Abstract: The modelling of metabolic activation of the benzofuran nucleus is important to obtain eco-sustainable degradation methods and to understand the related mechanisms. The present work reports the catalytic oxidation of benzofuran, 2-methylbenzofuran, and 3-methylbenzofuran by hydrogen peroxide, at room temperature, in the presence of different Mn(III) porphyrins as models of cytochrome P450 enzymes. Conversions above 95% were attained for all the substrates. The key step is the formation of epoxides, which undergo different reaction pathways depending on factors, such as the position of the methyl group and the reaction and work-up conditions used.

Keywords: benzofurans; biomimetic oxidation; catalysis; manganese porphyrins; hydrogen peroxide

1. Introduction

The enzymes of the cytochrome P450 (CYP) group play a central role in the metabolism of xenobiotics [1,2]. These enzymes have been identified in all forms of living organisms, from mammals to bacteria, and mainly define the biological action of drugs and pollutants, as well as their environmental fate [3]. CYPs act during phase I of metabolism, performing oxygenation of the substrate [1], and have a significant part in the overall metabolism, and were found to be responsible for about 75% of the known enzymatic reactions on drugs [4].

The possibility of modulating the metabolic activation of these enzymes using synthetic metalloporphyrins has been studied extensively in the last decades [5–9]. In this context, metalloporphyrins carrying electron-withdrawing moieties have succeeded in modelling CYPs active center that includes the iron complex of protoporphyrin IX (heme group) [10,11]. Efficient biomimetic approaches have advantages, as synthetic porphyrins are readily available and much easier to handle than the purified enzymes [7].

Biomimetic processes are also a convenient alternative for eco-sustainable oxidation processes, since they allow the use of green oxidants, such as H_{2}O_{2} or O_{2} (that afford water as the only by-product), and mild conditions [12–17]. This leads to a significant reduction of environmental impact relative to stoichiometric oxidants, such as Cr_{2}O_{7}^{2−}, MnO_{4}^{−}, and dimethyldioxirane (DMO), or milder but expensive oxidants that also generate sub-products, such as m-chloroperoxybenzoic acid (m-CPBA), PhIO, ClO^{−}, HSO_{5}^{−}, and IO_{4}^{−}.

Benzofurans are among the pollutants found in the environment as a result of waste incineration and as exhaust gases of gasoline and diesel engines [18]. The 2,3-benzofuran is known to be toxic and...
is associated with mutagenesis and carcinogenesis. As for other polycyclic aromatic compounds, its
toxicity is attributed to the formation of the reactive arene oxide in vivo during its metabolism [19],
which then readily reacts with biomolecules, including DNA. On the other hand, a broad spectrum
of clinically approved pharmaceuticals contain the benzofuran nucleus decorated with different
functionalities [20,21]. Compounds containing the benzofuran core structure show antimicrobial [22],
anti-inflammatory [23], antitumor [24], or antioxidant activity [25]. Moreover, a series of benzofuran
derivatives is already being used to treat Alzheimer’s disease [26]. Thus, the study of biomimetic
oxidations of benzofurans is important for a further understanding of their metabolic pathways and
toxicity mechanisms.

The oxidation of substituted 2,3-benzofurans has already been studied with m-CPBA or DMD as
oxidants, leading to reactive epoxides that can be further oxidized, affording ring-opening products,
such as keto esters, spiroepoxides, and benzodioxole (Figure 1; right side) [27]. The profile of these
reactions depends on the substituents, amount of oxidant, and temperature. Additionally, the epoxides
can be rearranged at room temperature, affording benzo[3]- and allylic alcohols from hydrogen transposition (Figure 1; left side) [27].

![Figure 1](image.png)

**Figure 1.** Most common isolated products from the oxidation of substituted benzofurans with m-CPBA or dimethyldioxirane (adapted from [27]).

