implies that the reaction may undergo a different pathway from that proposed for cytochrome P-450. In addition, the results of UV-vis spectroscopic studies of Co(II)(DPDME) by the action of O_2 and CH_3OH in the liquid phase suggest a "μ-peroxo-bridged dimer" mechanism, in which the key reactive intermediate (DPDME)Co^{IV}=O is produced from the decomposition of the μ-peroxo-bridged dimer (DPDME)Co^{III}OOCo^{III}(DPDME).

Consequently, a "μ-peroxo-bridged dimer" mechanism has been inferred for the Co(II)(DPDME) catalyzed oxidation of cyclohexane by air as shown in Fig. 16. By the action of O_2, the complex Co(II)(DPDME) is converted into the μ-peroxo dicobalt(III) complex, which decomposes easily to produce the active Co(IV)-oxo species under the reaction conditions. The very unstable Co(IV)-oxo species is used up as soon as produced. There are two pathways for the conversion of the Co(IV)-oxo species. On the one hand, it may oxidize the substrate directly (pathway a). on the other hand, it may be transformed into the relatively stable μ-oxo dicobalt(III) complex by the action of Co(II)(DPDME) (pathway b). The oxidation of cyclohexane starts with the activation of the C—H bond in the hydrocarbon molecule due to the abstraction of a proton by the axial ligand of the active complex and simultaneous injection of an electron in return. In the case of μ-oxo dicobalt(III) complex, the electron-donating substituents on the macrocyclic porphyrin periphery can weaken the Co–O–Co bond and facilitate splitting this bond (pathway c).

$$C_6H_{11}OO\cdot \longrightarrow C_6H_{11}OOOOC_6H_{11} \longrightarrow C_5H_{10}C{=}O \ + \ C_6H_{11}OH \ + \ O_2 \qquad (2)$$

$$C_6H_{11}OO\cdot \ + \ Co^{II} \longrightarrow C_6H_{11}OOCo^{III} \longrightarrow C_5H_{10}C{=}OH + \overset{III}{Co}{-}OH \qquad (3)$$

The predominant reaction of the escaped radical ($C_6H_{11}\cdot$) is being trapped by dioxygen (pathway d) to give cyclohexyl peroxyl radical ($C_6H_{11}OO\cdot$). Subsequent reactions of the latter radical mainly include dimerisation followed by cleavage to produce cyclohexanol and cyclohexanone (eq. 2), and complexation with Co(II)(DPDME) followed by elimination to give cyclohexanone (eq. 3).

7. Summary and outlook

The catalytic conversion of alkanes selectively to alcohols or carbonyl compounds using dioxygen or air, as a means of converting these available and inexpensive hydrocarbons to valuable oxygenated products, is currently a challenging research topic of greatly strategic significance in the synthetic chemistry as well as in the chemical industry. Accordingly, a series of M(DPD) complexes have been synthesized from the naturally occurring heme as catalysts for the catalytic air-oxidation of cyclohexane without any additives. The investigation on the influences of the factors, including reaction temperature, pressure, the substituent on the macrocyclic periphery, the central metal and axial ligand, on the catalytic property of M(DPD), indicate that they are efficient catalysts for the selective conversion of cyclohexane to cyclohexanol and cyclohexanone in the liquid phase under very mild conditions. In the catalytic air-oxidation of cyclohexane without any additives, Co(II)(DPDME) exhibited higher catalytic activity than any of the tested synthetic Co(II)-TAP complexes, including Co(II)(TPP), Co(II)[T(p-OCH$_3$)PP] and Co(II)[T(p-Cl)PP]. A "μ-peroxo-bridged dimer" mechanism, inferred from the results of UV-vis spectroscopic studies of Co(II)(DPDME) by the action of O_2 and CH_3OH at 25 ℃ in the liquid phase, has been proposed for the Co(II)(DPDME) catalyzed air-oxidation of cyclohexane without any additives.

Although M(DPD) have shown excellent catalytic activity in alkane oxidations, a vast amount of basic investigations still need to be made for their further application. An area for future effort is characterization of the active intermediates in the catalytic cycle of M(DPD). With the help of new approaches such as spectroscopic analysis of cryogenic samples, the realization and exploitation of the photoreductive powers of X-rays, and developments in quantum chemical analysis, the mechanism for the formation and decomposition of these intermediates may be clarified, thus providing a complete and definite pathway for the hydrocarbon oxidation reaction catalyzed by M(DPD). Another investigation is expected to provide theoretical basis for the design and preparation of high-performance metalloporpyrin biomimic catalysts by the mechanistic study on the decomposed ring opening reaction of M(DPD).

8. Acknowledgements

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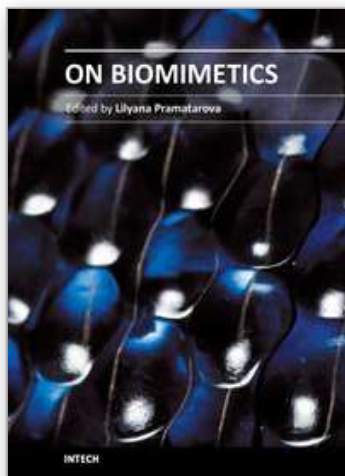
On Biomimetics

Edited by Dr. Lilyana Pramatarova

Bio-mimicry is fundamental idea â€˜How to mimic the Natureâ€™ by various methodologies as well as new ideas or suggestions on the creation of novel materials and functions. This book comprises seven sections on various perspectives of bio-mimicry in our life; Section 1 gives an overview of modeling of biomimetic materials; Section 2 presents a processing and design of biomaterials; Section 3 presents various aspects of design and application of biomimetic polymers and composites are discussed; Section 4 presents a general characterization of biomaterials; Section 5 proposes new examples for biomimetic systems; Section 6 summarizes chapters, concerning cells behavior through mimicry; Section 7 presents various applications of biomimetic materials are presented. Aimed at physicists, chemists and biologists interested in biomineralization, biochemistry, kinetics, solution chemistry. This book is also relevant to engineers and doctors interested in research and construction of biomimetic systems.

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