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Oxidation of monoterpenes catalysed by a water-soluble Mn(III) PEG-porphyrin in a biphasic medium

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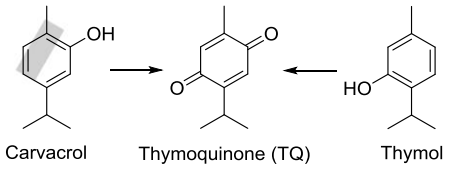
Abstract: It is well established that the transformation of abundant and cheap natural products, such as terpenoids, can produce other more valuable compounds. Thymoquinone, which has a commercial value significantly higher than that of its precursors, can be obtained by oxidation of carvacrol and thymol. In this work, a new water-soluble Mn(III) PEG-porphyrin is reported as catalyst in a water/hexane (1:1) biphasic medium for the oxidation of carvacrol and thymol into thymoquinone. The reactions were performed using *tert*-butyl hydroperoxide as oxidant in the presence of ammonium acetate as co-catalyst, reaching 94% and 78% of conversion after 5 h of reaction for thymol and carvacrol, respectively. Experiments with oregano essential oil as substrate revealed selective transformation of thymol and carvacrol into thymoquinone. The main advantage of this biphasic system based on a water-soluble catalyst and on substrates and products soluble in hexane, is the straightforward isolation, recovery and recycling of the catalyst by simple phase separation. Recycling studies of the Mn(III) PEG-porphyrin using thymol as substrate showed high conversion values throughout four catalytic cycles.

Introduction

Thymoquinone (TQ) is a valuable compound that has therapeutic effects in numerous diseases, but is only available in limited amounts from natural sources such as *Nigella sativa L.* and *Monarda fistulosa L.* plants.[1–7] However, it can be obtained in high amounts through the oxidation of carvacrol and thymol (Scheme 1), which are abundantly available in oregano essential oils. Carvacrol and thymol have been identified as the active molecules responsible for the antibacterial, antifungal and antioxidant properties of oregano essential oils,[8–11] which make them very attractive for pharmaceutical and food applications.[12,13] Thus, the search for processes for the synthesis of TQ starting from cheaper and abundant substrates is a subject of great interest.



Scheme 1. Structures of the substrates (carvacrol and thymol) and the product (thymoquinone).

Dockal *et al.* prepared thymoquinone by homogeneous oxidation of thymol and carvacrol in DMF using Co(II) (salen) catalysts, under oxygen flow at low pressure.[14] Thymoquinone was also efficiently obtained by oxidation of thymol and carvacrol in acetonitrile in the presence of homogeneous Mn(III) porphyrins and hydrogen peroxide as oxidant.[15] Similar oxidation reactions catalysed by an Y zeolite supported tetracationic Mn(III) porphyrin complex led to <25% conversion of carvacrol and <18% conversion of thymol after 24 h of reaction, in acetonitrile, with 100% selectivity towards TQ.[16] The leaching of the Mn(III) porphyrin complex to the reaction solution in the presence of H_2O_2, accompanied by the partial collapse and changes of the crystalline structure, causing irreversible deactivation, led to a complete loss of activity when it was recycled.[16] A mixture of thymoquinone, thymohydroquinone, and other benzoquinones was obtained when the oxidation of carvacrol was performed in the presence of zeolite-encapsulated metal-*N*,*N*'-bis(salicylidene)propane-1,3-diamine complexes [M(salpn)-NaY; M=Cr, Fe, Zn, Ni, Bi] as catalysts and hydrogen peroxide as oxidant, in acetonitrile.[17] The oxidation of carvacrol and thymol in the presence of Keggin-type heteropolyanions and hydrogen peroxide, in acetonitrile at reflux, was also less selective, affording a mixture of benzoquinones as products, in moderate conversion.[18] Recently, the oxidation of thymol and carvacrol was studied by using potassium peroxymonosulfate ($KHSO_5$) as oxidant in the presence of Fe(III) phthalocyanine tetrasulfonate (FePcTS) and a mixture of methanol:water (8:1) as solvent.[19] The selectivity for thymoquinone was lower than 34% for carvacrol and lower than 21% for thymol. When H_2O_2 or *tert*-

