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Oxidation of aromatic monoterpenes with hydrogen peroxide catalysed by Mn(III) porphyrin complexes

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Abstract

The oxidation of carvacrol **1**, thymol **2** and *p*-cymene **3** with hydrogen peroxide catalysed by Mn(III) porphyrins is reported. The oxidation of **1** and **2** selectively originates thymoquinone **6**. From the oxidation of *p*-cymene **3**, the isolated major products **7**–**10**, were formed from the oxidation of positions 7 and 8 of the substrate, although minor amounts of thymoquinone **6** were also formed. The efficiency and selectivity of the catalytic systems and the structural characterisation of the products obtained will be discussed.

Keywords: Hydrogen peroxide; Oxidation; Mn(III) porphyrin catalysts; Carvacrol; Thymol; *p*-Cymene

1. Introduction

Carvacrol **1**, thymol **2** and *p*-cymene **3** are *p*-menthane type aromatic monoterpenes, which can be found in the essential oils of many aromatic plants [1]. It is well established that the chemical transformation of abundant and cheap natural products can make available other more valuable compounds [2–4]. Following such line of research interests, the oxidation of compounds **1**–**3** with hydrogen peroxide, catalysed by Mn(III) porphyrin complexes **4.a**–**b**, **5.a**–**b** will be reported in this work (Scheme 1).

The use of synthetic porphyrin metal complexes with several oxygen donors to mimic the cytochrome P_{450} activity, has been a subject of intensive studies [5–8]. Moreover, the possibility of using 'environmentally clean' oxidants, such as hydrogen peroxide, makes the research in this area even more interesting [9].

It is already reported that manganese (III) porphyrin complexes can act as good catalysts in the presence of hydrogen peroxide as the oxidant, if a cocatalyst, like imidazole or ammonium acetate is used [5,10]. The cocatalyst is used to facilitate the desired heterolytic cleavage of H_2O_2 and to stabilise the porphyrin Mn(V) = O complex formed in the oxidation cycle [5]. Recently, ammonium acetate has been considered to be an excellent cocatalyst for the epoxidation of alkenes and for the hydroxylation of alkanes with hydrogen peroxide catalysed by Mn(III) porphyrin complexes [10]. Due

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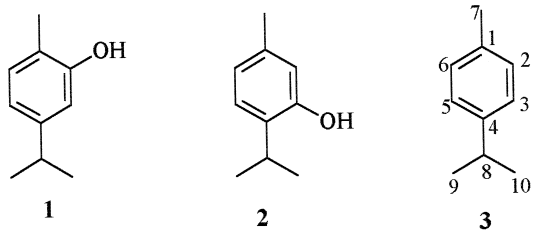


1 2 3

Scheme 1.

to this fact, and also based on our previous experience [2], the use of ammonium acetate was taken into consideration in this work (Scheme 2).

2. Results and discussion

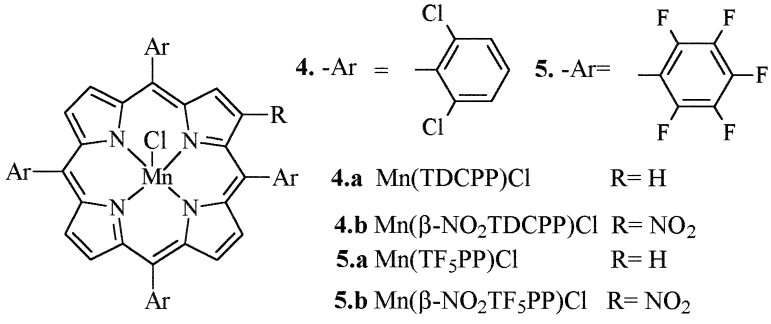
*2.1. Oxidation of carvacrol **1** and thymol **2***

Carvacrol **1** and thymol **2** were submitted to hydrogen peroxide oxidation procedure as described in the experimental part. The GC analysis of the reaction mixtures has shown, in each case, the formation of only one oxidation product; the two reaction products have shown the same retention time and by GC–MS experiments it revealed the same fragmentation pattern for them. In this way the structure **6** has been considered for such products. After purification by silica gel thin layer chromatography and based on NMR and mass spectrometry results, thymoquinone **6** has been unambiguously identified. Proton resonances for such compound were assigned based on their characteristic chemical shifts and multiplicities as shown in Section 4.2.

