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Mechanistic studies on metalloporphyrin epoxidation reactions with hydrogen peroxide: evidence for two active oxidative species

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Abstract

New evidence concerning the mechanism of oxidation reactions of alkenes and aromatic compounds catalyzed by metalloporphyrins with H_2O_2 were obtained based on the evaluation of results from structurally different substrates. A systematic change in metalloporphyrin structure and reaction conditions was accomplished with *cis*-cyclooctene as a model. Two maximum performance systems were obtained and then applied to the oxidation of selected substrates, namely 17β-acetoxy-4-androstene, (+)-3-carene, geraniol, and naphthalene. Substantial differences in reaction conversion and product selectivity were found. These systematic studies confirmed the evidence of two different active oxidation species, assigned as the hydroperoxy or oxo ones. The use of more electronegative porphyrins, iron as central metal, and protic solvent and the absence of co-catalyst favor the formation of a hydroperoxy active species. On the other hand, the oxo species was considered to be the main acting entity in the presence of less electronegative porphyrin ligands, manganese as central atom, aprotic solvent, and a buffering substance as co-catalyst. This state of knowledge makes it possible to modulate the reaction selectivity by the selection of the appropriate catalytic system.

Keywords: Metalloporphyrins; Epoxidation; Hydrogen peroxide; Mechanism; Oxo species; Hydroperoxy species

1. Introduction

The oxygenation mechanism operating in cytochrome P_{450} enzymes and in synthetic metalloporphyrin models has been the aim of numerous studies in recent decades [1,2]. However, the putative character of the active oxidants in the catalytic cycles remains of great interest in the elucidation of this topic. The existence of the proposed intermediates can only be indirectly inferred [3–9], and their relative contribution to the complex reactivity of cytochrome P_{450} enzymes and synthetic models is still a controversial matter [10–12].

In the reductive oxygen activation by cytochrome P_{450} (Scheme 1a), three different species have been considered as possible active oxidants: one presenting a nucleophilic character, a peroxy species (**A**) [2,13,14], and two other possible oxidizing intermediates, both with electrophilic character [15], also present in the short cycle of cytochrome P_{450} with H_2O_2 (Scheme 1b). These are a hydroperoxy species (**B**) and an oxo species in a high valence oxidation state (**D**), which can be written as a resonance hybrid of three main forms (Scheme 1, **C**–**E**).

Initially, the oxo species was considered to be the only active intermediate for oxygen transfer [1]. In cytochrome P_{450} monooxygenations, increasing experimental data support the intervention of a hydroperoxy species (**B**) as a second plausible electrophilic oxidant [16]. The action of the oxo or hydroperoxy species seems to be dependent on the structure of the active site in the enzymatic complex, and

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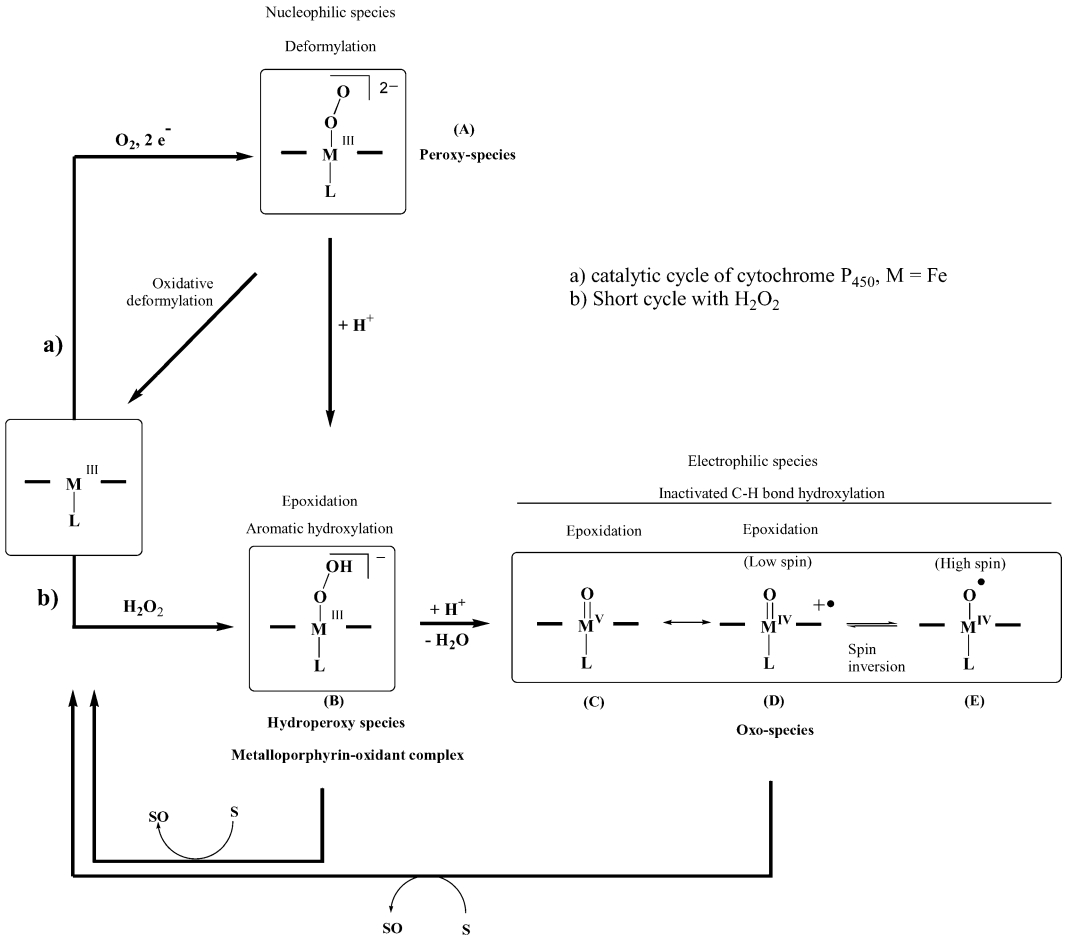


Scheme 1.

pertinent studies were done based on enzyme mutants, where the key amino acids at the active site have been changed [17,18]. An active site structure that prevents the hydroperoxy bond cleavage leads to an enzyme form that is able to catalyze the epoxidation of alkenes and the hydroxylation of aromatics, although it is unable to catalyze the hydroxylation of inactivated C–H bonds in alkanes, confirming the reactivity of a hydroperoxy-ferric state of cytochrome P_{450} [19–22]. The hydroxylation of C–H bonds was attributed to the high valent oxo-species.

Further suggestion of the low reactivity of the hydroperoxyferric state was provided by theoretical calculations by Shaik and co-workers [10], who classified the hydroperoxy species as a "sluggish oxidant" and explained P_{450} reactivity differences with a two-spin-state model (Scheme 1, species **D** and **E**).

The oxo/hydroperoxy debate has been simultaneously extended to synthetic metalloporphyrins as model systems and different oxidants. Similarly to cytochrome P_{450} mechanistic proposals, the involvement of two different active oxidation species was postulated: a metalloporphyrin-oxidant adduct (analogous to **B** in Scheme 1) or a metalloporphyrin oxo species (Scheme 1, **C**–**E**). With the use of different metalloporphyrins in the presence of a series of peroxyacids [23–26], iodosylarenes [27], or *t*-BuOOH [28] for competitive epoxidation of alkenes, evidence of two different oxidizing species was found. When the performance was dependent on the oxidant used, a metalloporphyrin-oxidant adduct was considered to be the active oxidizing species.

Hydrogen peroxide is a particularly interesting oxidant because it leads to intermediates in the catalytic cycle that are identical to the corresponding species observed in cytochrome P_{450} mechanism, namely the hydroperoxy species [29], and, consequently, it can help in the clarification of the enzyme action. Furthermore, hydrogen peroxide is the second oxidant, after oxygen, that is suitable for green chemistry studies. Knowledge of the mechanism of those reactions can help in the design of more efficient and clean catalytic processes.