The oxidation of benzofuran (BF), 2-methylbenzofuran (2MBF), and 3-methylbenzofuran (3MBF)
in the presence of an Fe(III) porphyrin and hydrogen peroxide was recently reported by us, and
afforded a one-pot, green, and versatile method for the synthesis of novel and biologically active
compounds [28]. The significantly different reactivity observed for iron and manganese porphyrins
has been ascribed to the formation of different catalytic intermediates [10,29]. Some Mn(III) porphyrins
have been used with success as models of CYPs in the oxidation of aromatic compounds, leading
mainly to arene oxide products [19,30]. These systems required the presence of a co-catalyst for the
activation of H\textsubscript{2}O\textsubscript{2} [31] and their action has been ascribed to the typical reactivity of a metalloporphyrin
oxo-species [Mn(V)=O] intermediate [29].

The present study describes the oxidation of BF, 2MBF, and 3MBF by hydrogen peroxide in
the presence of the three manganese(III) porphyrin complexes depicted in Figure 2. The product
mixtures are analyzed and mechanisms proposed for the transformations of the benzofurans using
these biomimetic conditions.
When using H₂O₂ as the oxidant, the absence of a co-catalyst leads to inactivation of the biomimetic systems [31]. The catalytic reactions were carried out at room temperature with acetonitrile as the reaction solvent and in the presence of a co-catalyst that mimics the proton-donating amino acids in the active site of CYPs (Figure 2b) [10]. The co-catalysts provide the appropriate proton concentration for generation of the active oxidant, which is considered to be the high-valent oxo-species. This is proposed to occur by successive deprotonation and protonation steps (Figure 2c). Ammonium acetate (buffer pH ~7) was shown to be an efficient co-catalyst for CAT I and CAT II [31,34], whereas for CAT III the best co-catalyst was acetic acid [35]. This difference can be explained by the presence of positive groups in CAT III, which induce greater acidity at the Mn center and lead to the need for a more acidic medium in the protonation and dehydration steps (Figure 2c). When using H₂O₂ as the oxidant, the absence of a co-catalyst leads to inactivation of the biomimetic systems [31].

The hydrogen peroxide was progressively added to the reaction mixture at a constant rate of 0.6 mmol/h (two equivalents of oxidant per hour for each equivalent of substrate) and the reactions were monitored by GC-FID until no additional conversion of substrate was observed. Figure 3 shows the results obtained with a catalyst loading of 0.3 mol%. The systems based on CATs I and III show a substrate conversion always higher than 95%, while systems based on CAT II are slightly less efficient and show substrate conversions in the range 80%–94%. The reaction times depend on the substrate and catalyst, but the reactions were typically complete after 2 to 4 h. The slightly lower activity of CAT II compared to CAT I might be explained by a higher oxidation potential (due to the electron-withdrawing fluorine groups) hampering formation of the oxo-species (Figure 2c) [29]. A higher catalyst loading of 0.7 mol% was also tested (see the Supplementary Material, Section S1, Figure S1). Reaction completion times were the same as or shorter than those shown in Figure 3. Higher conversions were also observed, especially for CAT II.

**Figure 2.** Biomimetic systems: (a) structures of the Mn(III) porphyrins used as catalysts; (b) adapted representation of P450cam active site [10]; (c) mechanism proposed for the biomimetic generation of oxo-species, where the co-catalysts mimic the action of proton-donating amino acids from the P450 active site.

### 2. Results and Discussion

#### 2.1. Comparisons of Metalloporphyrin Catalyst Performance

The oxidation of benzofurans by hydrogen peroxide was evaluated in the presence of the second generation manganese(III) catalysts presented in Figure 2a and referred to from now on as CAT I, II, and III. Neutral Mn(III) porphyrins I and II were prepared by a microwave procedure in eco-sustainable conditions using nonhazardous solvents [32,33]. The catalytic reactions were carried out at room temperature with acetonitrile as the reaction solvent and in the presence of a co-catalyst that mimics the proton-donating amino acids in the active site of CYPs (Figure 2b) [10]. The co-catalysts provide the appropriate proton concentration for generation of the active oxidant, which is considered to be the high-valent oxo-species. This is proposed to occur by successive deprotonation/protonation steps (Figure 2c). Ammonium acetate (buffer pH ~7) was shown to be an efficient co-catalyst for CAT I and CAT II [31,34], whereas for CAT III the best co-catalyst was acetic acid [35]. This difference can be explained by the presence of positive groups in CAT III, which induce greater acidity at the Mn center and lead to the need for a more acidic medium in the protonation and dehydration steps (Figure 2c). When using H₂O₂ as the oxidant, the absence of a co-catalyst leads to inactivation of the biomimetic systems [31].
Control experiments were performed for the three substrates. No substrate conversion was observed during a period of 3 h before H$_2$O$_2$ addition, indicating that molecular oxygen is not being used as an oxidant by the catalysts. For reactions in the absence of catalyst, no significant conversion of the substrate was detected (<10%).