Based on the proton assignments, and using HETCOR ($^1H/^{13}C$) experiments it was also possible to assign all carbon resonances except for those of carbonylic carbons. For these carbon resonances a one-dimensional selective INEPT experiment was carried out [11]. Such experiment gives the connectivity of a selected proton, by irradiation of the corresponding resonance, to the carbon atoms to which it is coupled and can be optimised for different long-range J (C/H) coupling values. Upon irradiation of the H-8 proton resonance, optimised for 7.5 Hz long-range (C/H) coupling values, an enhancement of the signal at δ 187.5 ppm was observed; this resonance was then attributed to C-5 and the resonance at δ 188.6 ppm was subsequently attributed to C-2. In the same experiment enhancements of the signals at δ 21.4, 130.3 and 154.9 ppm were also observed, and were attributed, respectively, to the resonances of C-9,10, C-3 and C-4 being in agreement with the previous assignments based on HETCOR ($^1H/^{13}C$) experiments (Scheme 3).

*2.2. Oxidation of p-cymene **3***

The GC analysis of the reaction mixture allowed us to detect the presence of five products **6**–**10** resulting from the oxidation of *p*-cymene **3**. These products were identified by comparing



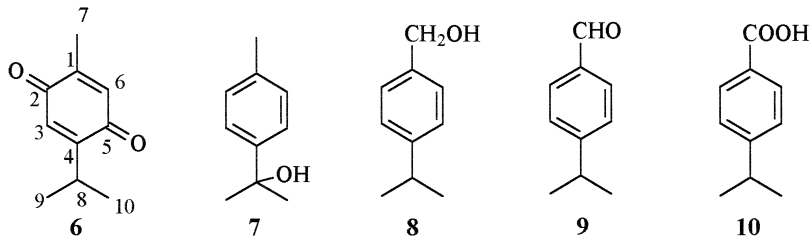
4.a Mn(TDCPP)Cl R= H

4.b Mn(β-NO_2TDCPP)Cl R= NO_2

5.a Mn(TF_5PP)Cl R= H

5.b Mn(β-NO_2TF_5PP)Cl R= NO_2

Scheme 2.



6 7 8 9 10

Scheme 3.

their mass spectra with the GC–MS data base, with a printed mass spectral library [12] and also by considering the NMR results.

The major oxidation products identified resulted from the oxidation of **3** in its benzylic positions 7 and 8, although small amounts of thymoquinone **6** were also found. Based on the presence of molecular ions at m/z 150, two compounds were identified as hydroxylated products of *p*-cymene. The differentiation between such alcohols was possible since *p*-cymenol **7** originates a fragment at m/z 132, corresponding to the loss of a water molecule; with compound **8** such fragmentation does not occur since there is no vicinal proton to the OH group. These results were confirmed by the NMR spectra of both compounds obtained after purification of the reaction mixture by silica gel thin layer chromatography.

2.3. Catalysts' efficiency and selectivity

As can be concluded from Table 1, carvacrol **1** and thymol **2** have shown a quite similar behaviour when the same catalyst was used in their oxidative transformations, suggesting that despite the differences in their structures, they have quite the same reactivity.

As far as the catalysts are concerned, it can be seen that in the oxidation of compounds **1** and **2** (Table 1), and **3** (Table 2), the type **4** porphyrins are more effective catalysts than the type **5** ones since higher conversions of both substrates were found with the former catalysts.

It was shown that the presence of a nitro group in a β-pyrrolic position does have different influences in the conversion of the substrates. However, in the case of type **4** porphyrins, the presence of such substituent does not seem to have any major influence on the activity of the corresponding catalyst used in the oxidation of the two highly activated compounds **1** and **2**, while it clearly enhances the efficiency of the catalyst in the oxidation of *p*-cymene **3**.

For type **5** catalysts, it can be stated that the presence of the β-nitro group enhances the efficiency of the catalyst in the oxidation of **1** and **2**, but it decreases such efficiency in the oxidation of compound **3**.