Recently we reported [30] an efficient catalytic epoxidation system of steroids, with H_2O_2 as oxidant and metalloporphyrins as catalysts. The diastereoselectivity of the products was found to be dependent on the porphyrin structure, central metal ion, reaction conditions, and media. The results were rationalized in terms of the action of an oxo or hydroperoxy species and their different approaches to the substrate. The reaction solvent effect was also studied by Nam and co-workers [31,32], but the assignment of the ac-

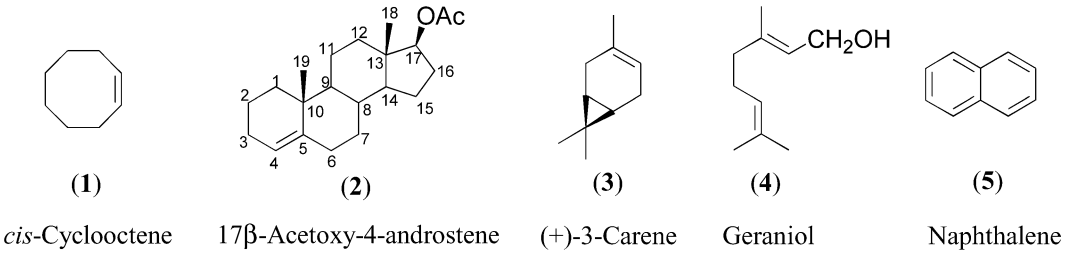


Fig. 1. Probe substrates for mechanistic studies.

tive species is in contradiction to our results [30] and other published findings [33].

In this publication we are extending those results to a systematic study involving manganese and iron porphyrins as catalysts, with different electron-withdrawing groups, in the epoxidation reaction of structurally different substrates (Fig. 1). The solvent and co-catalyst effects were also analyzed, and the stereo-, regio-, and chemoselectivities of the reactions were used as a probe for the nature of the active intermediate, hydroperoxy or oxo species.

2. Experimental

2.1. Catalyst synthesis

The porphyrin free bases (Fig. 2) were prepared according to described procedures [34]. The metallation of the free bases was performed with $MnCl_2$ or $FeCl_2$ according to conventional methods [35,36].

2.2. Catalyst testing

2.2.1. General procedure for oxidations in acetonitrile

In a typical experiment, the *cis*-cyclooctene (**1**) (0.3 mmol), the desired metalloporphyrin (0.5 μmol), and the co-catalyst (0.2 mmol, when used) were dissolved in acetonitrile (2 ml) and stirred at 22 °C. Aqueous hydrogen peroxide (30% w/w) diluted in the reaction solvent (1:10) was added to the reaction mixture in small aliquots every 15 min (150 μl; 0.15 mmol H_2O_2). For the oxidation reaction conditions of substrates **2**–**5**, see Tables 2–5, respectively.

To follow the reaction evolution, aliquots were withdrawn from the reaction mixture and injected directly into the GC injector. The addition of H_2O_2 was stopped when the relative proportions of the compounds remained constant after two successive GC analyses. The reaction time required for each particular substrate is presented in Tables 1–5. Naphthalene oxidation was shown to be a slower reaction, affording only 30% conversion after 60 min of reaction in the presence of Mn(TDCPP)Cl, attaining 91% after 6 h of reaction.

2.2.2. General procedure for oxidations in methanol:dichloromethane

In a typical experiment, the *cis*-cyclooctene (**1**) (0.3 mmol), the desired metalloporphyrin (0.5 μmol), and the co-catalyst (0.2 mmol, when used) were dissolved in 2 ml of methanol:dichloromethane (3:1) and stirred at 22 °C. Aqueous hydrogen peroxide (30% w/w) diluted in the reaction solvent (1:10) was added to the reaction mixture in small aliquots every 15 min (150 μl; 0.15 mmol H_2O_2). For the oxidation reaction conditions of substrates **2**–**5**, see Tables 2–5, respectively. The reaction was monitored as described above.

The reaction oxidation products of *cis*-cyclooctene [37], 17β-acetoxy-4-androstene [30], (+)-3-carene, geraniol [38], and naphthalene [39] were identified by comparison with the GC behavior of authentic samples and characterized by GC-MS, ^{13}C, and ^{1}H NMR techniques.

2.3. Analytical methods

^{1}H and ^{13}C NMR spectra of compounds were acquired in $CDCl_3$ solutions, at 500.13 or 300.13 MHz and at 125.76 or 75.47 MHz, respectively, with Bruker DRX 500 and 300 spectrometers. Mass spectra were collected in a VG AutoSpec Q, operating in FAB^+ (fast atom bombardment) ionization mode at 70 eV, with $CHCl_3$ as solvent and NBA

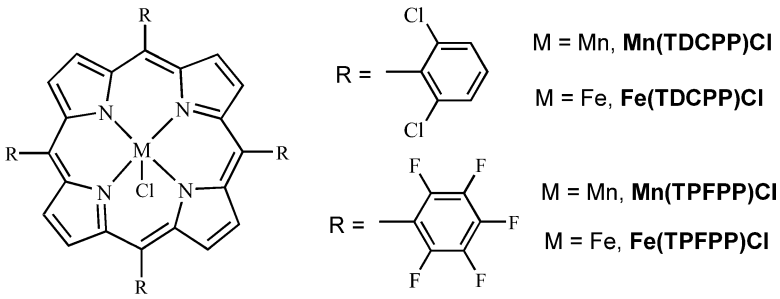


Fig. 2. Metalloporphyrins used in catalytic studies.

Table 1
Epoxidation of *cis*-cyclooctene (**1**) with different catalytic systems, using H_2O_2 as oxidant[a]

Entry	Conditions		Catalyst							
	Solvent	Co-catalyst	Mn				Fe			
			TDCPP (i)		TPFPP (ii)		TDCPP (iii)		TPFPP (iv)	
			Conv.[b]	Stab.[c]	Conv.[b]	Stab.[c]	Conv.[b]	Stab.[c]	Conv.[b]	Stab.[c]
1	CH_3CN	NH_4AcO	**100**	34	**60**	0	**0**	0	**1**	0
2	CH_3CN	–	**0**	100	**0**	70	**1**	8	**12**	0
3	CH_3OH:CH_2Cl_2[d]	NH_4AcO	**2**	89	**5**	26	**1**	7	**1**	0
4	CH_3OH:CH_2Cl_2[d]	–	**1**	76	**1**	43	**10**	6	**82**	3
5	CH_3OH:CH_2Cl_2[d]	Imidazole	**24**[e]	78[e]	–	–	–	–	**1**	2

[a] Reaction conditions: the substrate (0.3 mmol) and the co-catalyst (0.2 mmol, when used) were dissolved in 2 ml of the catalyst solution (0.25 $\mu mol_{cat}/ml$) and stirred at 22 °C; 0.15 mmol of H_2O_2 (150 µl of the 1:10 diluted solution) were added to the reaction mixture every 15 min.
[b] Substrate conversion (%) determined by GC analyses, after 45 min.
[c] Catalyst stability (%) determined by UV–visible spectroscopy, after 45 min.
[d] 3:1.
[e] Conversion after 45 min (when the reaction was left for 24 h, with addition of 1.0 mmol of H_2O_2, the substrate conversion was 98% and the metalloporphyrin stability was 48%).

(3-nitrobenzylic acid) as matrix. The UV–vis spectra were acquired with a Uvikon 922 spectrophotometer. GC/MS analyses were performed with a Finnigan Trace GC/MS (Thermo Quest CE instruments) and helium as the carrier gas (35 cm/s). GC-FID analyses were performed with a Varian Star 3400 CX gas chromatograph and hydrogen as the carrier gas (55 cm/s). In both cases fused silica Supelco capillary columns SPB-5 (30 m × 0.25 mm i.d. × 0.25 µm film thickness) were used.

Preparative thin-layer chromatography (TLC) was carried out on silica gel plates (Riedel–de Haën silica gel 60 DGF_{254}). Hydrogen peroxide (30 wt% solution in water) and acetonitrile were purchased from Riedel–de Haën. All other chemicals and solvents were obtained from commercial sources and used as received or distilled and dried by standard procedures. Light petroleum was the fraction of b.p. 40–60 °C.

