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Jacobsen catalyst as a P450 biomimetic model for the oxidation of an antiepileptic drug

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Abstract

In this work, we investigated carbamazepine (CBZ) oxidation by 3-chloroperoxybenzoic acid (*m*-CPBA), *tert*-butyl hydroperoxide 70 wt.% (*t*-BuOOH) or hydrogen peroxide 30 wt.%, mediated by a salen complex in homogeneous medium or encapsulated in a polymeric matrix based on poly(dimethylsiloxane) (PDMS). The formation of carbamazepine 10,11-epoxide (CBZ-EP) is highly dependent on the oxidant, pH, solvent and co-catalyst. CBZ oxidation by *m*-CPBA, *t*-BuOOH and H_2O_2 is more efficient at low pH values, although the pH influence is small in the case of *m*-CPBA and *t*-BuOOH, in the entire pH range. This shows that the presence of substituents linked to the −OOH group of *m*-CPBA and *t*-BuOOH affects the catalytic activity of the studied system significantly. The encapsulated Jacobsen catalyst proved to be an efficient catalyst for carbamazepine oxidation by the oxidants *t*-BuOOH and *m*-CPBA. However, the hybrid polymeric membrane acted as a barrier against the oxidant H_2O_2, preventing it from reaching the bulk of the membrane, making substrate oxidation impossible in this case.

Keywords: Carbamazepine; Salen complex; Catalysis; Biomimetic models

1. Introduction

A number of biomimetic systems have been developed to mimic the function of P-450 enzymes [1]. Development in this area is based on different strategies with the aim of designing selective, stable and high-turnover catalytic systems [2]. Salen complexes, such as the Jacobsen catalyst, and metalloporphyrins have been used as cytochrome P450 models and have been found to be highly efficient homogeneous catalysts for alkene and alkane oxidation in the presence of terminal oxidants such as iodosylbenzene, sodium hypochlorite, sodium periodate, *tert*-butylhydroperoxide and hydrogen peroxide [3–14]. However, there are relatively few reported studies on drug oxidation using metalloporphyrins as catalyst; some examples include carbamazepine [15,16], lidocaine, odapipam, aminopyrine [17], acetaminophen [18,19], and others [20,21]. Recent reviews by Bernadou and Meunier [22] and Mansuy [23] have compiled most of these studies. As for salen complexes, reports on their use as catalysts for drug oxidations are even scarcer in the literature.

Carbamazepine (CBZ), 5-H-dibenz[b,f]azepine-5-carboxamide (Fig. 1) is an antiepileptic drug used in clinical practice as first-line treatment for generalized tonic–clonic and partial seizures [24]. This anticonvulsant is a suitable substrate for epoxidation studies, and it was first used by Meunier in *in vitro* studies using water-soluble metallopophyrins as catalyst. Over the last two decades, 33 CBZ metabolites have been isolated and identified in the urine from patients on an oral dose [25,26]. Of these metabolites, carbamazepine 10,11-epoxide (CBZ-EP) is the most important from a clinical point of view (Fig. 1). In experimental animals, CBZ-EP is as pharmacologically active as the parent compound.

Homogeneous catalysis often provides the best results in terms of product yield, whereas heterogeneous catalysis offers advantages such as easy product purification, potential cat-

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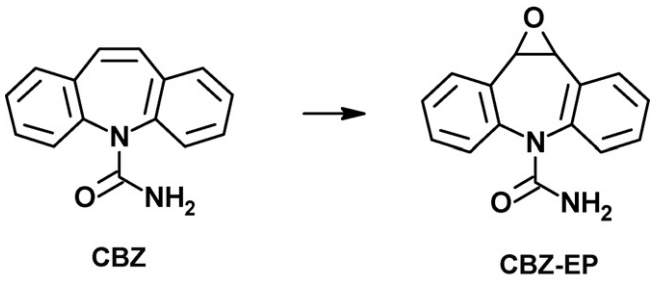

Fig. 1. Carbamazepine (CBZ) and its major metabolite (CBZ-EP).

alyst recycling, and ability to mimic the protein active site of the enzyme [27–30] with regard to the Jacobsen catalyst, another advantage of supporting this complex is obtaining increased stability, since the main deactivation process observed in homogeneous phase, formation of inactive dimeric μ-oxo manganese(IV) species, is hindered when the complex is immobilized on a matrix [31]. A variety of solid supports have been tested, including inorganic matrices such as silica, alumina, zeolites, cationic and anionic clays, as well as polymeric supports [32–36].