Table 1
Selectivity in the formation of **6** from carvacrol and thymol catalysed by porphyrins **4** and **5**

Catalyst	Selectivity (%)	
	From **1**	From **2**
Mn(TDCPP)Cl, **4.a**	98.8	98.9
Mn(β-NO_2TDCPP)Cl, **4.b**	99.6	99.7
Mn(TF_5PP)Cl, **5.a**	69.9	67.7
Mn(β-NO_2TF_5PP)Cl, **5.b**	85.1	84.6

Table 2
Conversion and selectivity in the oxidation of *p*-cymene **3** catalysed with Mn(III) porphyrin complexes

Catalyst	Conversion of **3**	Selectivity (%)				
		6	7	8	9	10
Mn(TDCPP) Cl, **4.a**	60.9	2.3	24.6	5.7	2.3	64.0
Mn(β-NO_2TDCPP) Cl, **4.b**	73.8	6.8	18.2	4.6	1.2	69.2
Mn(TF_5PP)Cl, **5.a**	38.9	22.6	57.3	4.4	2.8	12.9
Mn(β-NO_2TF_5PP) Cl, **5.b**	15.0	27.3	52.0	16.0	4.7	0

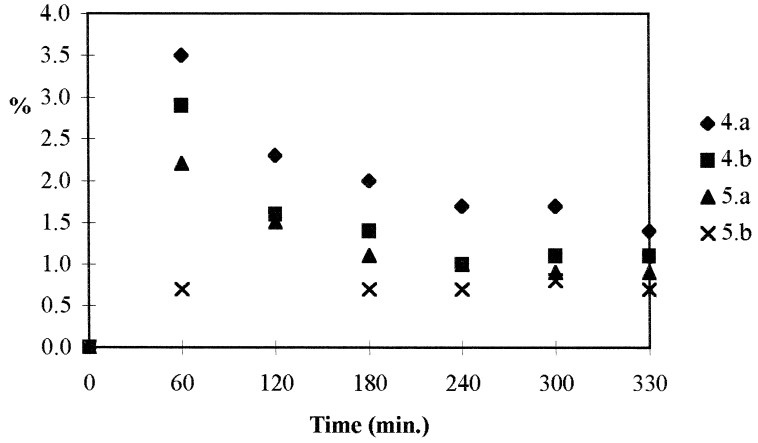


Fig. 1. Formation of *p*-isopropylbenzyl alcohol **8** catalysed by porphyrins **4** and **5** as a function of time.

The yields of the various oxidation products of *p*-cymene **3**, also depend on the catalyst used (Table 2). However, in this case the situation seems to be more complex than the observed for the substrates' conversion; thus the major oxidation product found was the acid **10** when type **4** catalysts were used, and the alcohol **7** when using type **5** catalysts; also, the presence of the β-nitro group increases the substrate conversion when using type **4** catalysts and decreases it when using type **5** catalysts.

Most of these observations are in agreement with the fact that metalloporphyrins bearing electron withdrawing groups in β-positions should in principle be better catalysts than the ones with those groups only on the phenyl substituents, since a higher resistance to oxidative destruction and a considerable electronic activation of the catalyst must be achieved [13].

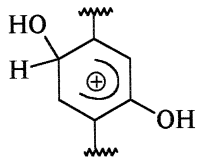
The unexpected results obtained with catalyst **5.b** as far as *p*-cymene **3** is concerned is probably due to the fact that the abstraction of the hydrogen atom by the high valent oxomanganese porphyrin complex occurs preferentially in the more reactive benzylic position 8. The steric hindrance caused by the two methyl groups makes the oxidation of that position markedly affected by the structure of the porphyrin ligand, therefore, as catalyst **5.b** is more sterically hindered it will be less efficient than **5.a**.

As far as type **4** catalysts are concerned the steric hindrance caused by the 2,6-dichlorophenyl substituents is even more important than that observed with type **5**, and therefore the oxidation of position 8 of *p*-cymene will be even more attenuated and, in such way, the other benzylic position will be preferentially oxidised.