3. Results and discussion

Comparative studies of epoxidation reactions with structural different substrates were carried out with the metalloporphyrins shown in Fig. 2 as catalysts.

In many metalloporphyrin-catalyzed oxidation reactions with H_2O_2 the use of a buffering substance as a co-catalyst was demonstrated to be essential for efficient processes [40,41]. It is also considered that such a co-catalyst facilitates oxo species formation, either by acting as an electron-donating axial ligand or by taking part in the dehydration step (Scheme 1, **B**–**C**) [42].

With *cis*-cyclooctene (**1**) as a model substrate, the performance of the four metalloporphyrins (Fig. 2) was studied, with acetonitrile as an aprotic solvent or methanol:dichloromethane (3:1) as a protic solvent mixture, in the presence or in the absence of a co-catalyst. 1,2-Epoxycyclooctane was obtained as the only product; the results are collected in Table 1.

In the presence of acetonitrile and with ammonium acetate as a co-catalyst, 100 and 60% of epoxide were formed with catalysts Mn(TDCPP)Cl and Mn(TPFPP)Cl, respectively (entries 1(i) and 1(ii)). Under the same reaction conditions but with the use of the corresponding iron(III) complexes, no epoxidation was observed (entries 1(iii) and 1(iv)). We also observed that the catalytic systems using manganese complexes are completely inactivated in the absence of ammonium acetate (entries 2(i) and 2(ii)). However, with iron complexes, the system is inactive with TDCPP (entry 2(iii)), but it is able to transfer oxygen to the substrate with the use of Fe(TPFPP)Cl, a strong electron-withdrawing porphyrin complex (12% conversion, entry 2(iv)).

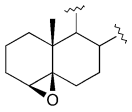
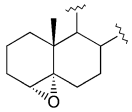
With the use of the mixture methanol:dichloromethane (3:1) and in the presence of ammonium acetate, none of the catalytic systems are able to promote efficiently the epoxidation reaction (entry 3).

When the same solvent is used but in the absence of a co-catalyst, the manganese complexes are inactive, but the iron complexes Fe(TDCPP)Cl and Fe(TPFPP)Cl afford 10 and 82% of 1,2-epoxycyclooctane, respectively (entry 4).

These results indicate that manganese porphyrins reach the maximum activity in an aprotic solvent and in the presence of a co-catalyst (entries 1(i) and 1(ii)); under these conditions, Mn(TDCPP)Cl gives higher substrate conversion than Mn(TPFPP)Cl. On the other hand, iron porphyrins reach their maximum performance in a protic solvent mixture, without a co-catalyst (entries 4(iii) and 4(iv)), and the Fe(TPFPP)Cl is a considerably better catalyst than Fe(TDCPP)Cl.

When manganese porphyrins do not transfer oxygen to the substrate (entries 2(i)–4(i) and 2(ii)–4(ii)), the porphyrins remain almost intact, which suggests the inactivation of the catalysts under the reaction conditions. However, for iron porphyrins the low conversions were always accompanied by high levels of porphyrin degradation (entries 1(iii)–3(iii) and 1(iv)–3(iv)). In all of those reactions the iron

Table 2
Oxidation of 17β-acetoxy-4-androstene (**2**) with different catalytic systems, using H_2O_2 or *m*-CPBA as oxidants[a,b,h]

Entry	Catalyst	Solvent	Co-catalyst	Conversion (%)[c]	Selectivity (%)[c]		
					 **2a**	 **2b**	Allylic oxidation
1[d]	Mn(TDCPP)Cl	CH_3CN:CH_2Cl_2[e]	NH_4AcO	88	56	20	18
2[d]	Mn(TPFPP)Cl	CH_3CN:CH_2Cl_2[e]	NH_4AcO	61	43	37	19
3	Fe(TDCPP)Cl	CH_3OH:CH_2Cl_2[f]	–	< 4	–[g]	–[g]	–[g]
4[d]	Fe(TPFPP)Cl	CH_3OH:CH_2Cl_2[f]	–	100	33	57	0
5[d]	*m*-CPBA[h]	CH_2Cl_2	–	99	33	51	5

[a] Reaction conditions: the substrate (0.03 mmol) and ammonium acetate (0.08 mmol, when used) were dissolved in 2 ml of the catalyst solution (0.1 µmol of catalyst/ml) and stirred at 22 °C; 0.015 mmol of H_2O_2 (30 µl of a 1:20 diluted solution) were added to the reaction mixture every 15 min.
[b] Complete characterization of the reaction products in reference [30].
[c] Substrate conversion and product selectivity determined by ^{1}H NMR spectroscopy of the reaction mixtures, after 60 min.
[d] Results from [30].
[e] 1:1.
[f] 3:1.
[g] Quantity of products too low for quantification.
[h] Reaction carried out without catalyst and *m*-CPBA as oxidant.

porphyrin stability was lower than 10%, which indicates a strong degradation of the catalyst.

The inactivation of Mn(TDCPP)Cl in methanol is partially eliminated when ammonium acetate is replaced by imidazole as an axial ligand (entry 5(i)); the activity of the manganese porphyrin increases and a conversion of 24% is obtained after 45 min of reaction. With a reaction time of 24 h and after the addition of 1.0 mmol of H_2O_2, a 98% yield of epoxide is obtained. Imidazole, as a stronger electron-donating ligand, can replace methanol as an axial ligand and reactivate the catalyst [43], establishing a reaction equilibrium that can be responsible for the longer reaction times.

These significant differences in the *cis*-cyclooctene epoxidation reaction, depending on the metalloporphyrin structure and on the reaction medium, suggest the involvement of different active species in the reaction mechanism. These results prompted us to extend such studies to other substrates in order to corroborate that mechanistic proposal.

Recently we have reported an efficient catalytic system for the promotion of the epoxidation of different steroid compounds with the type of catalyst and reaction conditions used [30]. Remarkable differences in the diastereoselectivity of the resulting epoxides were obtained. In the present paper we report further studies of steroid oxidation with the most active catalytic systems described in Table 1 for the *cis*-cyclooctene oxidation.

To promote the epoxidation of 17β-acetoxy-4-androstene (**2**), we used the manganese complexes in acetonitrile in the presence of ammonium acetate and the iron complexes in methanol:dichloromethane without the co-catalyst. The oxidation results are collected in Table 2; the main products obtained have been previously characterized as 17β-acetoxy-4,5β-epoxyandrostane (**2a**) and 17β-acetoxy-4,5α-epoxyandrostane (**2b**). The products resulting from oxidation at the allylic position were identified as 17β-acetoxy-4-androsten-3-ol, 17β-acetoxy-4-androstene-3-one, and 17β-acetoxy-4,5-epoxyandrostan-3-ol [30].

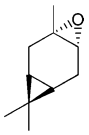
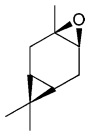
In the epoxidation of **2** with Mn(TDCPP)Cl as a catalyst, the β-epoxide was preferentially obtained (56% selectivity against 20% for the α-epoxide, entry 1, Table 2). With Mn(TPFPP)Cl a significant decrease in β-epoxide (43%) was observed with a concomitant increase in the amount of α-epoxide (37%, entry 2, Table 2).

The Fe(TDCPP)Cl shows a very low activity (entry 3, Table 2), but with Fe(TPFPP)Cl full conversion is obtained and the α-epoxide is preferentially formed (57% selectivity against 33% for the β-epoxide, entry 4, Table 2). This last result is in agreement with the epoxidation reaction promoted by *m*-CPBA (entry 5, Table 2), suggesting the involvement of a metallo-hydroperoxide species.

The stereochemical hindrance of the substrate and different intervening species can control the approach of the metalloporphyrin complex to the substrate from either the α or β side. Despite the presence of the 19-methyl group in the β-face of the steroid nucleus, it is well established that Δ^4-steroids present the most stable conformation in a partially folded structure along the A and B ring fusion, consequently leaving the α-face more hindered [44].