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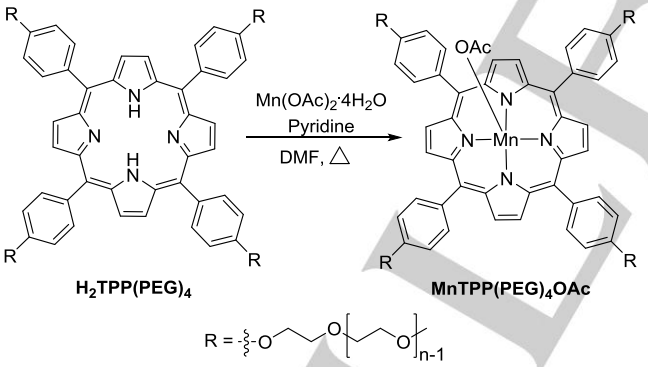
butyl hydroperoxide (TBHP) were used as oxidants, the yield of TQ was <1 %. Moreover, by recycling the catalyst, FePcTS, the authors observed that both thymol and carvacrol conversions dropped to <5% in the second cycle.[19] Milos compared the catalytic efficiency of the Fe(III) complexes of *meso*-tetraphenylporphyrin and of phthalocyanine in the oxidation of an oregano essential oil using $KHSO_5$ or H_2O_2 as oxidant, in acetonitrile.[20] The essential oil was rich in thymol and carvacrol (47.6% and 25.1%), *p*-cymene (21.4%), γ-terpinene (2.0%) among other constituents (<1%). Both catalysts were efficient using $KHSO_5$ with a complete or almost complete conversion of carvacrol and thymol within 1 h (19.1–63.3% yields for TQ), and the co-catalyst, ammonium acetate, did not influence the catalytic process. When H_2O_2 was used as oxidant, a relatively slower conversion and lower yields for TQ were observed and the presence of ammonium acetate affected the oxidation profile with both catalysts, while *p*-cymene and γ-terpinene remained unchanged.[20]

Results and Discussion

In the present study, taking advantage of the high water-solubility of porphyrins functionalized with polyethylene glycol (PEG) chains,[21] the Mn(III) complex of $H_2TPP(PEG)_4$ was prepared to be tested as catalyst for oxidation reactions in a biphasic medium (Scheme 2). The obtained manganese complex $MnTPP(PEG)_4OAc$ was characterized by UV-Vis (Figure S1), size exclusion chromatography (SEC; Figure S2) and MALDI-TOF MS (Figures S3 and S4).



Scheme 2. The synthetic strategy to obtain the $MnTPP(PEG)_4OAc$ from the $H_2TPP(PEG)_4$.

Figure S1 compares the UV-Vis spectra of the free-base porphyrin $H_2TPP(PEG)_4$ with the corresponding manganese complex, $MnTPP(PEG)_4OAc$. The manganese complexation of the free-base porphyrin resulted in a pronounced change in the Q bands region, with the disappearance of two of the Q bands. In addition, a bathochromic shift (to higher wavelengths) of the Soret band and the presence of the metal transition bands at 350-450 nm were observed. SEC revealed that the $MnTPP(PEG)_4OAc$ has a narrow molar mass distribution with a dispersity value below 1.15. Additionally, the successfully loading of manganese in the core of porphyrin was also confirmed by the MALDI-TOF MS spectra (Figures S3 and S4) revealing the expected increase in molar mass after the Mn(III) coordination.

In the oxidation reactions, the solvent used was a water/hexane (1:1) mixture and the substrates selected were carvacrol and thymol, due to their high solubility in hexane and low solubility in water. In this way, it was possible to develop a biphasic system in which the catalyst is water-soluble and the substrate is soluble in the organic solvent. The product obtained is also poorly soluble in water, thereby allowing an easy separation of the catalyst from the substrate and/or product by a simple phase separation. Other solvent mixtures, such as water/acetone and water/ethyl acetate were also tested, but in these cases no oxidation of the substrates was observed.