Polymeric membranes have been considered innovative materials for immobilization of salen complexes. This support offers many advantages, such as its higher affinity for reagents. The hydrophobic membrane acts as a barrier, isolating and controlling the access of both the substrate and the oxidant to the active site, thus avoiding the presence of excess polar substances in its vicinity, and rendering a hydrophobic environment for substrate binding [30,37,38].

In the present study, we have investigated carbamazepine oxidation mediated by the Jacobsen catalyst, Mn(salen), in homogeneous medium, in order to understand the effect of the axial ligand, solvent, oxidant and pH on the catalytic activity of this complex. We also investigated the role of the polymeric membrane on the reactivity of the encapsulated Jacobsen catalyst in CBZ epoxidation. Although the metabolic pathways of CBZ epoxidation are known, this is the first report on use of the Jacobsen catalyst immobilized on a solid support for drug oxidation.

2. Experimental

2.1. Materials

The Jacobsen catalyst was purchased from Acros Oganics. The synthetic procedure employed for the encapsulation of the catalyst into a polymeric PDMS-based membrane, Mn(salen)-PM (Fig. 2) and the characterization of Mn(salen)-PM by UV–vis spectroscopy, TGA, DTA, DSC, and SEM techniques have been described elsewhere [30].

Carbamazepine (CBZ) and 10,11-carbamazepine oxide (CBZ-EP) were purchased from Sigma–Aldrich Chemical Co. *tert*-butyl hydroperoxide (*t*-BuOOH), 70 wt% solution in water, and 3-chloroperoxybenzoic acid (*m*-CPBA) were acquired from Acros Oganics. Hydrogen peroxide (H_2O_2, 30% in water) was supplied by Fluka and stored at 5 °C; it was periodically titrated to confirm its purity. Acetonitrile (ACN) HPLC grade was purchased from Mallinckrodt. Water used in the experiments was purified by a Milli-Q, Millipore system. Imidazole, 4-*tert*-butylpyridine, trimethylamine *N*-oxide, ammonium acetate, and sodium bicarbonate were acquired from Acros Oganics. Pyridine was obtained from Fluka.

2.2. CBZ epoxidation

In a typical experiment, reactions were carried out in a 3 mL vial containing a screw cap. Briefly, to a vial containing the Jacobsen catalyst (6.0×10^{-7} mol) in solution or immobilized on a polymeric membrane containing 0.02% or 2%