The porphyrin oxo species (analogous to **C** in Scheme 1) has the active oxygen atom very near the large porphyrin plane, which makes difficult the access to the α-face, where the double bond has a tight access; consequently, the oxo species should preferentially produce the β-epoxide. However, the metalloporphyrin-hydroperoxy complex has a peripheral atom bridge, analogous to *m*-CPBA, that can approach the double bond from both sides; in this case the presence of the 19β-methyl group can determine the preference for the α-epoxide.

Table 3
Oxidation of (+)-3-carene (**3**) with different catalytic systems, using H_2O_2 as oxidant[a,b]

Entry	Catalyst	Solvent	Co-catalyst	Conversion (%)[c]	Selectivity (%)[c]			α/β **3a**/**3b**
					 **3a**	 **3b**	Allylic oxidation	
1	Mn(TDCPP)Cl	CH_3CN	NH_4AcO	98	34	20	46	1.7
2	Mn(TPFPP)Cl	CH_3CN	NH_4AcO	34	42	14	44	3
3	Fe(TPFPP)Cl	CH_3OH:CH_2Cl_2[d]	–	98	84	8	6	10.5

[a] Reaction conditions: the substrate (0.3 mmol) and ammonium acetate (0.2 mmol, when used) were dissolved in 2 ml of the catalyst solution (0.25 μmol of catalyst/ml) and stirred at 22 °C, protected from light; 0.15 mmol of H_2O_2 (150 μl of the 1:10 diluted solution) were added to the reaction mixture every 15 min.
[b] Complete characterization of the reaction products in reference [38].
[c] Reaction conversion and product selectivity determined by GC analyses after 60 min of reaction.
[d] 3:1.

The different β/α epoxide ratio is new evidence for the involvement of different catalytic active species in the oxygen transfer mechanism. Mn(TDCPP)Cl catalyst can act through an oxo-species mechanism, and Fe(TPFPP)Cl catalyst through a hydroperoxy-species one.

In previous papers our group described the oxidation of (+)-3-carene (**3**), geraniol (**4**) [38], and, more recently, naphthalene (**5**) [39] in the presence of several manganese(III) porphyrins. Here we extend those studies to the systems 1(i), 1(ii), 4(iii), and 4(iv) described in Table 1, in order to obtain evidence for the mechanistic proposal. The identification and characterization of the oxidation products are described in those previous publications.

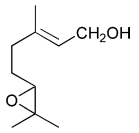
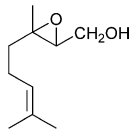
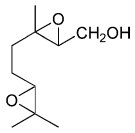
The oxidation reaction of (+)-3-carene (**3**) can lead to α-epoxycarane (**3a**), β-epoxycarane (**3b**), and allylic oxidation products (Table 3). Again we observe a remarkable difference in the diastereoselectivity of the products depending on the catalyst and reaction conditions. The system Mn(TDCPP)Cl/acetonitrile/co-catalyst gives a mixture of α and β epoxides (34:20), along with other products resulting from allylic oxidation (46%, entry 1, Table 3). When Mn(TPFPP)Cl is used, the amount of α-epoxide increases (entry 2). On the other hand, Fe(TPFPP)Cl in methanol:dichloromethane gives 98% conversion with 84% selectivity for the α-epoxide, and only 6% of allylic oxidation was observed (entry 4, Table 3).

These results also emphasize the contribution of the oxidant species formed. In fact, the manganese porphyrins in an aprotic solvent, and in the presence of a co-catalyst, provide a high reactive oxidation intermediate capable of both α- and β-epoxidation and allylic hydroxylation, indicative of the involvement of an oxo species. On the other hand, the presence of iron, several fluorine atoms in the porphyrin ring, and a protic solvent seems to favor the existence of an active oxidizing species, which is highly selective for α-epoxycarane, similar to the results obtained with *m*-CPBA [38], suggesting once more the involvement of a metallo-hydroperoxide species. It is worth noting that the same diastereoselectivity was observed for the metallo-peroxo species proposed for the tungstoborate-catalyzed epoxidation reactions with H_2O_2 [45].

Geraniol (**4**) is another interesting substrate that can be used to prove the nature of active intermediates, because of the presence of two competitive double bonds. The results of the oxidation of this monoterpene are presented in Table 4. With manganese porphyrins the 6,7-epoxygeraniol (**4a**) is the main product, followed by 2,3-epoxygeraniol (**4b**) and 2,3:6,7-diepoxygeraniol (**4c**) (entries 1 and 2, Table 4). This reactivity can be attributed to a highly active oxo species. The catalytic epoxidation of **4** in the presence of Fe(TPFPP)Cl gives full conversion with 98% selectivity for the 6,7-epoxide (entry 3, Table 4). With this system, the epoxidation takes place exclusively at the more nucleophilic double bond. Once more this is a typical behavior of a hydroperoxy species, which reacts faster with more electron-rich olefins [46].

The oxidation of polynuclear aromatic hydrocarbons by hydrogen peroxide in acetic acid provides a clean and often efficient process for the preparation of 1,4-quinones [47,48]. The reaction proceeds by double hydroxylation of the aromatic ring followed by an easy oxidation of the hydroquinone stage to the corresponding quinone. The epoxidation of polynuclear aromatic hydrocarbons was demonstrated to be a particularly difficult process, and the oxidation to the diepoxides was only obtained with peroxyacids in very low yields [49,50]. Recently we reported an efficient process for producing high yields of diepoxides from naphthalene and anthracene, with hydrogen peroxide as oxidant and manganese porphyrins as catalysts [39]. We have also observed that changes in the porphyrin structure lead to different product selectivities. Two reaction pathways were assigned, namely the direct epoxidation of the aromatic ring, leading to diepoxides (Scheme 2, pathway 1), or the hydroxylation of the aromatic ring, leading, in last instance, to quinones (Scheme 2, pathway 2).

Table 4
Oxidation of geraniol (**4**) with different catalytic systems, using H_2O_2 as oxidant[a,b]

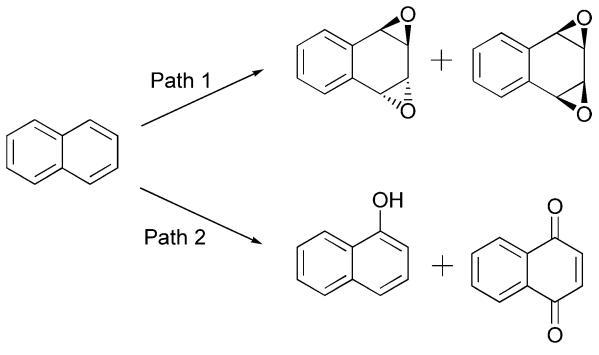
Entry	Catalyst	Solvent	Co-catalyst	Conversion (%)[c]	Selectivity (%)[c]		
					 **4a**	 **4b**	 **4c**
1	Mn(TDCPP)Cl	CH_3CN	NH_4AcO	94	55	7	32
2	Mn(TPFPP)Cl	CH_3CN	NH_4AcO	33	70	23	7
3	Fe(TPFPP)Cl	CH_3OH:CH_2Cl_2[d]	–	100	98	1	1

[a] Reaction conditions: the substrate (0.3 mmol) and ammonium acetate (0.2 mmol, when used) were dissolved in 2 ml of the catalyst solution (0.25 μmol of catalyst/ml) and stirred at 22 °C, protected from light; 0.15 mmol of H_2O_2 (150 μl of the 1:10 diluted solution) were added to the reaction mixture every 15 min.
[b] Complete characterization of the reaction products in reference [38].
[c] Reaction conversion and product selectivity determined by GC analyses after 60 min of reaction.
[d] 3:1

Table 5
Oxidation of naphthalene (**5**) with different catalytic systems, using H_2O_2 as oxidant[a,b]

Entry	Catalyst	Solvent	Co-catalyst	Conversion (%)[c]	Selectivity (%)[c]	
					Pathway 1	Pathway 2
1[d]	Mn(TDCPP)Cl	CH_3CN	NH_4AcO	91	88	12
2[d]	Mn(TPFPP)Cl	CH_3CN	NH_4AcO	44	22	78
3	Fe(TDCPP)Cl	CH_3OH:CH_2Cl_2[e]	–	0	–	–
4	Fe(TPFPP)Cl	CH_3OH:CH_2Cl_2[e]	–	34	0	100

[a] Reaction conditions: the substrate (0.3 mmol), the catalyst (1 μmol) and ammonium acetate (0.2 mmol, when used) were stirred in the solvent at 22 °C and protected from light; 0.15 mmol of H_2O_2 (37.5 μl of the 2:5 diluted solution) were added to the reaction mixture every 15 min.
[b] Complete characterization of the reaction products in reference [39].
[c] Substrate conversion and product selectivity determined by ^1H NMR spectroscopy of the total reaction mixtures after 6 h of reaction.
[d] Results from [39].
[e] 3:1.