Catalytic studies with Mn(TPP)acac under homogeneous conditions

Before investigating the proposed biphasic catalysis, the best reaction conditions, namely the substrate/catalyst molar ratio and the oxidant to be used, were optimized under homogeneous conditions with Mn(TPP)acac as catalyst, using carvacrol as substrate, ammonium acetate as co-catalyst and acetonitrile as solvent at ambient temperature. The oxidant was initially added in portions with intervals of 15 min, each addition corresponding to 0.5 equiv relatively to the molar amount of the substrate. When H_2O_2 was used as oxidant no oxidation reaction occurred, even for a substrate/catalyst molar ratio of 25. Additionally, a change in the catalyst colour from green to red/brown was observed after some time indicating a possible destruction/deactivation of the catalyst with H_2O_2, which was confirmed by UV-Vis spectrophotometry as the Soret band disappeared (Fig. 1).

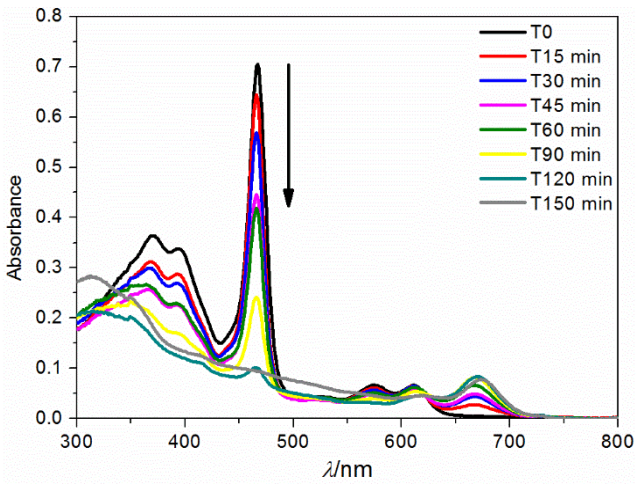


Figure 1. UV-Vis monitoring of the Mn(TPP)acac catalyst stability in the homogeneous oxidation of carvacrol in acetonitrile using H_2O_2 as oxidant for a substrate/catalyst molar ratio of 25.

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A totally different result was obtained with *tert*-butyl hydroperoxide (TBHP) as oxidant revealing total conversion of the substrate after 45 min and high stability of the catalyst as indicated by UV-Vis spectrophotometry (Fig. 2).

It is well known from the literature that, in general, the use of aqueous H_2O_2 can be disadvantageous for the integrity of the catalysts in oxidation reactions, since a cooperative action of water and H_2O_2 can cause catalyst destruction and / or metal leaching, which is usually in contrast to what happens with anhydrous TBHP (a solution in decane was used in the present work) as oxidant. The fact that TBHP is a bulkier molecule than hydrogen peroxide and the steric effects related with this, are also mentioned as features that make TBHP less reactive towards catalyst structure decomposition. The so-called first generation metalloporphyrin catalysts are particularly prone to oxidative degradation in the presence of aqueous hydrogen peroxide, which is the case of the Mn(TPP)acac.[22–26]

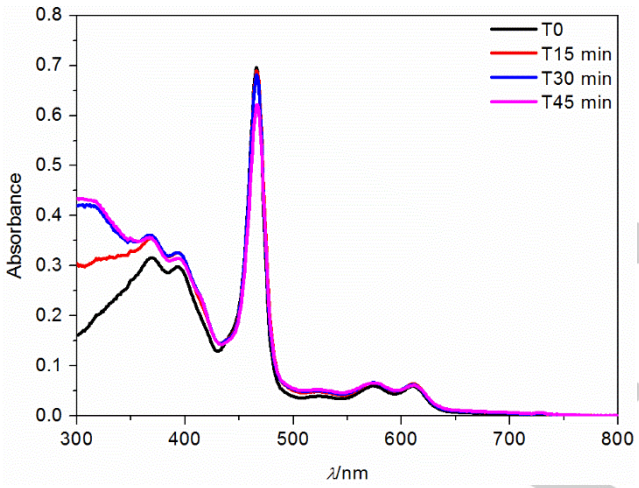

Figure 2. UV-Vis monitoring of the Mn(TPP)acac catalyst stability in the homogeneous oxidation of carvacrol in acetonitrile using TBHP as oxidant for a substrate/catalyst molar ratio of 25.