2.2. Benzofuran (BF) Oxidation Reactions

Analysis by GC-FID of the BF oxidation reactions using the CAT I/NH$_4$AcO catalytic system showed high substrate conversion even though only a single small product peak was detected (Figure 4). The product was identified by GC-MS as salicylaldehyde [1 (SA), Scheme 1] (M$^+$ at m/z 122.1). After 3 h corresponding to a ratio oxidant/substrate (Ox/S) of 6, SA was obtained in a 15% yield (based on the SA concentration in the mixture measured by the GC internal standard method).

The formation of SA can be explained as proposed in Scheme 1 for BF (R$_1$ = R$_2$ = H), leading to SA and formaldehyde.

The low yield of SA shows that other compounds are being formed which are not detected by GC. In order to identify other possible reaction products, the BF reaction mixtures formed in the presence of CAT I and NH$_4$AcO were analyzed by high resolution mass spectrometry with electrospray ionization in the positive mode (HRMS-ESI$^+$) and tandem MS$^n$ studies.

Previous work on the biomimetic oxidation of BF using iron porphyrins has shown that the products formed depend on the solvent evaporation temperature and on the Ox/S ratio [28]. Lower Ox/S ratios resulted in less degradation of the BF ring system. For reactions investigated with an Ox/S ratio of 4, the compositions of the final reaction mixtures were analyzed by MS studies before solvent evaporation, after solvent evaporation at RT, and after solvent evaporation at 30 °C (Figure 5a–c). Then, the mass spectra of reactions with Ox/S ratios of 4 and 6 were compared for solvent evaporation at RT (Figure 5b,d).
The ions detected (Figure 5e) were analyzed by detailed HRMS<sup>n</sup> studies. The MS<sup>n</sup> spectra of the 15 products (1a, 2–4, 5a, 6–15) and the observed fragments are given in Figures S2–S16 of the Supplementary Materials. A detailed reaction scheme with suggested mechanisms for the formation of these products is shown in Scheme 2.

All the ions detected contained nitrogen, indicating reactions with ammonia from the NH<sub>4</sub>AcO co-catalyst. Protonation in the MS source is much easier for the nitrogen versus oxygen groups, probably contributing to the predominance of signals observed for the protonated nitrogen species. Most of the products were only identified by mass spectrometry, but compounds 1a and 5a were isolated as the carbonyl derivatives 1 and 5 (see below).

The observed products can be justified by considering the initial reaction of BF oxide (BF-O) to afford SA (1) and BF-NH<sub>2</sub> as primary products (Scheme 2a). Nucleophilic attack of BF-O by NH<sub>3</sub> present in the reaction media (from the NH<sub>4</sub><sup>+</sup>/NH<sub>3</sub> equilibrium of the NH<sub>4</sub>AcO co-catalyst) might afford BF-NH<sub>2</sub>, and NH<sub>3</sub> might also react with the carbonyl group SA to form the corresponding imine (1a, Scheme 2a).

Oxirane ring opening by SA affords compound 5 (Scheme 2b), which may undergo further reactions, such as imine formation to 5a, oxidation to the o xo derivative (5-ox), and elimination of water, which are key steps in the formation of the other derivatives (2, 4, 8, 9, 10, 11) presented in Scheme 2b.

The products presented in Scheme 2c can be explained as a result of dimerization reactions between two salicylic units, followed by transformations such as oxidation (3 and 6), reaction with BF-O, and elimination of water (12).