Scheme 2.

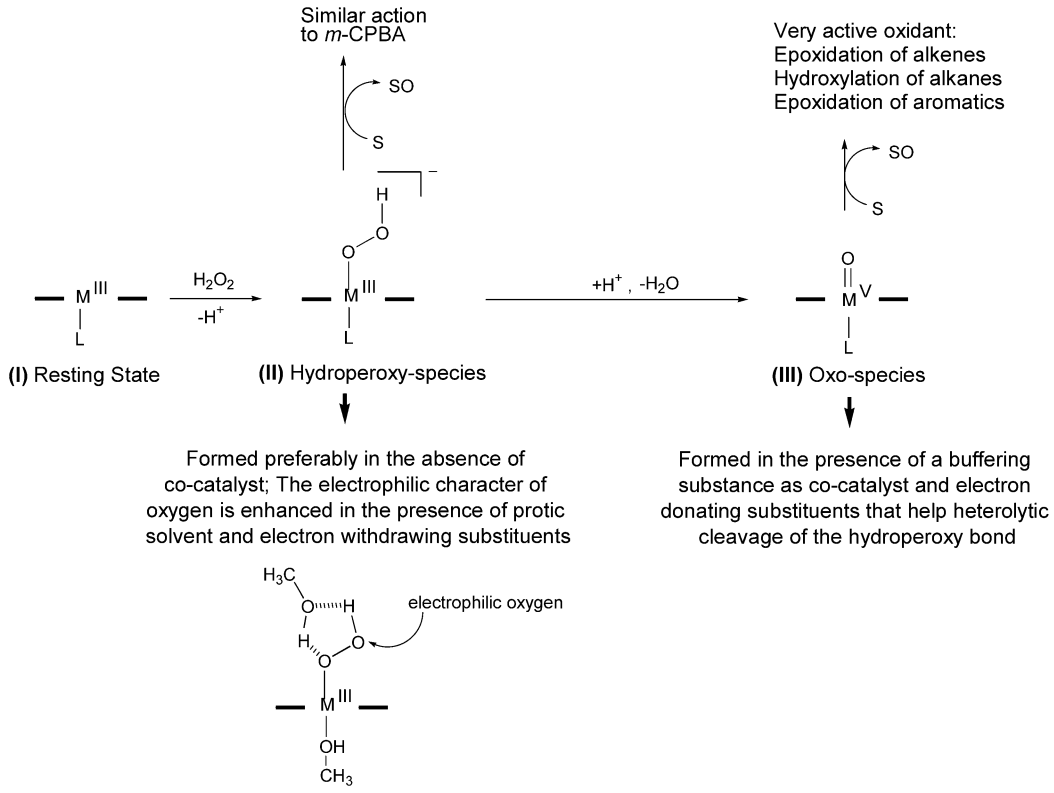
Extending the oxidation of naphthalene by using iron porphyrins in protic solvent as catalysts (Table 5), we observed only the formation of 1-naphthols and 1,4-naphthoquinones, which corresponds to the exclusive accomplishment of pathway 2.

Diepoxidation of polynuclear aromatic hydrocarbons in vivo is considered to occur by intervention of cytochrome P_{450} enzymes, possibly by the involvement of an oxo species. The same mechanism is probably occurring with Mn(TDCPP)Cl in the presence of CH_3CN and NH_4AcO (total selectivity of 88% for *cis*- and *trans*-diepoxides, entry 1, Table 5). When Mn(TPFPP)Cl catalyst is used (entry 2, Table 5), an almost opposite result is obtained, which may indicate the main involvement of the hydroperoxy species.

For the Fe(TPFPP)Cl catalyst in methanol:dichloromethane, only 1-naphthol and 1,4-naphtoquinone are obtained. This result is in agreement with a hydroperoxy oxidizing species, which probably is ineffective in aromatic epoxidation reactions, but it is capable of aromatic hydroxylation, by analogy to other peroxy oxidants used for aromatic compounds [48].

The results obtained so far can be understood if they are based on the different actions of two possible intermediates: a metalloporphyrin-hydrogen peroxide complex or a high-valence oxo species. These two species have different formation propensities and different reactivities in the different catalytic systems studied; these results are summarized in Scheme 3.

Considering our results and the data from the literature [27], we assume the initial formation, in all of these catalytic systems, of a hydroperoxy-species (**II**) as a consequence of the addition of H_2O_2 to the resting state of the metalloporphyrin (**I**). The hydroperoxy species can transfer



Scheme 3.

oxygen to the substrate or can evolve to a higher oxidation state forming the oxo species (**III**), a high active oxidizing intermediate. The reaction conditions, the electron-withdrawing characteristics of the porphyrin nucleus and the electronegativity of the metal (1.83 for Fe and 1.55 for Mn), determine the preferential formation of (**II**) or (**III**) as the oxidizing intermediate and its inherent activity.

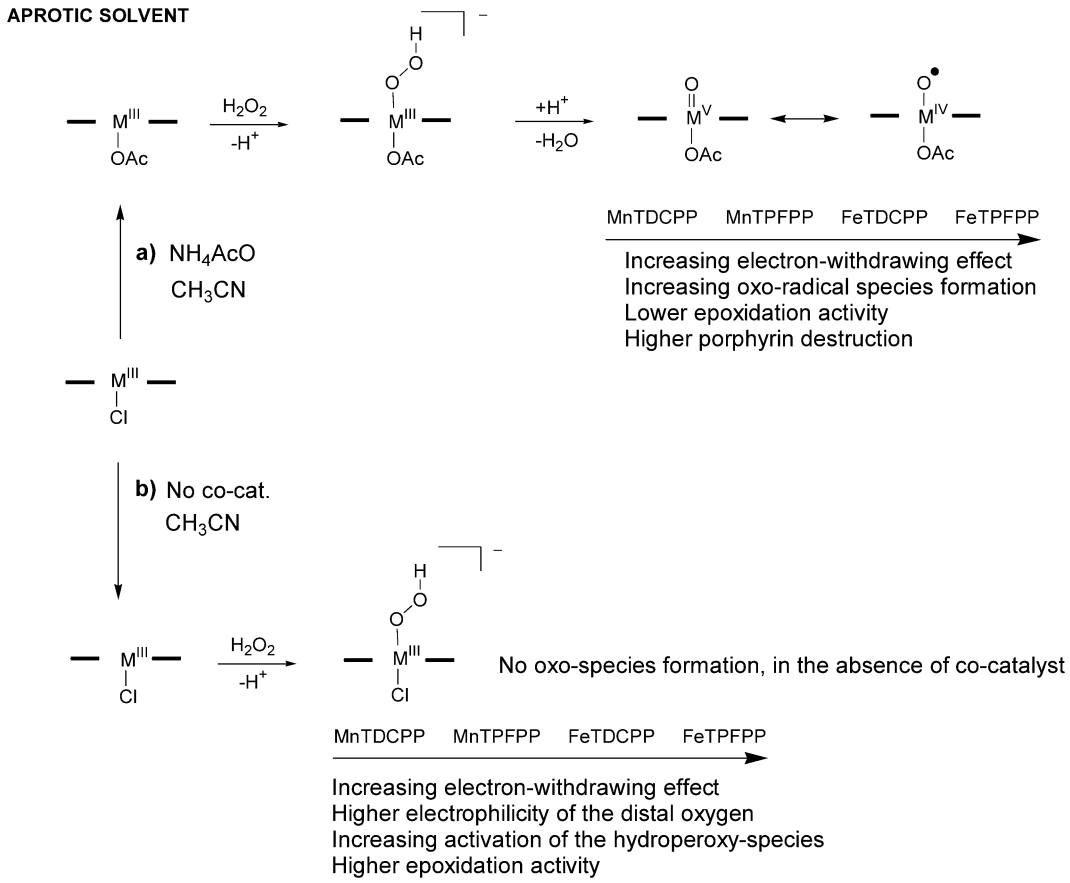
The reactivity of Mn(TDCPP)Cl catalyst in the presence of CH_3CN and ammonium acetate can be assigned to an oxo species (Scheme 3, **III**) as the oxidizing species, based on the high activity of this system (1(i), Table 1), the capability for allylic hydroxylation in addition to epoxidation (entry 1, Table 3), and the preferential formation of 17β-acetoxy-4,5β-epoxyandrostane (entry 1, Table 2) and of naphthalene dioxides (entry 1, Table 5). However, the formation and reactivity of this oxidizing species can be sensitive to various factors.