These good results for the homogeneous catalysis with TBHP as oxidant led us to test other substrate/catalyst molar ratios with a smaller amount of catalyst. Almost total conversion of carvacrol was obtained, after 45 min (Fig. 3), for a substrate/catalyst molar ratio of 100 (94%), and the efficiency of the catalyst was maintained for a substrate/catalyst molar ratio of 200 (93% conversion, after 45 min). The same result was obtained using MnTPP(PEG)$_4$OAc as catalyst and acetonitrile as solvent, i.e. under homogeneous conditions (Fig. 3).

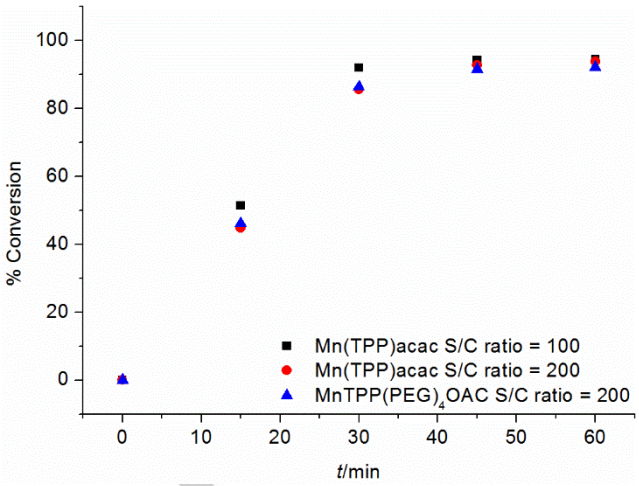

Figure 3. Carvacrol conversion using Mn(TPP)acac or MnTPP(PEG)$_4$OAc as catalyst, TBHP as oxidant (0.5 equiv every 15 min) and acetonitrile as solvent.

Catalytic studies with MnTPP(PEG)$_4$OAc in a biphasic medium

In a next step, the performance of MnTPP(PEG)$_4$OAc was evaluated using a water/hexane (1:1) biphasic medium, under vigorous stirring. In this case, and using TBHP with additions of 0.5 equiv every 15 min, the reaction was slower and after 120 min (4 equiv of oxidant added) the conversion of carvacrol was around 70%. The slower reaction was anticipated as the reaction will mainly occur at the interphase between the aqueous and organic phases. The reaction mixture was already in the presence of a large excess of oxidant, since even without adding TBHP, carvacrol continued to be oxidised to thymoquinone. In this case, further additions of oxidant would only lead to destruction of the catalyst. Therefore, the oxidant was added at once (4 equiv of TBHP) and a conversion of 78% was obtained after 300 min (Fig. 4). The same conditions were used in the oxidation of thymol reaching 94% of conversion after 300 min (Fig. 4), with thymoquinone being the only product detected. Blank experiments, without adding the catalyst and the co-catalyst were performed and no oxidation was observed.

