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Journal of Molecular Catalysis A: Chemical 113 (1996) 23–34

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

Enantioselective epoxidation of olefins by single-oxygen atom donors catalyzed by manganese-glycoconjugated porphyrins

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Received 18 August 1995; accepted 19 September 1995

Abstract

New chiral porphyrins bearing glycosyl substituents (glucose, maltose or lactose) at *ortho* or *meta* positions of the *meso*-phenyl groups have been synthesized. Their manganese complexes, associated with hydrogen monopersulfate, lithium hypochlorite, hydrogen peroxide, or iodosylbenzene, have been used as enantioselective catalysts for the epoxidation of 4-chlorostyrene and 1,2-dihydronaphthalene.

Keywords: Glycosylated metalloporphyrins; Metalloporphyrins; Porphyrins; Enantioselectivity; Epoxidation

1. Introduction

Cytochrome P-450 enzymes are ubiquitous in nature, and represent a versatile class of biological oxidation catalysts in animals, plants and bacteria [1]. With molecular oxygen and NADPH, these monooxygenases catalyze the insertion of an oxygen atom into a C–H bond leading to, for instance, epoxidation of olefins and hydroxylation of alkanes. Catalytic systems using a synthetic metalloporphyrin and a single oxygen atom donor have been widely developed [2]: they are able to mimic the 'short cycle' of P-450, leading to similar products, with catalytic turnover numbers which can be up to 200 times greater than those of cytochrome P-450 itself [3].

Beside the efficiency of the enzymatic systems, one of the major advantages is their enantioselectivity. P-450 has been shown to perform enantioselective epoxidations [4,5] and hydroxylations [6]. The asymmetric epoxidation of alkenes is of particular relevance to synthetic organic chemistry, especially when the desired products have pharmaceutical or agrochemical interest. For this purpose, the development of optically active catalysts is needed. Efficient enantioselective oxygenation of carbon–carbon double bonds have been performed by Sharpless et al. for the epoxidation of allylic alcohols [7–11] and olefins dihydroxylation [12–14]. The latter reaction is also efficient in the case of terminal olefins [15]. Chiral Schiff base com-

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1381-1169/96/$15.00 Published by Elsevier Science B.V.
PII S1381-1169(96)00038-6

plexes based on optically active 1,2-diaminocyclohexane have been successfully used in the epoxidation of *cis*-disubstituted olefins [16–18] and sulfide oxidation [19,20].

Due to the high efficiency of metalloporphyrin-based catalytic epoxidation systems, work has been concentrated on the synthesis and catalytic activities of metalloporphyrins bearing chiral motifs [21,22].

The first olefin epoxidation catalyzed by a chiral metalloporphyrin was reported by Groves and Myers [23] in 1983; with iodosylbenzene as oxidant, 30 to 50% enantiomeric excess (ee) was obtained in the epoxidation of styrene derivatives catalyzed by the iron(III) complex of tetrakis-[*o*-(*R*)-hydratropamidophenyl] porphyrin and tetrakis-(binaphthylcarboxamidophenyl)porphyrin (α,β,α,β-atropoisomers).

Since then, the major emphasis of the reported literature systems has been on iodosylbenzene associated with iron or manganese (less often) porphyrin complexes bearing binaphthyl residues. Groves et al. developed a bis-binaphthyl vaulted porphyrin metallated with iron or manganese for the catalytic epoxidation, hydroxylation and sulfoxidation of prochiral substrates [24]. With the manganese catalyst, 72% ee was obtained in the epoxidation of *cis*-β-methylstyrene when the reaction was performed at −15°C. (It has to be noted that this work, and a previous one of the same authors [25] was the only report of catalytic conversion of alkanes to optically active alcohols).

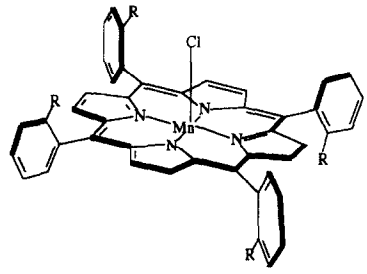
Naruta and Murayama employed an iron metalloporphyrin with rigid backbones of binaphthyl groups with 1,5-diphenylimidazole as co-catalyst and PhIO as oxidant [26]. Later they improved the selectivity of catalyzed epoxidations by designing 'twin coronet' porphyrin ligands [27–29], each face of the macrocycle being occupied by two binaphthyl units. Due to the difference of the binding mode of the chiral auxiliary, there are two topological isomers 'eclipsed' and 'staggered', which both have D_2 symmetry. The iron(III) complex of the eclipsed isomer was observed to be an enantioselective catalyst, robust enough to exhibit chiral epoxidation for more than 500 turnovers with good to excellent enantioselectivities (74–96%). The best ee's were obtained with olefins bearing electron-withdrawing substituents (74% with pentafluorostyrene, 89% with 2-nitrostyrene, 96% with 3,5-dinitrostyrene) [29]. These ee values are the highest stereoselectivities reported for the epoxidation of styrene derivatives catalyzed by chiral metalloporphyrins.