As can be seen in Table 1, entry 1, the increasing electron-withdrawing capabilities of the metalloporphyrin are responsible for its higher destruction and lower activity levels. The increasing contribution of the radical form of the oxo species probably must be considered (Scheme 4a), since it could explain the lower epoxidation yields and higher porphyrin degradation.

In the absence of ammonium acetate, the Mn(TDCPP)Cl catalyst is inactive (Table 1, entry 2(i)), and 100% porphyrin stability is observed at the end of reaction. This result is probably due to the lower electrophilic character of the hydroperoxy species formed, which is unable to transfer oxygen (Scheme 4b). For a more electronegative catalyst, the hydroperoxy species formed [HOO-Fe(TPFPP)Cl] is more active for oxygen transfer to the olefins (Table 1, entry 2(iv)), because of the presence of strong electron-withdrawing fluorine atoms and iron as a central metal.

In the presence of methanol, Mn(TDCPP)Cl is also inactive, even in the presence of ammonium acetate (high porphyrin stability was observed; see 3(i) and 4(i), Table 1). We have also seen that methanol is an inactivating solvent for the catalytic system, and not dichloromethane. In two reactions carried out in conditions 1(i) of Table 1, some drops of dichloromethane or methanol were added. Upon the addition of dichloromethane, the system reproduced the results presented. However, the addition of methanol lowered the conversion to 4%. As considered in Scheme 5, the binding of methanol to the lower electron-withdrawing metalloporphyrin can prevent the oxo-species formation, even in the presence of ammonium acetate (Scheme 5a). The lack of activity of the HOO-Mn(TDCPP) species has already been mentioned. It is worth noting that Gross et al. also observed methanol inactivation catalysis by the electron-donating Fe complexes of 5,10,15,20-tetrakis(mesityl)porphyrin [51].

For the catalytic system composed of Fe(TPFPP)Cl, protic solvent, and no co-catalyst (Table 1, 4(iv)), we propose the exclusive formation of the hydroperoxy species, as can be indicated by (a) the same diastereoselectivity obtained in the epoxidation of Δ^4-steroids with *m*-CPBA (Table 2, entry 5), (b) highly selective α-epoxidation of (+)-3-carene (Table 3, entry 4), (c) exclusive epoxidation at the more nu-



Scheme 4.

cleophilic 6,7-double bond of geraniol (Table 4, entry 4), and (d) the exclusive accomplishment of pathway 2 in the oxidation of naphthalene (Table 5, entry 4). However, methanol seems to have an important role, as observed in the oxidation of *cis*-cyclooctene (Table 1, entries 2(iv) and 4(iv)), where the conversion increased from 12% in CH_3CN to 82% in CH_3OH:CH_2Cl_2. Such behavior is in accordance with the results obtained in the activation of hydrogen peroxide by trifluorinated alcohols [52] and can be justified by the higher electrophilicity of the hydroperoxy oxygen (Scheme 5b).

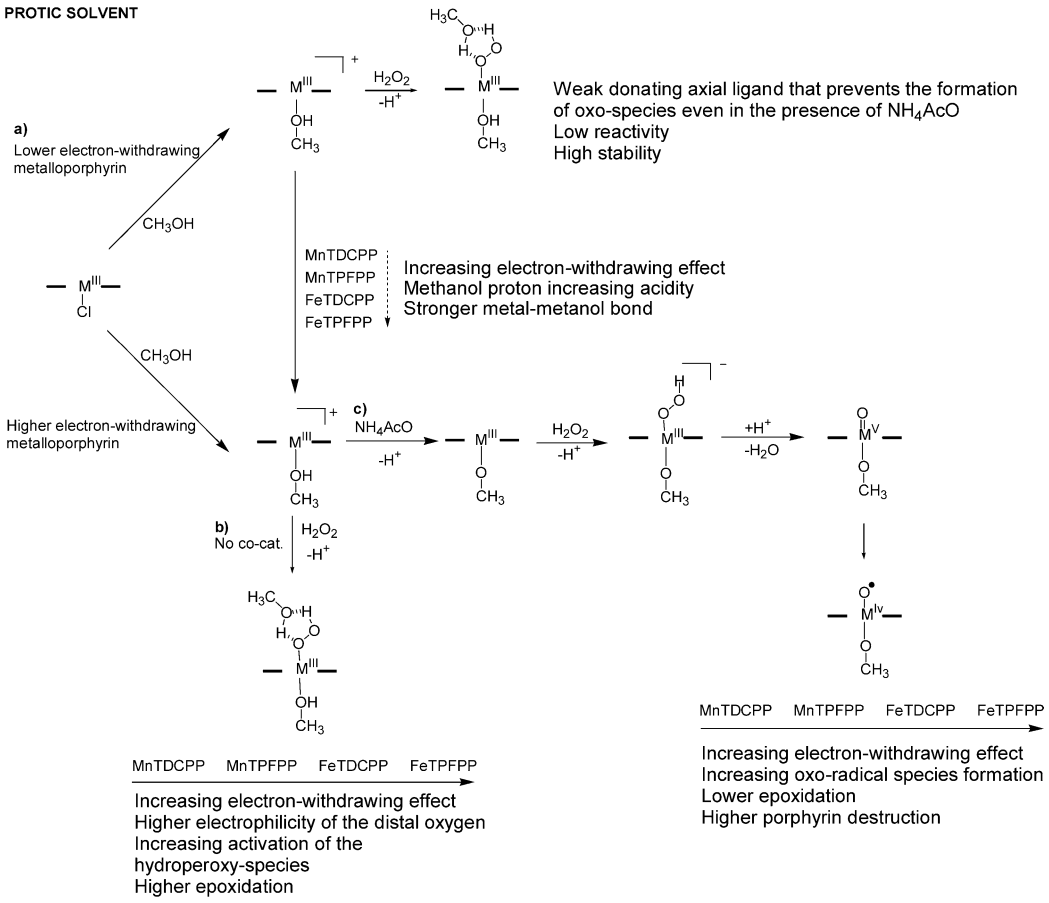
It remains to justify the different stability of MnTDCPP and FeTPFPP in methanol and in the presence of ammonium acetate (Table 1, entries 3(i) and 3(iv)). In the presence of FeTPFPP (more electronegative than MnTDCPP), the acetate ion is able to remove a proton from the methanol complex, and the metoxy group as an axial ligand is now able to favor the oxo species formation (Scheme 5c).