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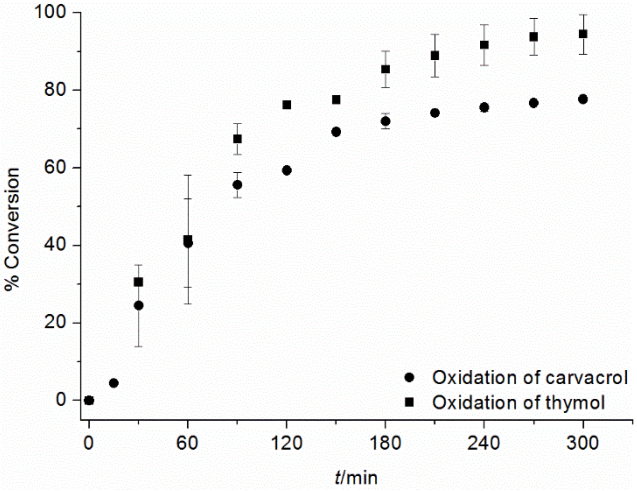

Figure 4. Conversion of carvacrol and thymol using MnTPP(PEG)$_4$OAc as catalyst and TBHP as oxidant (4 equiv added at once) in a biphasic medium of water/hexane (1:1).

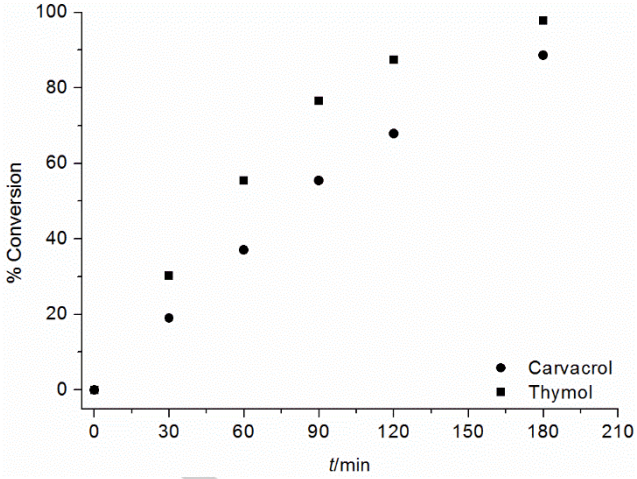

Figure 5. Conversion of carvacrol and thymol in the oxidation of the essential oil of *Origanum vulgare* using MnTPP(PEG)$_4$OAc as catalyst and TBHP as oxidant in a water/hexane (1:1) biphasic medium.

The same catalytic system was used in the oxidation of an essential oil of *Origanum vulgare*. The composition of the essential oil was determined by GC-MS (Figure S5) revealing carvacrol (33.2%), thymol (17.0%), and *p*-cymene (15.3%) as the main components (Table 1). Other minor components included terpinen-4-ol (6.6%), *trans*-caryophyllene (5.6%) and β-bisabolene (6.3%). The oxidation reaction was monitored by GC-FID and by GC-MS (Figure S5) to identify the oxidation products. In line with a previous report by Milos,[20] it was observed that the reaction was selective for the oxidation of thymol and carvacrol. After 3 hours of reaction, thymol and carvacrol were almost totally converted into thymoquinone (98% and 89%, respectively – Fig. 5) and the other components remained practically intact.

Additional assays were performed in order to evaluate if the separation of thymoquinone was not affected by the recycling of the catalyst. These experiments were carried with MnTPP(PEG)$_4$OAc in water-hexane (1:1) by using thymol as substrate and a substrate/catalyst molar ratio of 50.

Table 1. Volatile compounds present in the composition of the oregano essential oil

Retention time (min)	Compound	%
8.25	α-Thujene	1.3
8.58	α-Pinene	<1.0
10.58	Sabinene	1.9
11.56	β-Myrcene	1.1
13.08	Terpinolene	1.0
13.64	*p*-Cymene	15.3
14.36	*trans*-β-Ocimene	<1.0
14.99	*cis*-β-Ocimene	<1.0
15.66	γ-Terpinene	1.9
18.53	*cis*-Sabinene hydrate	1.1
23.80	Terpinen-4-ol	6.6
27.74	Carvacrol methyl ether	2.3
32.09	Thymol	17.0
32.68	Carvacrol	33.2
39.08	*trans*-Caryophyllene	5.6
41.29	α-Humulene	<1.0
42.91	Germacrene D	<1.0
44.79	β-Bisabolene	6.3
48.88	Caryophyllene oxide	2.7

After each cycle, the catalyst was isolated from the reaction mixture by simple phase separation, for subsequent reuse. The evolution of thymol conversion for each catalytic cycle was monitored by GC-FID and is shown in Fig. 6.