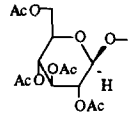
Iron complexes of a binaphthyl capped porphyrin were also used by Collman et al. [30] with rather good enantioselectivities (ee's were 50% and 56% for the epoxidation of 4-chlorostyrene and 4-nitrostyrene respectively). Very recently, Collman et al. reported the synthesis and catalytic properties of threitol-strapped manganese porphyrins [31]. When associated with bulky co-catalysts such as 1,5-dicyclohexylimidazole, these catalysts yielded 70 and 77% ee in the epoxidation of 4-chlorostyrene and *cis*-β-methylstyrene, respectively.

Chiral auxiliaries other than the binaphthyl moiety have also been used. L-Phenylalanine in basket-handle porphyrin ligands metallated with iron gave 50% ee in the epoxidation of 4-chlorostyrene [32,33]. *p*-Xylylene-strapped manganese complexes based on dihexyldeuteroporphyrin catalyze the enantioselective epoxidation of olefins with ee's in the range 42% (styrene) to 58% (dihydronaphthalene) [34]. Iron or manganese derivatives of tetraphenylporphyrin, substituted in one *ortho* position of each phenyl group by a glucosylated residue have been synthesized. Their use as epoxidation catalysts with PhIO allowed the authors to obtain 24–33% ee in the epoxidation of 4-chlorostyrene [35].

One of the limitations of these enantioselective epoxidations with PhIO, catalyzed by chiral metalloporphyrins, is that the olefin is often in large excess versus the oxidant (usually 10-fold excess), allowing only a low conversion of the substrate. Further, the ee decreases at high turnover numbers independently of the rate at which the iodosylbenzene is added to the reaction.

Very few publications report enantioselective epoxidations with oxidants other than PhIO. Only four reports describe the use of sodium hypochlorite as oxidant, with catalysts bearing chiral motives directly connected to the *meso* positions of a manganese porphyrin. With a

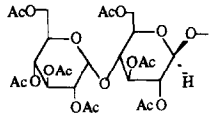


R = 

(Tetraacetyl-Glucose)

Atropoisomers : 1a αβαβ
1b ααββ
1c αααβ

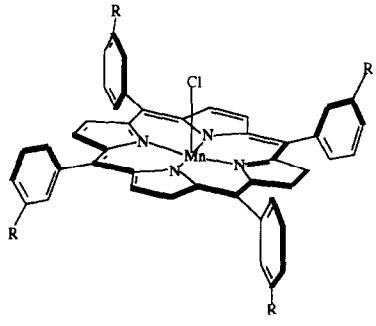
1-Mn[a]

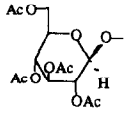
R = 

(Heptaacetyl-Maltose)

2-Mn

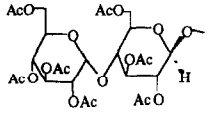
Mn(III)[Tetrakis-(2-glycosylphenyl)-porphyrin]Cl



R = 

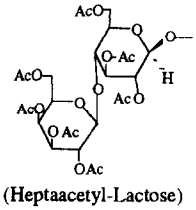
(Tetraacetyl-Glucose)

3-Mn



(Heptaacetyl-Maltose)

4-Mn



(Heptaacetyl-Lactose)

5-Mn

Mn(III)[Tetrakis-(3-glycosylphenyl)-porphyrin]Cl

[a]. Free ligands are noted **1** to **5**.