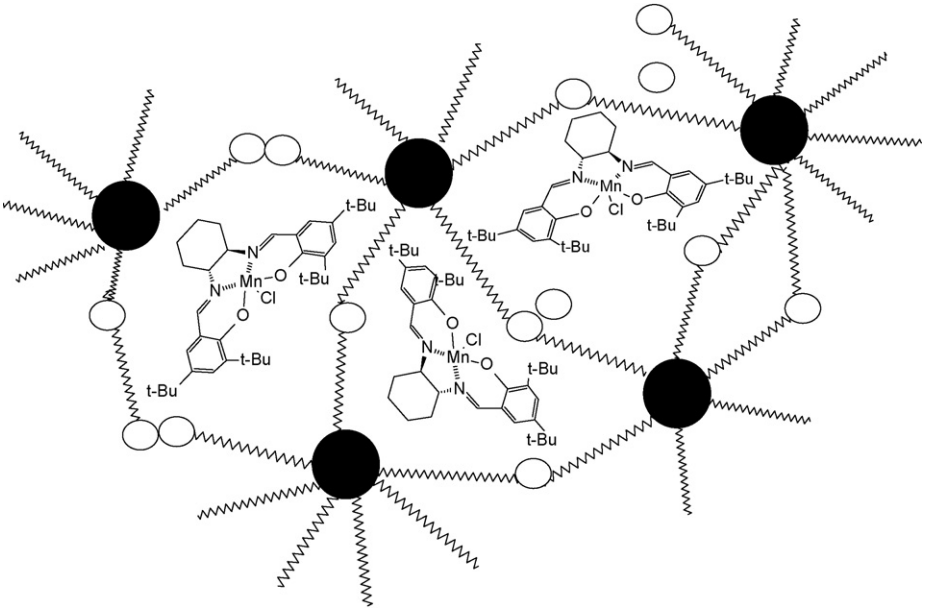

Fig. 2. Jacobsen catalyst encapsulated in a polymeric PDMS-based membrane. Black circle: silica oligomers; white circle: PETA/AS clusters; zigzag line: PDMS.

of Mn(salen) in relation to the total mass of the polymeric membrane (1800 and 18 mg, respectively) we added 5.0 mg of carbamazepine (2.1×10^{-5} mol) and 2.4×10^{-5} mol of the oxidant (*m*-CPBA, *t*-BuOOH or H_2O_2) in buffered aqueous solution and acetonitrile 1:1 (2 mL). Reactions at pH 2 were performed in phosphate buffer, H_3PO_4/NaH_2PO_4 (0.1 mol L^{-1}), at pH 4 in acetate buffer (0.1 mol L^{-1}), at pH 6–8 in phosphate buffer, NaH_2PO_4/Na_2HPO_4 (0.1 mol L^{-1}), and the pH of the reaction solution was adjusted by adding either HCl (0.5 mol L^{-1}) or NaOH (0.5 mol L^{-1}) solutions whenever it was necessary. Reactions were carried out for 2 h homogeneous medium or 24 h heterogeneous medium, under magnetic stirring at room temperature, at a catalyst:oxidant:drug molar ratio of 1:40:35. At the end of the reaction, magnetic stirring was interrupted, and an aliquot of the reaction mixture (50 μL) was withdrawn. After Mn(salen) extraction, this aliquot was analyzed by high performance liquid chromatography (HPLC). Mn(salen) extraction was carried out by addition of hexane (500 μL) and a mobile phase (500 μL). The mixture was vortex-mixed and centrifugated; the aqueous phase (mobile phase) was then injected into the chromatographic system. This clean-up procedure did not remove unreacted carbamazepine or the oxidation products. The oxidation product was identified by comparing its retention time with those of an authentic CBZ-EP standard. Yields are based on the added drug and were determined by a calibration curve.

The axial ligand effect was investigated for reactions performed in the presence of imidazole, pyridine, 4-*tert*-butylpyridine, trimethylamine *N*-oxide, ammonium acetate or sodium bicarbonate, at a Mn(salen):axial ligand molar ratio of 1:10.

Control reactions were carried out under the same conditions in the absence of the catalyst and in the presence of the polymeric membrane alone.

2.3. HPLC analyses

The HPLC analyses were performed on a SHIMADZU liquid chromatograph equipped with an LC-10AS solvent pump, an SPD-M 10A VP spectrophotometric detector coupled to a CTO-10A VP column oven, and an SCL-10A VP system controller. Separation of the carbamazepine and the oxidation product (CBZ-EP) was carried out in a Lichrospher 100RP-18 column, with a particle size of 5 μm (125 mm × 4 mm), supplied by Merck. The analytical column was protected by a Lichrospher guard column (4 mm × 4 mm). The mobile phase consisted of Milli-Q water/acetonitrile 70:30 (v/v), flow rate of 1 mL/min, detection was carried out at 210 nm. The isocratic system was operated at ambient temperature and required less than 15 min of chromatographic time.

3. Results and discussion

3.1. The effect of different solvents on the epoxidation of carbamazepine by m-CPBA catalyzed by Mn(salen)

In order to choose the best reaction medium, acetonitrile, methanol, ethanol, dichloromethane and dichloroethane were tested for carbamazepine oxidation reactions. The results are shown in Table 1.