From a comparison of Mn(TDCPP)Cl with Mn(TPFPP)Cl in the same reaction conditions, it can be seen that the latter system leads to lower yields of 1,2-epoxycyclooctane, lower selectivity for β-epoxycarane, and higher selectivity for 6,7-epoxygeraniol, as well as higher levels for pathway 2 in the naphthalene oxidation. This behavior approaches that of system 4(iv) (Table 1) and can be understood by consideration of the electron-withdrawing capabilities of Mn(TPFPP)Cl relative to Mn(TDCPP)Cl and suggests a more difficult formation of the oxo species [O=Mn(TPFPP)OAc]. Consequently, higher amounts of metalloporphyrin can stay in the hydroperoxy form [HOO–Mn(TPFPP)OAc], which can be active for electrophilic oxidation because of its more electron-withdrawing porphyrin ring. As a result, the catalytic behavior of Mn(TPFPP)Cl could be explained by the partial action of either an oxo or a hydroperoxy species.

Another hypothesis to consider is also based in the higher electronegativity of Mn(TPFPP)Cl relative to Mn(TDCPP)Cl, which could dictate the presence of the oxo species in the high spin state [Mn(IV)–O·] to some degree [53]. This species could be responsible for the changes in the reactivity of Mn(TPFPP)Cl compared with Mn(TDCPP)Cl: lower epoxidation yields and higher levels of aromatic hydroxylation in naphthalene oxidation (Table 5, entry 2).

Further confirmation of a two-mechanism possibility is obtained by visible spectrophotometry of the systems 1(i), 1(ii), 4(iii), and 4(iv) (Table 1). To the initial catalytic system in the absence of substrate (Fig. 3a), a 15 µmol aliquot of H_2O_2 was added and UV–visible spectra were taken after 1 min (Fig. 3b); one drop of *cis*-cyclooctene was then added to the spectrophotometer cell (Fig. 3c). The results are presented in Fig. 3.

In the first two experiments, with the use of manganese complexes of TDCPP and TPFPP, a decrease in the Soret band at 478 nm is observed, with a concomitant increase



Scheme 5.

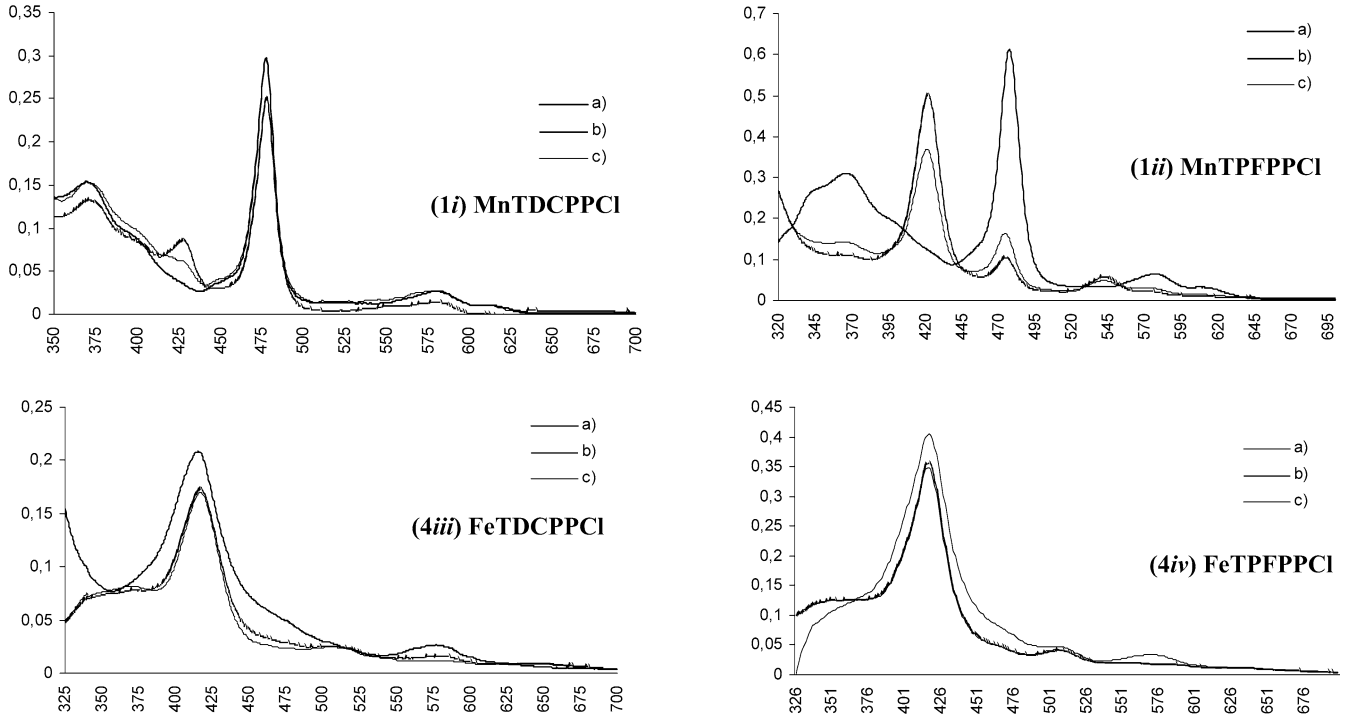


Fig. 3. Evolution of UV–visible spectra of catalytic reactions corresponding to entries 1(i), 1(ii), 4(iii), and 4(iv) of Table 1: (a) at the beginning of the reaction in the absence of substrate and H_2O_2; (b) after the addition of H_2O_2; (c) after the addition of one drop of *cis*-cyclooctene.

in a band at near 425 nm (429 and 423 nm, respectively, Fig. 3b). The addition of one drop of substrate (Fig. 3c) causes a decrease in the band near 425 nm and an increase in the porphyrin Soret band. The GC control of these reactions revealed the formation of the epoxide, which is indicative of the presence of an active oxidation species.

On the other side, for reaction conditions described in experiment 4(iii) [Fe(TDCPP)Cl, in CH_3OH:CH_2Cl_2, without a co-catalyst], a short band at ∼370 nm is observed, with a concomitant decrease of the Soret band, upon the addition of hydrogen peroxide, indicating a very low involvement of an oxo mechanism.

The addition of hydrogen peroxide to the system [Fe(TPFPP)Cl/CH_3OH:CH_2Cl_2/no co-catalyst] causes a decrease in the Soret band, and, upon the addition of substrate, no changes in the visible spectra were observed, and a complete absence of the oxo-mechanism can be inferred for these conditions.

4. Conclusions

Experimental evidence for two different oxidizing species was obtained, based on the variation of reactivity and selectivity induced by the substrate and porphyrin structure, and by the central metal and reaction conditions. Based on our results, we propose that the system (protic solvent, iron as central metal, high electron-withdrawing porphyrin ligand, absence of a co-catalyst) favors the main formation of a hydroperoxy active species, as shown by identical reactivity to *m*-CPBA in the oxidation of 17β-acetoxy-4-androstene, with the preferential formation of α-epoxide, in the exclusive formation of α-epoxycarane in the oxidation of (+)-3-carene, in the exclusive epoxidation at the 6,7-double bond of geraniol, and in the preferential formation of 1-naphthol and 1,4-naphthoquinone in the oxidation of naphthalene. On the other hand, the oxo species is considered to be the main acting entity in the system involving aprotic solvent, the presence of a buffering substance as co-catalyst, porphyrin ligands with lower redox potential, and manganese as the central atom.