Scheme 1. Manganese glycoconjugated porphyrin complexes.

chiral wall ligand having binaphthyl residues directly linked to the *meso* positions of the macrocycle, 40% ee was obtained in the epoxidation of *cis*-β-methylstyrene [36]. The introduction of fenchylidenyl derivatives into the *meso* position of a manganese porphyrin did not increase the ee above 16% in the epoxidation of styrene or aliphatic olefins [37]. Two other reports describe the use of rather similar catalysts, bearing chiral octahydroanthracene derivatives [38] or nopinone residues [39]. These D_4-symmetric tetra-arylporphyrins have the major advantage that no atropoisomerism is possible. In these later cases, the best results obtained were in the epoxidation of *cis*-β-methylstyrene (76% ee in Ref. [38]).

Among the possible oxygen atom donors in epoxidation reactions, diluted hydrogen peroxide has always been regarded as very attractive because it is cheap, and water is the only side-product. However, catalytic oxidations with metalloporphyrins and H_2O_2 have been limited because both catalytic dismutation of H_2O_2 and fast oxidative destruction of the catalyst are usually competing with the desired epoxidation reaction [40].

In the field of enantioselective epoxidation with H_2O_2, the only attempt made was with a manganese porphyrin bearing four 2-chloro-6-(acetyl-β-glucosyl)phenyl substituents in *meso* positions [41]. The obtained ee's were modest (22–23% with 4-chlorostyrene) and slightly higher, but not far from those obtained when PhIO was used as oxidant with the same catalyst (16–20%). Further these metalloporphyrins were highly stable in the reaction mixture, even with a large excess of H_2O_2, allowing the recycling of the catalyst and reuse in a new run in which the same ee's were obtained.

We have developed a new series of porphyrins bearing acetylated-β-D-sugar moieties (glucose, maltose or lactose) which are covalently linked to the *ortho* or *meta* positions of phenyl groups of tetraphenylporphyrin (Scheme 1) [42]. The β-D-glycosyl groups induce a chiral environment [35] and a strong steric hindrance on one or both faces of the macrocycle. These steric and stereochemical factors can be modulated by the nature and the binding positions of the acetylated sugars. Here we now report some catalytic properties of the manganese complexes of these new ligands. The test reactions used are the asymmetric epoxidation of 4-chlorostyrene and 1,2-dihydronaphthalene, using several different oxygen atom donors: PhIO, LiOCl, $KHSO_5$ or H_2O_2.

2. Materials and methods

2.1. Chemicals

CH_2Cl_2 was distilled over K_2CO_3 for the synthesis of the porphyrin ligands. All chemicals used were of reagent grade. When necessary, olefins were purified by chromatography over alumina. Iodosylbenzene was prepared from commercially available iodobenzene diacetate [43]. The following porphyrin ligands: αβαβ, ααββ and αααβ atropoisomers of 5,10,15,20-tetrakis[2-(2,3,4,6-tetra-acetyl-β-D-glucosyl)-phenyl] porphyrin (**1**) and the mixture of atropoisomers of 5,10,15,20-tetrakis[2-(2,3,6,2′,3′,4′,6′-hepta-acetyl-β-D-maltosyl)-phenyl] porphyrin (**2**) were prepared by the previously described method [42].

Silica gel 60, 0.04–0.06 mm (Merck), was used for column chromatography. Precoated plates of silica gel 60, 2 mm (Merck) were used for preparative TLC.

2.2. Instrumentation

Elemental analyses were carried out by the Service Central de Microanalyse du CNRS, Solaize, France. Optical spectra in the Soret and visible regions were recorded using a Varian DMS-200 spectrophotometer. ^1H NMR spectra were recorded on a Bruker AM 200 spectrometer and chemical shifts values are given in ppm relative to TMS. GC analyses were performed on a chromatograph equipped with a flame ion-

ization detector, using a wide bore CP-Sil-5-CB (25 m × 0.53 mm) column from Chrompack or a β-cyclodextrin coated Cydex B (25 m × 0.22 mm) column from SGE.

The enantiomeric excesses (ee's) of the produced epoxides were determined either by direct analyses of the reaction mixtures on a chiral phase GC column (see above) or by ^{1}H NMR (using tris-[3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato]-europium) after isolation of the products.

2.3. Synthesis of 3-(2,3,6,2′,3′,4′,6′-hepta-acetyl-β-D-maltosyl)-benzaldehyde

A solution of 3-hydroxybenzaldehyde (5 g, 40.9 mmol) in CH_2Cl_2 (45 ml) was vigorously stirred at room temperature with an aqueous solution of NaOH (5%, 63 ml) and tetrabutylammonium bromide (2 g, 5.2 mmol). A CH_2Cl_2 solution (15 ml) of crude compound α-1-bromo-2,3,6,2′,3′,4′,6′-hepta-acetylmaltose [42] (15.3 g, 22 mmol) prepared just before use was added to the mixture and the resulting solution was stirred for 3 days at room temperature. After separation of the layers, the organic layer was washed with aqueous NaOH solution (5%, 2 × 50 ml), with water, then dried over sodium sulphate, filtered and evaporated under vacuum. The yellow oil was chromatographed on a silica gel column using a mixture of ethyl acetate and hexane (1/1, v/v) to afford the title product (5 g, 31%).