Table 1
The effect of different solvents on carbamazepine epoxidation catalyzed by Mn(salen) using *m*-CPBA as oxidant

Entry	Solvent	Epoxide yield (%)[a]
1	Acetonitrile (CAN)	69
2	Methanol (MeOH)	44
3	Ethanol (EtOH)	41
4	Dichloromethane (DCM)	9
5	Dichloroethane (DCE)	13

Catalyst:co-catalyst:substrate:oxidant molar ratio = 1:10:40:35. Blank reactions (absence of catalyst): CBZ-EP not detected.
[a] Epoxide yields (%) were measured relative to the CBZ at pH 4.

Carbamazepine solubility was a determinant of the epoxide yield, once the studied drug is a solid with limited solubility in apolar solvents. Therefore, in the case of dichloromethane and dichloroethane, in which carbamazepine could not dissolve completely, low catalytic activity was obtained (Table 1, entries 4 and 5). In contrast, high CBZ-EP yields were obtained in polar solvents, where the drug was soluble (Table 1, entries 1–3).

Among the polar solvents, the efficiency of the Jacobsen catalyst in methanol and ethanol was lower compared to acetonitrile. This is because the alcohol can act as a substrate, thus competing with carbamazepine for the catalytic species, leading to the formation of unwanted by-products. In acetonitrile, which does not compete with CBZ for the catalitically active species, the Jacobsen catalyst was able to oxidize the drug with yields as high as 69%. Such high yields are due to the higher ability of ACN to stabilize the intermediate catalytic species oxo-manganese (V) since this solvent has a high donor number (DN = 14.1) [39,40]. ACN was also the most efficient in several other reported systems involving salen complexes [14,41,42].

3.2. The effect of different oxidants and pH on carbamazepine epoxidation catalyzed by Mn(salen)

Several oxygen donors such as $KHSO_5$, *m*-CPBA and *t*-BuOOH have been used for carbamazepine oxidation in systems involving water-soluble metalloporphyrins [43,44]. These studies showed the important dependence of CBZ-epoxide formation on the pH of the reaction solutions. CBZ conversion was above 70% in acidic solutions, with a decrease in the catalytic efficiency above pH 6 [43]. In contrast, when iron and manganese complexes of cross-bridged tetraazamacrocycles were used as catalyst, the oxidation at pH 10 produced four more times CBZ-EP compared to the reaction at pH 7, using H_2O_2 as oxidant [45]. In studies with cobalt-containing polyoxotungstate $[Co(PW_{11}O_{39})]^{5-}$ and $KHSO_5$ as oxidant, the oxide product yield was high at pH 5, whereas only small amounts of CBZ-EP were obtained at low and high pH values (e.g., pH <3 and >6). As for the oxidants *t*-BuOOH and H_2O_2 they did not produce any CBZ-EP in the presence of $[Co(PW_{11}O_{39})]^{5-}$ as catalyst [46]. In view of these contrasting results, we decided to study the pH effect on carbamazepine oxidation by *m*-CPBA, *t*-BuOOH and

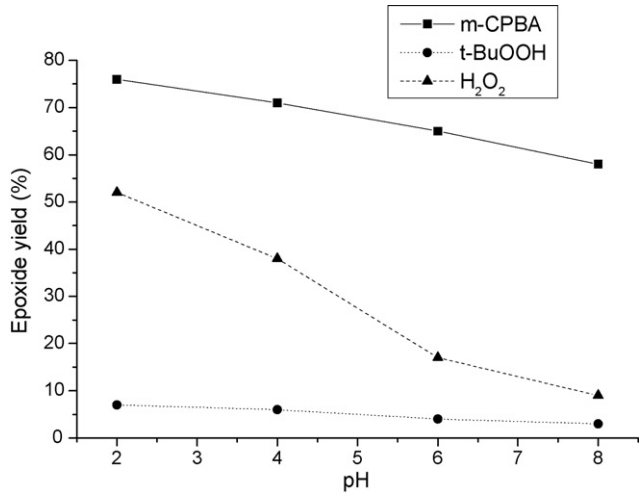

Fig. 3. The effect of pH on the epoxide yield in carbamazepine oxidation catalyzed by the Jacobsen catalyst with different oxidants, in acetonitrile media. Blank reactions under similar acidic conditions (absence of catalyst): CBZ-EP not detected.