Another set of products results from the reaction between BF-NH<sub>2</sub> and BF-O (Scheme 2d) to afford intermediate BF-2 through successive epoxide ring opening, oxidation of hydroxyl group to an oxo derivative, and dehydration. BF-2 is the key intermediate in the intramolecular cyclisation reaction (through imine—double bond reactions) to afford compound 7 [36] and in the reaction with SA (imine form, 1a) to afford 13. Further reaction of 7 with SA affords 14. Derivative 15 results from the condensation reaction of BF-NH<sub>2</sub> with the imine form of 5-ox.
reaction mixtures show major ions corresponding to products with \(m/z > 200\). The products formed also depend on the evaporation temperature. Finally, when the work-up consists of solvent evaporation at RT and an Ox/S ratio of 4 vs. 6 (Figure 5b,d), similar molecular ions are observed. However, for Ox/S 6 the most intense signal is seen for the more oxygenated species \((m/z = 258)\) instead of \((m/z = 242)\).

It is noteworthy that the mass spectrum pattern is different before and after solvent evaporation (Figure 5a–c). This can be explained by reactions between the primary products being formed (Scheme 2a), which increases during the concentration of the reaction mixture. After evaporation, the reaction mixtures show major ions corresponding to products with \(m/z > 200\). The products formed also depend on the evaporation temperature. Finally, when the work-up consists of solvent evaporation at...
RT and an Ox/S ratio of 4 vs. 6 (Figure 5b,d), similar molecular ions are observed. However, for Ox/S 6 the most intense signal is seen for the more oxygenated species 6 (m/z 258) instead of 3 (m/z 242).

Scheme 2. Reaction schemes proposed for the formation of BF products occurring by: (a) reaction of BF oxide (BF-O) with H2O or NH3; (b) reaction of BF-O with salicylaldehyde (SA); (c) reaction between two salicyl units; (d) reaction of BF-O with an amino derivative (BF-NH2). (i) imine formation (NH3; -H2O); (ii) intramolecular cyclization. The m/z values correspond to [M + H]+ ions identified by HRMS. Compounds 1 and 5 were also characterized by NMR spectroscopy.
With the objective of isolating some of the compounds detected by mass spectrometry, the reaction mixture resulting from BF oxidation using an Ox/S ratio of 4 was fractionated by preparative TLC before solvent evaporation (conditions of Figure 5a). The position of the compounds in the TLC plates was revealed with concentrated H₂SO₄ (see Experimental Section). TLC fractionation afforded compounds 1 (30% yield) and 5 (25% yield) (Scheme 2b, inside a dashed frame) which were analyzed by NMR spectroscopy (see Experimental Section and Figures S19 and S20). The higher yield obtained for 1 (SA) in the present conditions (30%) relative to that obtained by GC-FID analysis (15%) can be justified by the lower Ox/S ratio (4 vs. 6) and by the high temperature of the FID injector (200 °C) which can promote coupling reactions involving SA leading to non-volatile products.

The fractionation by TLC of a similar reaction after solvent evaporation in the hood at 16 to 18 °C (conditions of Figure 5b) afforded a fraction containing the ion m/z 265.10 that was assigned to compound 7 (Scheme 2d and Figure S8). The compound corresponding to the intense peak at m/z 242 (3, Scheme 2c) was not isolated by preparative TLC, probably because it results from hemiacetal formation between two SA units (Scheme 2c), which is a reversible reaction, and oxidation to the ester occurs in the MS source.

Notably, when the oxidation reaction of BF in the presence of CAT III with acetic acid as co-catalyst and an Ox/S ratio of 6 was analyzed by GC–MS (EI), only a single product is observed with a molecular ion at m/z 140 corresponding to SA plus a water molecule.

According to a SciFinder™ search, compound 5 has not previously been reported.