Anal. calcd for $C_{33}H_{40}O_{18}(2H_2O)$: C, 52.11; H, 5.83. Found: C, 52.36; H, 5.55. ^{1}H NMR ($CDCl_3$) δ ppm: 9.97 (s, 1H, CHO), 7.65–7.40 (bm, 3H, H-phenyl), 7.25 (bm, 1H, H-phenyl), 5.35–5.00 (bm, 8H, H ose), 4.25–4.10 (bm, 4H, H ose), 4.00–3.80 (bm, 2H, H ose), [2.07, 2.05, 2.04, 2.02, 1.99 (5 × s, 21H, acetyl)].

2.4. Synthesis of 3-(2,3,6,2′,3′,4′,6′-hepta-acetyl-β-D-lactosyl)-benzaldehyde

The procedure used was the same as described above, using α-1-bromo-2,3,6,2′,3′,4′,6′-hepta-acetyl-lactose as starting material (4.2 g, 26%).

Anal. calcd for $C_{33}H_{40}O_{18}(2H_2O)$: C, 52.11; H, 5.83. Found: C, 51.91; H, 5.63. ^{1}H NMR ($CDCl_3$) δ ppm: 9.94 (s, 1H, CHO), 7.60–7.45 (bm, 3H, H-phenyl), 7.22 (bm, 1H, H-phenyl), 5.50–5.40 (bm, 2H, H ose), 5.28 (bm, 1H, H ose), 5.18–5.05 (bm, 3H, H ose), 4.25–4.00 (bm, 6H, H ose), 4.00–3.80 (bm, 2H, H ose), [2.15, 2.06, 2.05, 2.04, 2.03, 2.00, 1.98 (7 × s, 21H, acetyl)].

2.5. Synthesis of 5,10,15,20-tetrakis[3-(2,3,6,2′,3′,4′,6′-hepta-acetyl-β-D-maltosyl)-phenyl] porphyrin **4**

Pyrrole (0.22 ml, 3.2 mmol) in CH_2Cl_2 (30 ml) and the glycosylated aldehyde (2.3 g, 3.2 mmol) in the same solvent (30 ml) were added successively to CH_2Cl_2 (240 ml) under an argon atmosphere and stirred for 30 min. The mixture was purged with argon for a further 10 min after which a BF_3–etherate solution (1 ml, 0.5 M) in CH_2Cl_2 was added. The stirring was continued for 20 h at room temperature in the dark. *p*-Chloranil (0.64 g, 2.6 mmol) was then added. After reflux for 4 h, 10 g of silica gel was added to the solution and the solvent was evaporated under vacuum. The absorbed products were placed at the top of a silica gel column and eluted with a mixture CH_2Cl_2/acetone (5/1, v/v). The porphyrin (red band) was collected and purified by thin layer chromatography on silica gel plates, eluted twice with toluene/acetonitrile (3/2, v/v). The pure product crystallized from CH_2Cl_2/heptane (50 mg, 2%).

Anal. calcd for $C_{148}H_{166}N_4O_{72}$: C, 56.40; H, 5.31; N, 1.78. Found: C, 55.95; H, 5.32; N, 1.61.

^{1}H NMR ($CDCl_3$) δ ppm: 8.86 (bs, 8H, H pyr), [7.80, 7.65, 7.45 (3 × m, 16H, H-phenyl)], [5.50–4.90, 4.90–4.70, 4.50–3.75, 3.60–3.40 (4 × bm, 56H, H ose)], [2.12, 2.06, 2.05, 2.04, 2.01, 1.99, 1.97 (7 × s, 84H, acetyl)], −2.90 (s, 2H, NH).

UV–Vis ($CHCl_3$) λ_{max}, nm (ε, l $mmol^{-1}$ cm^{-1}): 419 (314), 514 (18), 551 (8), 588 (6), 644 (4).