H_2O_2 catalyzed by the Jacobsen catalyst, in order to understand the pH influence on the O–O bond cleavage.

Fig. 3 shows that the pH dependence is related to the oxidant. There is slight pH dependence in the case of *m*-CPBA and *t*-BuOOH in the entire pH range, while the pH effect is essential for H_2O_2. This may imply that the O–O bond cleavage depends on solution pH. O–O bond homolysis, which leads to low epoxide yields, prevails at high pH, while O–O bond heterolysis, responsible for high epoxide formation, becomes a predominant pathway at low pH. The presence of a high proton concentration helps stabilize the charge-separated heterolytic transition state, with formation of Mn^V(O)salen species, which efficiently promote oxygen transfer to CBZ, producing CBZ-EP [43].

Fig. 3 also shows that peroxide O–O bond cleavage is sensitive to the substituents linked to the –OOH group. The O–O bond containing an electrondonating *tert*-alkyl group tends to be cleaved homolytically, resulting in low epoxide yields (Fig. 3). In contrast, an electronwithdrawing substituent such as an acyl group in *m*-CPBA facilitates O–O bond heterolysis, resulting in the formation of oxo-manganese (V) species, which lead to higher epoxide yields (76%, pH 2, Fig. 3).

3.3. The effect of different co-catalysts on carbamazepine epoxidation by H_2O_2 catalyzed by Mn(salen)

The effect of various axial ligands such as imidazole, pyridine, 4-*tert*-butylpyridine, trimetylamine *N*-oxide, ammonium acetate and sodium bicarbonate as co-catalyst was investigated in carbamazepine epoxidation by H_2O_2, to mimic the effect of the axially coordinated histidine and thiolate residue in peroxidase and cytochrome P-450 enzymes, respectively. Results are presented in Table 2.

Good yields were achieved in reactions carried out in the presence of the nitrogen bases imidazole, 4-*tert*-butylpyridine, and trimethylamine *N*-oxide (Table 2, entries 2, 4 and 5, respectively). These ligands can coordinate to the manganese ion in

Table 2
The effect of different axial ligands on carbamazepine epoxidation by H_2O_2 catalyzed by Mn(salen)

Entry	Co-catalyst	Epoxide yield (%)[a]
1	Absence of co-catalyst	38
2	Imidazole	59
3	Pyridine	39
4	4-*tert*-Butylpyridine	47
5	Trimethylamine *N*-oxide	53
6	Ammonium acetate	66
7	Sodium bicarbonate	61

Catalyst:co-catalyst:substrate:oxidant molar ratio = 1:10:40:35. Blank reactions (absence of catalyst): CBZ-EP not detected.
[a] Epoxide yields (%) were measured relative to CBZ at pH 4.

the position *trans* to the metal–oxo bond, thus stabilizing the intermediate catalytic species Mn^V(O)salen [47]. This intermediate is responsible for efficient, stereoselective oxidations. The presence of these axial ligands also prevent reduction of the Mn^V(O)salen species to Mn^{IV}(O)salen, which is responsible for non-selective and little efficient radicalar reactions. Imidazole also acts as an acid–base catalyst, favoring heterolytic cleavage of the peroxide bond, with formation of the high-valent oxo–metal intermediate. As expected, pyridine has no significant effect on the epoxide yields, because it has weaker ligand affinity for the Mn(III) ion [47]. The donor strength of the *trans*-axial ligand influences the electron density on the metal–oxo moiety of the active complex, either through σ- or π-charge donation, and is responsible for the different activities observed with the different co-catalysts. σ-Donation is expected to increase the rate of oxygen loss from the catalyst. Conversely, significant axial π-donation should decrease the ability of the catalyst to epoxidize a given substrate, by raising the energy of the catalyst's critical acceptor orbital [48]. Pyridine is a better π-donor than imidazole, which may account for the poorer results obtained when the former was employed as co-catalyst.