It was also observed that when type **4** catalysts were used, the formation of *p*-isopropylbenzyl alcohol **8** (Fig. 1), and in a similar way, of 4-isopropylbenzaldehyde **9**, rapidly increased in the beginning of the reaction, then they decreased and tended to stabilise at a constant value. This behaviour should be due to the conversion of these two products into 4-isopropylbenzoic acid **10**, suggesting that the oxidation mechanism is via benzylic hydroxilation. When catalysts **5.a** and **5.b** were used such variations are less evident; this can be due to the fact that when using these catalysts the selectivity in the formation of products **8**, **9** and **10** is much smaller than the one corresponding to the formation of the alcohol **7**.

3. Conclusions

The formation of compound **6**, either from carvacrol **1** or thymol **2**, is a result of the selective hydroxylation of the aromatic ring in



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Scheme 4.

the *para* position relatively to the OH group, followed by the subsequent oxidation of the resulting hydroquinone to the quinone stage [5]. This hydroquinone derivative might arise from a protonated intermediate, the *p*-hydroxylated species **11**. Such intermediate is stabilised by the OH substituent present in the reagents **1** and **2** [14] (Scheme 4).

Thymoquinone **6**, a compound with a commercial value considerably higher than those of its precursors, can be easily obtained by using type **4** and an environmentally clean oxidising agent.

For *p*-cymene **3**, the oxidation takes place mainly at the benzylic positions 7 and 8 and, in a lower extent, at the aromatic ring. This reaction pathway might involve a benzylic H-abstraction, generating a radical, which recombines with the high valent hydroxomacrocycle, leading to the alcohols **7** and **8**, the latter being the precursor for the formation of aldehyde **9** and acid **10** [5,15].

4. Experimental

4.1. General details

^{1}H and ^{13}C NMR spectra were taken in deuteriochloroform solutions, using a Bruker AMX 300 at 300.13 and 75.47 MHz respectively; the chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS), as an internal reference. Preparative thin layer chromatography (tlc) was carried out on silica gel plates (Riedel silica gel 60 DGF_{254}). Column chromatography was also performed on silica gel (Merck silica gel 60, 70–230 mesh). Mass spectra were obtained at 70 eV electron impact ionisation, using a VG Autospec Q mass spectrometer. GC–MS analysis were performed using a Hewlett Packard 5890 chromatograph equipped with a mass Selective Detector MDS series II using helium as the carrier gas (35 cm s^{-1}); GC–FID was performed using a Varian Star 3400CX chromatograph and hydrogen as the carrier gas (55 cm s^{-1}). In both cases fused silica Supelco capillary columns SPB-5 (30 m $\times$ 0.25 mm i.d.; 25 μm film thickness) were used. The chromatographic conditions were as follows: initial temperature: 100°C; temperature rate: 5°C min^{-1}; final temperature: 220°C; injector temperature: 220°C; detector temperature: 230°C. The percentage of each compound in the reaction mixtures was estimated directly from the corresponding peak area.

Hydrogen peroxide (30%) was purchased from Riedel-de Haën; thymol, carvacrol and *p*-cymene were purchased from Aldrich. Porphyrin complexes were prepared according to known procedures [16,17]. All other chemicals and solvents used herein were obtained from commercial sources and used as received or dried using standard procedures. Light petroleum was the fraction of bp 40–60°C.

*4.2. Oxidation of substrates **1–3***

4.2.1. General procedure

In a typical experiment, the substrate **1–3** (0.325 mmol), the catalyst (5.18×10^{-3} mmol) and ammonium acetate (0.066 mmol) were dissolved in acetonitrile (2.0 ml) and stirred at room temperature. Hydrogen peroxide, diluted in acetonitrile (1:10), was added to the reaction mixture in aliquots (0.4 ml) every 40 min. Each reaction was followed by GC analysis and was stopped when the product yields remained constant after two successive GC analysis: 200 min in the oxidation of **1** and **2** and 300 min in the oxidation of **3**. The reaction mixtures were then poured into water and extracted with dichlormethane, the organic solution was then

dried over anhydrous sodium sulphate and concentrated in the rotary evaporator. The mixtures were then separated by preparative thin layer chromatography on silica gel, eluting with a ethyl acetate: light petroleum mixture (1: 20) for the purification of the thymol or carvacrol oxidation products; or with a dichloromethane: light petroleum mixture (1:1) for the *p*-cymene oxidation products (increasing R_f values: **10**, **7**, **8**, **9**).