2.3. Oxidation Products of 2-Methylbenzofuran (2MBF)

The oxidation reactions of 2MBF were also investigated in the presence of CAT I and NH₄AcO, using an Ox/S ratio of 4, and the solvent evaporated in the hood at 20 °C. These conditions are similar to those used for BF in Figure 5b. The products were identified by high resolution ESI-MS (Supplementary Materials, Figure S17). The reaction mixture was then fractionated by preparative TLC with the three fractions isolated showing mass spectra corresponding to compounds 16–18 (Scheme 3a). MS spectra and mass fragment analyses are collected in Figures S17 and S18 of the Supplementary Material. Compound 16 was also analyzed by NMR in CDCl₃ (see Experimental and Supplementary Material, Figure S21) as the oxo form (ring-opened). In DMSO-d₆, a hydrogen-bond acceptor solvent, the hemiacetal form (ring-closed) of 16 was detected [28].

A rationalization for the formation of compounds 16–18 is shown in Scheme 3b. Initial formation of 2MBF oxide (2MBF-O) is followed by a sequence of reactions after the epoxide ring-opening in the presence of nucleophiles (Scheme 3b). The AcOH required for the formation of compound 16 results from the use of NH₄AcO as the co-catalyst. Moreover, in accordance with Scheme 1 for 2MBF (R₁ = CH₃; R₂ = H), the cleavage of the 2MBF-diol intermediate and decarboxylation leads to SA (1) and acetaldehyde which are involved in the formation of compounds 17 and 18.

The nucleophilic attack on 2MBF-O at the less electron-deficient carbon (position-3) might be justified by the steric hindrance of the methyl group at position-2. Reaction of 2MBF-O with acetic acid produces compound 16. On the other hand, the attack of salicylaldehyde (SA) at position-3 of 2MBF oxide affords intermediate I and its open form (oxo) in a keto-enol equilibrium. The enol can undergo intramolecular cyclisation reaction between the double bond and the imine group (similar to that described for formation of compound 7) and evolve to six-side (I-s6) or five-side (I-s5) intermediates. Evolution of I-s6 through oxidation and reaction with NH₃ and acetaldehyde justifies the formation of compound 17. The I-s5 is proposed to evolve to 18 through the loss of a phenol moiety concomitant to aromatization followed by an imine–imine coupling reaction.

According to a SciFinder™ search, compound 16 (in closed or open forms) has not previously been reported.

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a) 

\[ \text{2MBF} + \text{H}_2\text{O}_2 \xrightarrow{\text{CAT I}} \text{2MBF-O} \]

\[ \begin{align*} \text{16} & \quad \text{17} \\ \text{18} & \quad \text{19} \end{align*} \]

b) 

\[ \text{2MBF} + \text{H}_2\text{O}_2 \xrightarrow{\text{CAT I}} \text{2MBF-O} \]

\[ \begin{align*} \text{16} & \quad \text{17} \\ \text{18} & \quad \text{19} \end{align*} \]

Scheme 3. (a) Major products identified by HRMSn studies in the 2MBF oxidation reactions and (b) a mechanistic proposal for their formation. Compound 16 was also identified by $^1$H and $^{13}$C NMR spectroscopy.

2.4. Oxidation of 3-Methylbenzofuran (3MBF)

Finally, the catalytic oxidation reactions of 3MBF were investigated. The final reaction mixture obtained in the presence of CAT I and NH$_4$AcO with Ox/S = 4 was analyzed by GC-MS; the major product was identified as the lactone 19 (3-methylbenzofuran-2(3$H$)-one), and the minor one as 2'-hydroxyacetophenone 20 (Scheme 4). $^1$H NMR analysis of the total reaction mixture confirmed the identification of the compounds (see Experimental Section and the Supplementary Material, Figures S22 to S25) and also that no other products were present in the reaction mixture except for traces of the substrate 3MBF.

\[ \text{3MBF} \xrightarrow{\text{Ox}} \begin{align*} \text{19} & \quad \text{20} \end{align*} \]

Scheme 4. Products from 3MBF oxidation reactions identified by GC-MS and $^1$H NMR of the total reaction mixtures. Compounds 19 and 20 were also identified by $^1$H NMR spectroscopy.