Nomenclature

m-CPBA *meta*-chloroperoxybenzoic acid;
TDCPP the dianion of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin;
TPFPP the dianion of 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin;
t-BuOOH *t*-butylhydroperoxide;
NH_4AcO ammonium acetate

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References

[1] J.T. Groves, Y.-Z. Han, in: P.R. Ortiz de Montellano (Ed.), Cytochrome P450. Structure, Mechanism and Biochemistry, second ed., Plenum Press, New York, 1995, p. 3.
[2] J.L. McLain, J. Lee, J.T. Groves, in: B. Meunier (Ed.), Biomimetic Oxidations Catalysed by Transition Metal Complexes, Imperial College Press, London, 2000, p. 91.
[3] R. Weiss, A. Gold, A.X. Trautwein, J. Terner, in: K.M. Kadish, K.M. Smith, R. Guilard (Eds.), The Porphyrin Handbook, vol. 4, Academic Press, San Diego, CA, 2000, p. 65.
[4] J.T. Groves, R.C. Haushalter, M. Nakamura, T.E. Nemo, B.J. Evans, J. Am. Chem. Soc. 103 (1981) 2884.
[5] J.T. Groves, J. Porphyr. Phthalocyan. 4 (2000) 350.
[6] J.T. Groves, J. Lee, S.S. Marla, J. Am. Chem. Soc. 119 (1997) 6269.
[7] N. Jin, J.T. Groves, J. Am. Chem. Soc. 121 (1999) 2923.
[8] J. Bernadou, B. Meunier, J. Chem. Soc., Chem. Commun. (1998) 2167.
[9] R. Zhang, M. Newcomb, J. Am. Chem. Soc. 125 (2003) 12418.
[10] S. Shaik, S.P. de Visser, D. Kumar, J. Biol. Inorg. Chem. 9 (2004) 661.
[11] W. Nam, Y.O. Ryu, W.J. Song, J. Biol. Inorg. Chem. 9 (2004) 654.
[12] P. Hlavica, Eur. J. Biochem. 271 (2004) 4335.
[13] E. McCandlish, A.R. Miksztal, M. Nappa, A.Q. Sprenger, J.S. Valentine, J.D. Strong, T.G. Spiro, J. Am. Chem. Soc. 102 (1980) 4268.
[14] D. Mansuy, P. Battioni, in: K.M. Kadish, K.M. Smith, R. Guilard (Eds.), The Porphyrin Handbook, vol. 4, Academic Press, San Diego, CA, 2000, p. 10.
[15] T.M. Makris, I.G. Denisov, S.G. Sligar, Biochem. Soc. Trans. 31 (2003) 516.
[16] Y. Watanabe, J. Biol. Inorg. Chem. 6 (2001) 846.
[17] S. Jin, T.M. Makris, T.A. Bryson, S.G. Sligar, J.H. Dawson, J. Am. Chem. Soc. 125 (2003) 3406.
[18] T.J. Volz, D.A. Rock, K.P. Jones, J. Am. Chem. Soc. 124 (2002) 9724.
[19] Y. Watanabe, in: K.M. Kadish, K.M. Smith, R. Guilard (Eds.), Porphyrin Handbook, vol. 4, Academic Press, San Diego, CA, 2000, p. 97.
[20] S. Jin, T.A. Bryson, J.H. Dawson, J. Biol. Inorg. Chem. 9 (2004) 644.
[21] N. Suzuki, T. Higuchi, T. Negano, J. Am. Chem. Soc. 124 (2002) 9622.
[22] J.T. Groves, Proc. Natl. Acad. Sci. USA 100 (2003) 3569.
[23] K. Machii, Y. Watanabe, I. Morishima, J. Am. Chem. Soc. 117 (1995) 6691.
[24] Y. Watanabe, K. Yamaguchi, I. Morishima, K. Takehira, M. Shimizu, T. Hayakawa, H. Orita, Inorg. Chem. 30 (1991) 2581.
[25] A.M.A.R. Gonsalves, A.C. Serra, J. Mol. Catal. A: Chem. 168 (2001) 25.
[26] H.R. Khavasi, S.S.H. Davanari, N. Safari, J. Mol. Catal. A: Chem. 188 (2002) 115.
[27] J.P. Collman, L. Zeng, R.A. Decréau, Chem. Commun. (2003) 2974.
[28] P. Wadhwani, M. Mukherjee, D. Bandyopadhyay, J. Am. Chem. Soc. 123 (2001) 12430.
[29] A.C. Serra, E.C. Marçalo, A.M.A.R. Gonsalves, J. Mol. Catal. A: Chem. 215 (2004) 17.
[30] S.L.H. Rebelo, M.M.Q. Simões, M.G.P.M.S. Neves, A.M.S. Silva, J.A.S. Cavaleiro, A.F. Peixoto, M.M. Pereira, M.R. Silva, J.A. Paixão, A.M. Beja, Eur. J. Org. Chem. (2004) 4778.
[31] W. Nam, H.J. Lee, S.-Y. Oh, C. Kim, H.G. Jang, J. Inorg. Biochem. 80 (2000) 219.
[32] W. Nam, M.H. Lim, H.J. Lee, C. Kim, J. Am. Chem. Soc. 122 (2000) 6641.

[33] J.P. Renaud, P. Battioni, J.F. Bartoli, D. Mansuy, J. Chem. Soc., Chem. Commun. (1985) 888.
[34] R.A.W. Johnstone, M.L.P.J. Nunes, M.M. Pereira, A.M.A.R. Gonsalves, A.C. Serra, Heterocycles 43 (1996) 1423.
[35] J.W. Buchler, in: D. Dolphin (Ed.), The Porphyrins, vol. 1, Academic Press, New York, 1978, p. 398, and references cited therein.
[36] A.D. Adler, F.R. Longo, F. Kampes, J. Kim, J. Inorg. Nucl. Chem. 32 (1970) 2443.
[37] M.M. Pereira, PhD Thesis, University of Coimbra, 1991.
[38] R.R.L. Martins, M.G.P.M.S. Neves, A.J.D. Silvestre, M.M.Q. Simões, A.M.S. Silva, A.C. Tomé, J.A.S. Cavaleiro, P. Tagliatesta, C. Crestini, J. Mol. Catal. A: Chem. 172 (2001) 33.
[39] S.L.H. Rebelo, M.M.Q. Simões, M.G.P.M.S. Neves, A.M.S. Silva, J.A.S. Cavaleiro, Chem. Commun. (2004) 608.
[40] S.L.H. Rebelo, M.M.Q. Simões, M.G.P.M.S. Neves, J.A.S. Cavaleiro, J. Mol. Catal. A: Chem. 201 (2003) 9.
[41] A. Thellend, P. Battioni, D. Mansuy, J. Chem. Soc., Chem. Commun. (1994) 1035.
[42] P. Battioni, J.P. Renaud, J.F. Bartoli, M. Reina-Artiles, M. Fort, D. Mansuy, J. Am. Chem. Soc. 110 (1988) 8462.
[43] A.M.A.R. Gonsalves, R.A.W. Johnstone, M.M. Pereira, J. Shaw, J. Chem. Soc., Perkin Trans. 1 (1991) 645.
[44] J.R. Bull, J. Floor, J. Chem. Soc., Perkin Trans. 1 (1977) 724.
[45] I.C.M.S. Santos, M.M.Q. Simões, M.M.M.S. Pereira, R.R.L. Martins, M.G.P.M.S. Neves, J.A.S. Cavaleiro, A.M.V. Cavaleiro, J. Mol. Catal. A: Chem. 195 (2003) 253.
[46] Peroxygen Compounds in Organic Synthesis, Interox, The Peroxygen Professionals, Internal Publication, AO.1.2, p. 12, Interox Société Anonyme – Export Department, Rue du Prince Albert 33, B-1050 Brussels.
[47] R.T. Arnold, R. Larson, J. Org. Chem. 5 (1940) 250.
[48] M.P. Cava, R.L. Shirley, J. Org. Chem. 26 (1961) 2212.
[49] R. Jeyaraman, R.W. Murray, J. Am. Chem. Soc. 106 (1984) 2462.
[50] K. Tshikawa, G.W. Griffin, Angew. Chem., Int. Ed. Engl. 16 (1977) 171.
[51] Z. Gross, S. Nimri, L. Simkhovich, J. Mol. Catal. A: Chem. 113 (1996) 231.
[52] M.C.A. van Vliet, I.W.C. E Arends, R.A. Sheldon, Synlett (2001) 248.
[53] J.F. Bartoli, O. Brigaud, P. Battioni, D. Mansuy, J. Chem. Soc., Chem. Commun. (1991) 440.