4.2.2. 2-Isopropyl-5-methylbenzoquinone (thymoquinone)

6 ^{1}H NMR δ ($CDCl_3$) 1.13 (d, J 6.9 Hz, H-9,10), 2.04 (d, J 1.6 Hz, H7), 3.02 (hept, J 6.9 Hz, H-8), 6.52 (s, H-3), 6.59 (q, J 1.6 Hz), H-6; ^{13}C n.m.r. δ 15.3 (C-7), 21.4 (C-9,10), 26.5 (C-8) 130.3 (C-3), 133.8 (C-6), 146.1 (C-1), 154.9 (C-4) 187.5 (C-5), 188.6 (C-2); mass spectrum, *m/z* 164 ($M^{+\bullet}$, 1%), 149 (26), 136 (82), 121 (90), 128 (91), 93 (100), 77 (44), 53 (55).

4.2.3. 2-(4-Methylphenyl)-2-propanol

7 ^{1}H NMR δ ($CDCl_3$) 1.57 (s, H-9, 10), 2.34 (s, H-7), 4.65 (s broad, OH), 7.15 (d, J 8.1 Hz, H-3,5), 7.38 (d, J 8.1 Hz, H-2,6), ^{13}C n.m.r. δ 20.9 (C-7), 31.7 (C-9,10), 72.4 (C-8), 124.3 (C-3,5), 128.9, (C-2,6), 136.2 (C-1), 146.2, (C-4); mass spectrum, *m/z* 150 ($M^{+\bullet}$, 10%), 135 (48), 132 (62), 117 (52), 115 (22), 91 (35), 65 (19), 43 (100), 39 (20).

4.2.4. 4-Isopropylbenzyl alcohol

8 ^{1}H NMR δ ($CDCl_3$) 1.21 (d, J 6.9 Hz, H-9,10), 2.86 (hept, J 6.9 Hz, H-8), 3.36 (s broad, 7-OH), 4.46 (s broad, H-7), 7.15 and 7.18 (AB, H-2,3,5,6); ^{13}C n.m.r. δ 23.9 (C-9,10), 33.7 (C-8), 64.5 (C-7), 126.3 (C-3,5), 127.0 (C-2,6), 138.2 (C-1), 147.9 (C-4); mass spectrum, *m/z* 150 ($M^{+\bullet}$,6%), 135 (50), 117 (3), 105 (2), 91 (10), 65 (6), 43 (100).

4.2.5. 4-Isopropylbenzaldehyde

9 ^{1}H NMR δ ($CDCl_3$) 1.25 (d, J 6.9 Hz, H-9,10), 2.95 (hept, J 6.9 Hz, H-8), 7.35 (d, J 8.1 Hz, H-3,5), 7.79 (d, J 8.1 Hz, H-2,6), 9.44 (s, H-7); ^{13}C n.m.r. δ 23.4 (C-9,10), 34.2 (C-8), 126.9 (C-3,5), 129.8 (C-2,6), 134.4 (C-1), 156.0 (C-4), 191.7 (C-7); mass spectrum, *m/z* 148 ($M^{+\bullet}$, 50%), 133 (90), 119 (29), 115 (6), 105 (100), 91 (41), 77 (67), 63 (14), 51 (48), 39 (31).

4.2.6. 4-Isopropylbenzoic acid

10 ^{1}H NMR δ ($CDCl_3$) 1.28 (d, J 6.9 Hz, H-9,10), 2.99 (hept, J 6.9 Hz, H-8), 7.33 (d, J 8.3 Hz, H-3,5), 8.05 (d, J 8.3 Hz, H-2,6); ^{13}C n.m.r. δ 23.7 (C-9,10), 34.3 (C-8), 126.6 (C-3,5), 126.9 (C-1), 130.4 (C-2,6), 155.3 (C-4), 172.2 (C-7); mass spectrum, *m/z* 164 ($M^{+\bullet}$, 48%),133 (90), 149 (100), 131 (15), 119 (34), 105 (35), 91 (10), 77 (20), 51 (8).

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