The formation of compound 19 can be explained as depicted in Scheme 5. After the epoxidation at the 2,3-positions of 3MBF, there is an internal rearrangement of the oxirane ring in 3MBF-O to the enol derivative (3-methylbenzofuran-2(3$H$)-ol). Once formed, the enol moiety can be in equilibrium with the corresponding keto form, which is a particularly stable structure due to the lactone group. An alternative pathway is the epoxide ring opening to the diol followed by water elimination. Compound 20 may form in accordance with the mechanism described in Scheme 1 for 3MBF (R$_1$ = H; R$_2$ = CH$_3$).
Scheme 5. Conversion of 3MBF oxide into the lactone derivative.

The number of products obtained when 3MBF is oxidized is strikingly small compared to the large number of compounds seen for the oxidation of BF. Moreover, a similar product profile was noted when GC-FID was used to quantify the products and to obtain the conversions and selectivities for the different catalysts I, II, and III (Table 1). Only minor differences in conversions and selectivities are observed (Table 1). CATs I and III led to near full conversion after 2 h using a catalyst loading of 0.3 mol% and after 1.5 h using 0.7 mol%. In contrast, in the presence of CAT II, 80% conversion is obtained after 4 h for 0.3 mol% of catalyst.

Table 1. Selectivity observed with Mn(III) catalysts I–III in the oxidation of 3MBF by H₂O₂.

| Catalyst | Loading (mol%) | Conversion (%) | Time (min) | Selectivity (η) a |
|----------|----------------|----------------|------------|------------------|
| I        | 0.3            | 99.7           | 120        | 91.9 (91.6)      |
| I        | 0.7            | 99.9           | 90         | 88.3 (88.2)      |
| II       | 0.3            | 79.9           | 240        | 86.8 (69.4)      |
| II       | 0.7            | 84.3           | 180        | 87.0 (73.3)      |
| III      | 0.3            | 99.8           | 120        | 98.8 (98.6)      |
| III      | 0.7            | 99.9           | 90         | 98.4 (98.3)      |

a Calculated from the GC-FID peak integration areas (average of two assays).

The reactions are selective for benzofuranone 19 and the decomposition of 3MBF-O to afford 20 (Scheme 5) seems to be a minor pathway. In the presence of CAT I, the selectivity for 19 is higher when using 0.3 mol% catalyst. Furthermore, the most selective catalyst is the cationic porphyrin III that affords 19 with a selectivity greater than 98%, while CATs I and II afford 19 with maximum selectivities of 92% and 87%, respectively. The higher selectivity observed with CAT III can be explained by the more acidic conditions used for this catalyst being more favorable for the epoxide rearrangement.

3. Materials and Methods

3.1. Reagents and Instrumentation

All the reagents and solvents were used as received without further purification. The reagents benzofuran (BF), 2-methylbenzofuran (2MBF), 3-methylbenzofuran (3MBF), chlorobenzene, salicylaldehyde redist. ≥ 99% and H₂O₂ 30% w/w (Pedrogen) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Ammonium acetate and glacial acetic acid were p.a. grade and acquired from Merck (Darmstadt, Germany). Acetonitrile, toluene, ethyl acetate, dichloromethane, and methanol were all p.a. grades and acquired from Fisher Chemicals (Waltham, MA, USA). The manganese porphyrins were prepared using literature procedures [32,33,35]. The chromatographic purifications were carried out using silica gel 60 F254 from Merck.

¹H NMR spectra (1D and 2D) were recorded on Bruker Avance instruments (Wissembourg, France) operating at a frequency of 300 or 400 MHz for ¹H experiments and 75 or 100 MHz for ¹³C experiments, with sample temperatures of 22 °C and using CDCl₃ or DMSO-d₆ as solvent (Euroisotop). Unless otherwise specified, TMS was used as an internal reference.

The GC-FID analyses were performed using a Varian 3900 chromatograph (Palo Alto, CA, USA) and GC-MS analyses were performed on a Finnigan Trace GC-MS (Thermo Quest CE instruments,
Waltham, MA. USA) using helium as the carrier gas. In both cases, DB-5-type-fused silica Supelco capillary columns were used (30 m, 0.25 mm i.d.; 0.25 μm film thickness) and the temperature program was: 70 °C (1 min), 20 °C min⁻¹, and 200 °C (5 min). The injector temperature was set at 200 °C and the detector temperature was set at 250 °C.