2.6. Synthesis of 5,10,15,20-tetrakis[3-(2,3,6,2',3',4',6'-hepta-acetyl-β-D-lactosyl)-phenyl] porphyrin 5

This compound was prepared by the same procedure used for compound **4** (100 mg, 4%).

Anal. calcd for $C_{148}H_{166}N_4O_{72}$: C, 56.40; H, 5.31; N, 1.78. Found: C, 55.60; H, 5.60; N, 2.16.

^1H NMR ($CDCl_3$) δ ppm: 8.85 (bs, 8H, H pyr), [7.85, 7.66, 7.45 (3 × bm, 16H, H-phenyl)], [5.50–5.15, 5.15–4.80, 4.60–4.50, 4.50–3.55 (4 × bm, 56H, H ose)], [2.11, 2.04, 2.00, 1.96, 1.90, 1.85, 1.83 (7 × s, 84H, acetyl)], −2.92 (s, 2H, NH).

UV–Vis ($CHCl_3$) λ_{max}, nm (ε, l $mmol^{-1}$ cm^{-1}): 419 (390), 515 (19), 549 (8), 589 (7), 644 (4).

2.7. Synthesis of 5,10,15,20-tetrakis[3-(2,3,4,6-tetra-acetyl-β-D-glucosyl)-phenyl] porphyrin 3

This ligand was synthesized from the corresponding tetra-acetylglucosyl benzaldehyde as previously described for the maltose derivative (compound **4**) (590 mg, 37%). Anal. calcd for $C_{100}H_{102}N_4O_{40}$: C, 60.10; H, 5.10; N, 2.80. Found: C, 59.80; H, 5.27; N, 3.09.

^1H NMR ($CDCl_3$) δ ppm: 8.87 (bs, 8H, H pyr), [7.91, 7.86, 7.67, 7.44 (4 × bm, 4 × 4H, H-phenyl)], 5.40–5.26 (bm, 12H, $H_{1'}$, $H_{2'}$, $H_{3'}$ ose), 5.20–5.10 (bm, 4H, $H_{4'}$ ose), 4.22–3.98 (bm, 8H, $H_{6'}$, $H_{6''}$ ose), 3.88–3.74 (bm, 4H, $H_{5'}$ ose), [2.07, 2.06, 2.02, 2.01, 1.98, 1.96, 1.46, 1.44, 1.42, 1.40, 1.39, 1.37, 1.36, 1.33 (14 × s, 48H, acetyl)], −2.90 (s, 2H, NH).

UV–Vis ($CHCl_3$) λ_{max}, nm (ε, l $mmol^{-1}$ cm^{-1}): 419 (463), 514 (22), 549 (10), 590 (9), 645 (6).

This porphyrin was also prepared recently by Tsugikatsu et al. [44].

2.8. Metallation of porphyrins with manganese

The chloromanganese(III) complexes of porphyrins **1** and **2** were prepared by treatment of the free base ligands (200 mg) with $MnCl_2$ (200 mg) in the presence of 4-nitrophenol (400 mg) and 2,6-lutidine (0.1 ml) in 90 ml of tetrahydrofuran under argon for 12 h at 40°C. After evaporation of the solvent to dryness, the residue was dissolved in CH_2Cl_2 and washed with water, several times with an aqueous NaOH solution to eliminate 4-nitrophenol and then with a saturated aqueous NaCl solution. The organic phase was dried over sodium sulphate and the solvent was evaporated under vacuum. The crude product was chromatographed on a silica gel column. The unreacted ligands were eluted with a mixture CH_2Cl_2/acetone (5/1, v/v) and the manganese complexes with CH_2Cl_2/CH_3OH (10/1, v/v). After evaporation of the solvents, the crude manganese complexes were dissolved in CH_2Cl_2 and washed twice with a saturated NaCl solution containing few drops of concentrated HCl. The chloromanganese complexes crystallized from a mixture CH_2Cl_2/heptane.

The chloromanganese(III) complexes of porphyrins **3**, **4** and **5** were obtained in a similar way as described above, but using dimethylformamide at reflux in the absence of 4-nitrophenol.