The results show that the efficiency of the catalytic biphasic system in the first cycle (99% after 120 min) is maintained in the second catalytic cycle (98% after 150 min). In the third cycle after 210 min of reaction a high conversion (83%) is still observed. In the fourth cycle the system was able to convert 50% of thymol after 240 min of reaction. The catalytic activity decrease of the first generation porphyrin metal complexes

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under oxidative conditions is well known from the literature.[22,23] Nevertheless, the present biphasic conditions seem to promote the MnTPP(PEG)$_4$OAc stability, allowing its recovery and reuse. In all catalytic cycles the only product obtained was thymoquinone, which was readily and efficiently separated from the catalyst by phase separation, thus allowing us to obtain the thymoquinone in the organic phase, concomitantly to the easy separation of the catalyst, which remained in the aqueous phase ready for a new run.

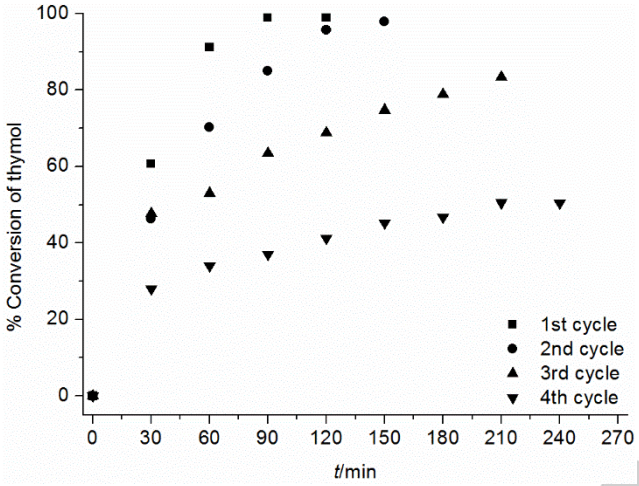

Figure 6. Catalyst recycling studies of the MnTPP(PEG)$_4$OAc catalyst using thymol as substrate, TBHP as oxidant and a substrate/catalyst molar ratio of 50 in a water/hexane (1:1) biphasic medium.

Conclusions

In summary, the water-soluble MnTPP(PEG)$_4$OAc is an efficient catalyst for the preparation of thymoquinone by oxidation of carvacrol and thymol in a water/hexane (1:1) biphasic medium, using *tert*-butyl hydroperoxide as oxidant and ammonium acetate as co-catalyst. The methodology can be applied directly to an oregano essential oil particularly rich in carvacrol and thymol. The catalyst is easily isolated and recovered by simple phase separation allowing its reutilization.

Experimental Section

Reagents and Methods

Thymol was purchased from Sigma, whereas carvacrol and *tert*-butyl hydroperoxide 5.0-6.0 M solution in decane were obtained from Aldrich. Ammonium acetate was purchased from Scharlau and chlorobenzene was obtained from Carlo Erba and used as internal standard for the determination of substrates' conversion by GC. The synthetic procedure of free base porphyrin was described in our previous work.[27] Mn(TPP)acac was prepared by the acetylacetonate method as described in the literature.[28] The oregano oil was gently provided by Dr. Susana Cardoso.

The GC-FID analyses were carried out on a Varian 3900 chromatograph using helium as the carrier gas (30 cm/s) equipped with a fused silica capillary DB-5 type column (30 m length, 0.25 mm i.d., 0.25 μm film thickness). The GC-FID chromatographic conditions were as follows: initial temperature, 100 ºC; temperature rate of 10 ºC/min up to 200 ºC, followed by a new temperature rate of 40 ºC/min up to 280 ºC which was maintained for 2 min; injector and detector temperatures were both set at 300 ºC.