Carboxylate salts, such as ammonium acetate and sodium bicarbonate, were more efficient co-catalysts than the nitrogen bases (Table 2, entries 6 and 7 versus 1–5) for salen-catalyzed carbamazepine epoxidation by H_2O_2. Similar results were reported in the literature [49] when carboxylate salts (ammonium acetate) were employed for alkene epoxidation in metalloporphyrin/H_2O_2 systems. The role of the carboxylate salts in Mn(salen) catalyzed oxidation reactions is not fully clear.

Carboxylate salts can promote the formation of HO_2^- from H_2O_2, which facilitates Mn^V(O)salen complex formation via a peroxyacylmanganese species. This peroxyacylmanganese can also oxidize carbamazepine as shown in Fig. 4 [50–53]. The peroxyacylmanganese species have been proposed by Yamada and other researchers as being the active species in other catalytic systems [51,54–56]. A similar catalytic route such as nos. 1–4 (Fig. 4) has been proposed for the Mn-porphyrin catalyzed oxidation of alkenes in the presence of a carboxylic acid co-catalyst [57,58].

The best results obtained with carboxilate salts can be also due to the larger stability of these ligands when compared with the nitrogen bases. Amine bases such as imidazole could themselves be oxidized to N-oxides [59,60]. Furthermore, there is

Table 3
Results obtained for carbamazepine oxidation reactions catalyzed by Mn(salen), Mn(salen)-PM-0.02% and Mn(salen)-PM-2%

Entry	Catalyst	Oxidant	Sorption measurements[a]	Epoxide yield (%)[b]
1	Mn(salen)-PM-0.02%	*m*-CPBA	3.3	73
2	Mn(salen)-PM-2%	*m*-CPBA	3.3	65
3	Mn(salen)-PM-0.02%	H_2O_2	0.9	nd
4	Mn(salen)-PM-2%	H_2O_2	0.9	nd
5	Mn(salen)-PM-0.02%	*t*-BuOOH	2.6	44
6	Mn(salen)-PM-2%	*t*-BuOOH	2.6	37

[a] mmol of oxidant/g of membrane. For the sorption measurements, membranes without catalyst were immersed in the oxidants. Membrane swelling was monitored until the film had reached a constant weight.
[b] Epoxide yields (%) were measured relative to the CBZ. Catalyst:substrate:oxidant molar ratio = 1:40:35. Blank reactions (absence of catalyst): CBZ-EP not detected.

the possibility that the acetonitrile used as solvent could participate in the epoxidation or destruction of imidazole through acetylperoxyimidic acid formation (Payne-type oxidation) [61].

3.4. Carbamazepine epoxidation by m-CPBA, t-BuOOH and H_2O_2 catalyzed by Mn(salen) occluded in a hybrid polymeric membrane

The hybrid polymeric membrane was evaluated because it mimic, the protein cavity of cytochrome P450. Therefore, this support could provide a change of mechanism or selectivity of the biomimetic reaction when compared to the conventional homogeneous catalysts. This material was prepared by a polycondensation reaction between poly(dimethylsiloxane) (PDMS) and the alkoxyde groups of pentaerythritholtriacrylate (PETA), 2-aminoethyl-3-aminopropyltrimethoxysilane (AS) and tetraethoxysilane (TEOS). The Jacobsen catalyst was encapsulated in the free volume of the PDMS polymeric network. The synthetic procedure and the characterization of Mn(salen)-PM by UV–vis spectroscopy, TGA, DTA, DSC and SEM techniques have already been described elsewhere [30].

In order to investigate whether catalyst leaching could occur during the oxidation reactions, the supernatant was filtered at the end of the oxidation and allowed to react further in the same conditions. No additional epoxide was produced from the carbamazepine oxidation, indicating that the catalytic activity of this supported material is truly heterogeneous in nature and this complex was not leached from the matrix.