High-resolution electrospray ionization mass spectra (HR-ESI-MS) were obtained using an LTQ-Orbitrap XL mass spectrometer (Thermo Scientific, Waltham, MA, USA). Evaporated samples were dissolved in acetonitrile while reaction mixtures were directly injected and infused into the electrospray ion source at 10 μL·min⁻¹. The spectrometer was operated in the positive ionization mode with the capillary voltage set to +3.1 kV, sheath gas flow to 6, and the temperature of the ion transfer capillary to 275 °C.

3.2. Catalytic Experiments

The catalytic experiments were performed using the following procedure: The substrate (0.3 mmol), the catalyst 0.3 mol% (1 μmol) or 0.7 mol% (2 μmol), and the co-catalyst (0.12 mmol, ammonium acetate for catalysts I and II or acetic acid for catalyst III) were dissolved in 2 mL of acetonitrile and stirred at 16 to 20 °C protected from light. When the reactions were followed by GC analysis, chlorobenzene (0.3 mmol) was added to the reaction mixture as an internal standard. Aqueous hydrogen peroxide (30% w/w) diluted in acetonitrile (1:10) was added to the reaction mixture at a constant rate of 0.6 mL·h⁻¹ (2 mol equivalents relative to the substrate/h) through a syringe pump (KDScientific, KDS 200, Havard Bioscience, Holliston, MA, EUA).

For the comparison of catalyst performance, the reactions were followed by GG-FID analysis every 30 min until a full conversion was reached or when no evolution was detected in two successive analyses. Quantification of SA in the reaction media was performed by the GC internal standard method after calculation of the SA response factor.

The final reaction mixtures were fractionated by TLC using a mixture of toluene:ethyl acetate (3:1) as solvent. The compounds were revealed on TLC plates with concentrated H₂SO₄ applied in a small strip on one of the side edges of the TLC plates. The compounds were removed from silica with a small plug of alumina, eluted with dichloromethane, and the solvent evaporated at 30 °C.

3.3. Characterization Data of Isolated Fractions

Salicylaldehyde (1) ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 6.99–7.06 (m, 2H, Ar-H), 7.52–7.59 (m, 2H, Ar-H), 9.91 (s, 1H, -CHO). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 122.06 (C-4), 119.9 (C-1), 120.5 (C-5), 132.1 (C-6), 137.0 (C-3), 161.3 (C-2), 196.6 (CHO). MS (EI) m/z: 122.1 [M⁺]. HRMS (ESI⁺) m/z: 122.0630 [M + H⁺], imine form, calculated: 122.06004, ∆m: 2.1 ppm.

Compound (5) Carbon numbering in accordance with Scheme 2b. ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 6.51 (d, 1H, J = 1.5 Hz, H-3), 6.84–6.92 (m, 3H, H-2,6,7), 7.01 (dd, 1H, J = 7.6 and 1.0 Hz, H-4), 7.14 (t, 1H, J = 7.6 and 1.0 Hz, H-5), 7.26 (dt, 1H, J = 7.6 and 1.7 Hz, H-4'), 7.48 (dd, 1H, J = 7.6 and 1.7 Hz, H-6'), 7.52 (dt, 1H, J = 7.6 and 1.7 Hz, H-5'), 7.82 (dd, 1H, J = 7.6 and 1.7 Hz, H-3'), 8.70 (s-broad, 1H, OH), 9.96 (s, 1H, CHO). HRMS (ESI⁺) m/z: 256.09628 [M + H⁺], imine form, calculated: 256.09744, ∆m: 2.1 ppm.