The GC-MS analyses were performed using a gas chromatograph mass spectrometer (GC-MS Shimadzu QP2010 Ultra) equipped with an AOC-20i autosampler (Shimadzu, Japan), with the electron impact ionization (EI) at 70 eV and high-performance quadrupole mass filter. The separation of compounds was carried out in a DB-5ms column (30 m length, 0.25 mm i.d., 0.25 μm film thickness) using helium as the carrier gas (40 cm/s). The GC-MS chromatographic conditions were as follows: initial temperature, 50 ºC which was maintained for 3 min; temperature rate of 2 ºC/min up to 250 ºC which was maintained for 10 min; injector temperature, 250 ºC. The mass spectrometer was operated over a range of *m/z* 34-450. The ion source was kept at 230 ºC and the interface temperature at 280 ºC. Chromatographic peaks were identified by comparing their mass spectra with the equipment mass spectral library (NIST14s MS Library Database or WILEY229 MS Library Database).

Size exclusion chromatography (SEC) was performed on an Agilent 1260-series HPLC system equipped with a 1260 online degasser, a 1260 ISO-Pump, a 1260 automatic liquid sampler, a thermostated column compartment, a 1260 diode array detector (DAD) and a 1260 refractive index detector (RID). Analyses were performed on a PPS Gram 30 column in series with a PPS Gram 1000 column at 50 ^{o}C. DMA containing 50 mM of LiCl was used as an eluent at a flow rate of 0.6 mL/min. The SEC traces were analysed using the Agilent Chemstation software with the GPC add on. Molar mass and PDI values were calculated against PMMA standards.

MALDI-TOF mass spectra were acquired with a Voyager DE-STR (PerSeptive Biosystem) using a simultaneous delay extraction procedure (20 kV applied after 233 ns with a potential gradient of 2545 V/mm and a wire voltage of 200 V) and detection in reflection mode. The instrument was equipped with a nitrogen laser (emission at 337 nm for 3 ns) and a flash AD converter (time base 2 ns). The *trans*-2-[3-(4-*t*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) was used as matrix.

Synthesis of MnTPP(PEG)$_4$OAc

MnTPP(PEG)$_4$OAc was prepared using the free-base porphyrin H_2TPP(PEG)$_4$, which was synthesized as previously described.[27] In a 25 mL round bottom flask, equipped with a reflux condenser and a magnetic stirrer, 50 mg of the free-base porphyrin were dissolved in 5.0 mL of DMF. The solution was refluxed in the dark, under a nitrogen atmosphere and then 0.5 mL of pyridine and 10 equivalents of manganese(II) acetate [$Mn(CH_3COO)_2.4H_2O$] were added. The progress of the reaction was monitored by UV-Vis. The UV-Vis spectrum shows a Soret band shift to a higher wavelength (λ_{max}=472 nm) and the disappearance of two Q bands of the free-base macrocycle, thereby confirming the presence of the complex (Figure S1). The absorption bands of manganese at λ_{max}=380 nm and 402 nm can also be observed. The reaction was complete after 4 h. The heating was switched off and the reaction mixture was kept under stirring overnight, in the open air and protected from light. The solvent was evaporated in the rotary evaporator with addition of toluene to facilitate the solvent removal. The residue was dissolved in dichloromethane and the organic phase was washed 2-3 times with water in a separating funnel. The organic phase was passed through a glass funnel with cotton wool and anhydrous sodium sulphate to remove

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traces of water. The manganese complexes were crystallized in hexane, after dissolution in a minimal amount of dichloromethane. The crystals were filtered under vacuum, using a Hirsch funnel with filter paper, and washed several times with hexane. The yield, based on the porphyrin, was over 90%. UV-Vis (CH_3CN) λ_{max}, nm (%): 380 (51), 402 (52), 472 (100), 581 (11), 620 (14).