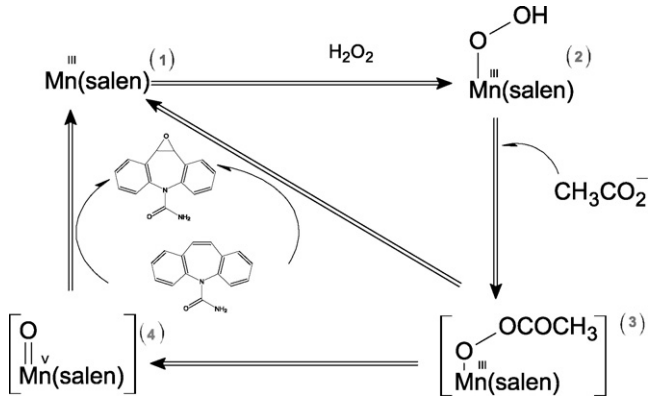

Fig. 4. Possible catalytic route for carbamazepine epoxidation catalyzed by the Jacobsen catalyst using carboxylate salts by H_2O_2 as oxidant.

In this catalytic system, product yields are essentially controlled by the sorption of reagents in the polymeric membrane *m*-CPBA and *t*-BuOOH have a moderate hydrophobic character, which favours their sorption in the polymeric membrane (Table 3, entries 2 and 7). As a result, the systems involving these oxidants proved to be efficient for carbamazepine oxidation, as shown in Table 3. However, with a more hydrophilic oxidant such as H_2O_2, Mn(salen)-PM is an inefficient catalyst since the hydrophobic polymeric membrane acts as a barrier against the hydrophilic oxidant H_2O_2, preventing its sorption in the membrane (sorption $H_2O_2 = 0.9\ mmol\ g^{-1}$, Table 3, entries 3 and 4).

The higher *m*-CPBA sorption value compared to that of *t*-BuOOH accounts for the higher epoxide yield obtained with the first oxidant (Table 3, entries 1 and 5). The polymeric membrane also exhibits lower affinity for the more polar oxidation product (CBZ-EP), promoting its fast desorption to the reaction media.

In order to investigate the effect of the membrane sorption capability on the oxidation reaction without changing the number of mol of catalyst, two membranes with different catalyst contents were prepared. These membranes enabled us to compare the influence of sorption using membrane pieces of different size, but maintaining the same number of mol of catalyst on each size. In Table 3 we can see there is a decrease of 7–8% in epoxide yields for reactions with Mn(salen)-PM 2%, when compared to the reactions using the membrane containing 0.02% catalyst, although both of them contain the same amount of catalyst (6.0×10^{-7} mol Mn(salen); Experimental, Section 2.2). Since the size of the more concentrated membrane (Mn(salen)-PM 2%) used in the reactions necessary to achieve 6.0×10^{-7} mol Mn(salen) was smaller than the size of the membrane Mn(salen)-PM 0.02%, there was lower substrate and/or oxidant sorption capacities, which seems to be the limiting reaction factor in these systems compared to the Mn(salen)-PM 0.02%.

4. Conclusions

Carbamazepine oxidation mediated by the Jacobsen catalyst in homogeneous medium and encapsulated in a polymeric PDMS-based membrane was investigated. CBZ-EP formation is highly dependent on the oxidant, pH, solvent and co-catalyst. The oxidants *m*-CPBA, *t*-BuOOH and H_2O_2 are more efficient at low pH values, although the influence of the pH is small for

m-CPBA and *t*-BuOOH in the entire pH range. This shows that the presence of substituents linked to the –OOH group of *m*-CPBA and *t*-BuOOH significantly affect the catalytic activity of the studied system. Carboxylate salts, such as ammonium acetate and sodium bicarbonate, are more efficient co-catalysts than nitrogen bases.

Despite the typical limitations of heterogeneous systems, the catalytic results show that the support is able to concentrate the reagents close to the catalyst in the case of the oxidants *m*-CPBA and *t*-BuOOH. The polymeric membrane used in this work is capable of controlling both the oxidant access to the active site and the reactivity of the active species, leading to selective oxidation reactions with *m*-CPBA and *t*-BuOOH as oxidant, so the support acts as a good model for the protein cavity of cytochrome P450, preventing inactivation via dimer formation. However, the oxidant H_2O_2 was not able to epoxidize CBZ in this catalytic system because the hydrophobic membrane creates a barrier against the hydrophilic hydrogen peroxide, preventing its sorption and, therefore, making carbamazepine oxidation impossible in this case.

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