1-(2-Hydroxyphenyl)-2-oxopropyl acetate (16, oxo-form) ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 2.20 (s, 3H, -CH₃), 2.21 (s, 3H, -CH₃), 6.12 (s, 1H, H-1'), 6.90–6.98 (m, 2H, H-Ar), 7.24–7.32 (m, 2H, H-Ar). APT ¹³C NMR (CDCl₃, 75 MHz) δ (ppm): 20.8 (CH₃ from OAc), 26.6 (CH₃-C=O), 78.4 (C1'), 118.1 (C3), 118.5 (C6), 121.3 (C5), 129.8 (C4), 131.5 (C6a), 155.4 (C2), 170.6 (COO), 203.9 (C=O). HRMS (ESI⁺) m/z: 231.06178 [M + Na⁺], calculated: 231.06278, ∆m: 4.3 ppm. MS² 231.06: (-CH₃COOH) m/z 171.04095.
3-methylbenzofuran-2(3H)-one (19) 1H NMR (CDCl3, 300 MHz) δ (ppm): 1.58 (broad d, 3H, J = 7.4 Hz, -CH3), 3.72 (q, 1H, J = 7.4 Hz, -CH), 7.11 (d, 1H, J = 7.6 Hz, H-Ar), 7.16 (dd, J = 7.6 and 0.95 Hz, 1H, H-Ar) 7.25–7.33 (m, 2H, H-Ar). MS (El) m/z: 147.8 [M]+•, calculated 148.0.

2'-hydroxyacetophenone (20) 1H NMR (CDCl3, 300 MHz) δ (ppm): 2.64 (s, 3H, -CH3), 6.90 (ddd, 1H, J = 1.0, J = 6.6 and J = 8.5 Hz, H-4' or H-5'), 6.98 (dd, 1H, J = 1.0 and J = 8.5 Hz, H-3' or H-6'), 7.48 (ddd, 1H, J = 1.7, J = 6.6 and J = 8.5 Hz, H-4' or H-5'), 7.74 (ddd, 1H, J = 1.7 and J = 8.5 Hz, H-3' or H-6'). MS (El) m/z: 135.8 [M]+•, calculated 136.0.

4. Conclusions

Three second generation Mn(III) porphyrins carrying neutral or cationic substituents (I, II, and III) were shown to be efficient catalysts for the oxidation of 2,3-benzofurans with hydrogen peroxide at room temperature and in the presence of an appropriate co-catalyst (ammonium acetate or acetic acid). Using an Ox/S ratio of 4 and porphyrin I with ammonium acetate co-catalyst as a reference system, significant differences were seen in the transformations observed for benzofuran (BF), 2-methylbenzofuran (2MBF), and 3-methylbenzofuran (3MBF). For example, with 3MBF, only two products were obtained: 3-methylbenzofuran-2(3H)-one (major product) and 2'-hydroxyacetophenone (minor product). This behavior can be contrasted with the plethora of products obtained for BF, where depending upon the work-up conditions of the reaction, 15 products were characterized by tandem mass spectrometry. For 3MBF, extremely high conversion (99%) and selectivity (99%) were achieved using the cationic catalyst III and acetic acid as co-catalyst.

The transformations observed can be justified by the initial epoxidation of the furan rings followed by subsequent reactions. The benzofuran and 2-methylbenzofuran oxides undergo decarboxylation to salicylaldehyde, which was isolated as a reaction product and also reacted with the oxirane rings through nucleophilic attack. When using the neutral catalyst CAT I and ammonium acetate co-catalyst, other products resulted from epoxide reactions with NH3 or acetic acid. Additional products are justified by the formation of imines and intramolecular cyclisation through imine–double bond reactions.

From a comparison of the present results on the oxidation of benzofurans in the presence of Mn(III) porphyrins with those previously reported for biomimetic oxidation by an Fe(III) porphyrin in ethanol [28], it can be observed that the hydroxylation of the benzene ring is minimized (it is not observed in the isolated products) and a number of new coupling reactions and transformation pathways are detected.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/10/1/62/s1. Section S1: Comparison of catalytic activity of Mn(III) porphyrins in the oxidation of benzofurans at 0.7 mol% loading. Section S2: Mass spectrometry studies of BF and 2MBF oxidation reactions in the presence of CAT I. Section S3. NMR spectra of products and reaction mixtures.

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