General procedure for the oxidation reactions

For the oxidation reactions under homogeneous conditions: a standard solution of the catalyst was previously prepared in acetonitrile and reserved in the fridge protected from light until next use. The volume of the catalyst solution was added to the reactor in accordance to the corresponding substrate/catalyst molar ratio (S/C). The co-catalyst (0.2 mmol ≈15 mg of ammonium acetate), the substrate (7.5×10^{-5} mol), the internal standard (7.5×10^{-5} mol of chlorobenzene) and acetonitrile were added until a final volume of 2 mL. The oxidant was added in aliquots of 0.5 equiv relatively to the molar amount of the substrate every 15 min.

For the oxidation reactions under biphasic conditions: the catalyst (3.75×10^{-7} mol; 3.19 mg for a S/C of 200) was dissolved in 1 mL of Milli-Q water, and the co-catalyst (0.2 mmol ≈15 mg of ammonium acetate) was added. The substrate (7.5×10^{-5} mol) and the internal standard (7.5×10^{-5} mol of chlorobenzene) were dissolved in 1 mL of hexane and added to the aqueous mixture. The oxidant used was *tert*-butyl hydroperoxide 5.0-6.0 M solution in decane and 4 equiv relatively to the molar amount of substrate (3×10^{-4} mol) were added at the beginning of the reaction. Blank experiments were performed under the same conditions without the catalyst and the co-catalyst.

For the recycling studies, thymol (7.5×10^{-5} mol; 11.3 mg) was chosen as substrate and 1.5×10^{-6} mol of $MnTPP(PEG)_4OAc$ (12.7 mg for a S/C of 50) were used under biphasic conditions. The reaction was stopped when the substrate was totally converted or when no significant conversion of the substrate was observed after two successive GC-FID analyses. At the end of the reaction, the organic phase containing the internal standard, the *tert*-butyl hydroperoxide, the thymoquinone and the unreacted thymol was separated from the aqueous phase containing the manganese porphyrin and the co-catalyst. The aqueous phase was washed several times with hexane and controlled by GC-FID to assure that the aqueous phase was deprived of any thymol, thymoquinone or internal standard. The aqueous phase was stored in the freezer protected from light until the next reuse. At each recycling assay, 4 equiv of oxidant were added. No further co-catalyst was added in the recycles.

For the oxidation of the oregano oil under biphasic conditions: the catalyst (3.75×10^{-7} mol; 3.19 mg) and the co-catalyst (0.2 mmol ≈15 mg of ammonium acetate) were dissolved in 1 mL of Milli-Q water. Next, 20 μL of the oregano oil and 7.5×10^{-5} mol of the internal standard were dissolved in 1 mL of hexane and added to the aqueous mixture. Finally, 3 $\times 10^{-4}$ mol of *tert*-butyl hydroperoxide 5.0-6.0 M solution in decane were added to start the reaction.

All the reactions were kept under vigorous stirring at 30 ± 1 °C and protected from light. The conversion of the substrate was monitored by GC-FID and the stability of the catalyst was checked by UV-Vis spectrophotometry.

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Keywords: manganese • porphyrin • monoterpenes • oxidation • biphasic catalysis

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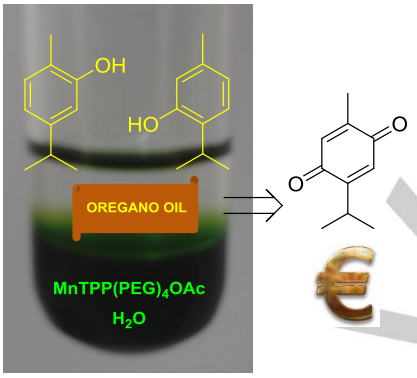
It is well established that the transformation of abundant and cheap natural products, such as terpenoids, can produce other more valuable compounds. Thymoquinone, which has a commercial value significantly higher than that of its precursors, can be obtained by oxidation of carvacrol and thymol. A new water-soluble Mn(III) PEG-porphyrin is reported as catalyst in a biphasic medium for the oxidation of carvacrol and thymol into thymoquinone.



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Oxidation of monoterpenes catalysed by a water-soluble Mn(III) PEG-porphyrin in a biphasic medium

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