1. Mn[(*o*-OGlucOAc$_4$)TPP]Cl αβαβ **1a-Mn** (yield: 15%). UV–Vis ($CHCl_3$) λ_{max}, nm (ε, l $mmol^{-1}$ cm^{-1}): 377 (46), 400 (45), 470 (82), 557 (12). Mn[(*o*-OGlucOAc$_4$)TPP]Cl ααββ **1b-Mn** (yield: 27%). UV–Vis ($CHCl_3$) λ_{max}, nm (ε, l $mmol^{-1}$ cm^{-1}): 377 (43), 401 (41), 473 (82), 569 (10).
2. Mn[(*o*-OGlucOAc$_4$)TPP]Cl ααaβ **1c-Mn** (yield: 26%). UV–Vis ($CHCl_3$) λ_{max}, nm (ε, l $mmol^{-1}$ cm^{-1}): 377 (49), 400 (48), 472 (92), 568 (12).
3. Mn[(*o*-OMaltOAc$_7$)TPP]Cl **2-Mn** (yield: 100%). UV–Vis ($CHCl_3$) λ_{max}, nm (ε, l $mmol^{-1}$ cm^{-1}): 378 (46), 401 (45), 477 (79), 582 (10), 616 (8).

4. Mn[(*m*-OGlucOAc$_4$)TPP]Cl **3-Mn** (yield: 64%). UV–Vis ($CHCl_3$) λ_{max}, nm (ε, l mmol^{-1} cm^{-1}): 378 (57), 404 (48), 480 (104), 582 (11), 617 (10).
5. Mn[(*m*-OMaltOAc$_7$)TPP]Cl **4-Mn** (yield: 70%). UV–Vis ($CHCl_3$) λ_{max}, nm (ε, l mmol^{-1} cm^{-1}): 375 (43), 402 (35), 480 (70), 582 (10), 615 (10).
6. Mn[(*m*-OLactOAc$_7$)TPP]Cl **5-Mn** (yield: 73%). UV–Vis ($CHCl_3$) λ_{max}, nm (ε, l mmol^{-1} cm^{-1}): 383 (56), 408 (49), 480 (91), 577 (13), 614 (11).

2.9. Experimental conditions for the oxidation reactions

All experiments were carried out at room temperature in a glass vessel, equipped with a stirring bar, under an air atmosphere except when PhIO was used as oxygen atom donor (then argon was used). With H_2O_2 as oxidant, the reaction conditions were similar to those previously described by Montanari et al. [45] (reaction temperature: 5°C). With other oxidants, standard conditions of metalloporphyrin catalyzed oxygenations were used [3,46]. Reaction times were measured from the addition of oxidant. At regular intervals, magnetic stirring was stopped, and when necessary the mixture decanted before withdrawing aliquot for GC analyses. At the beginning and at the end of the epoxidation reactions, aliquots were taken to determine by UV–Visible spectroscopy the relative amount of manganese complex which had disappeared. Spectra were recorded in a mixture $CH_2Cl_2/CH_3OH/H_2O$ (80/18/2, v/v/v) when PhIO was used and in CH_2Cl_2 in the other cases.

The reaction mixtures were analyzed by GC and epoxides compared with an authentic sample (commercially available 4-chlorostyrene oxide or dihydronaphthalene oxide prepared according to Ref. [47]). When the epoxidations were performed with PhIO, the products were isolated by a silica gel column chromatography under argon with pentane/diethyl ether (85/15, v/v) as eluent and enantiomeric excesses were determined in NMR using a chiral europium(III) salt. In other cases, enantiomeric excesses were determined by direct analysis of the reaction mixture on a GC chiral column.

Standard reaction conditions for epoxidation with PhIO were as follows: catalyst (1 μmol), 4-methylpyridine (200 μmol) and the olefin (4-chlorostyrene: 400 μmol or dihydronaphthalene: 120 μmol) were diluted in 1 ml of methylene chloride and degassed under argon. PhIO (150 μmol) was then added in three portions and the mixture was stirred under argon in the dark. Reaction time was 30 min.

Standard reaction conditions for epoxidation with LiOCl or $KHSO_5$. Organic phase: catalyst (0.5–0.65 μmol), benzyldimethyltetradecylammonium chloride (phase transfer catalyst, 25 μmol), 4-methylpyridine (30 μmol), olefin (250 μmol) and 1,4-dibromobenzene (internal standard for GC analyses, 140 μmol) were diluted in 1 ml of methylene chloride. Aqueous phase: (i) $KHSO_5$ or LiOCl (500 μmol) was diluted in 10 ml of phosphate buffer 0.25 M, pH 7 or 2 ml of distilled water respectively and then added at once.

Standard reaction conditions for epoxidation with H_2O_2. Catalyst (2.1 μmol), 4-*t*-butylpyridine (4 μmol), benzoic acid (40 μmol), 4-chlorostyrene or dihydronaphthalene (250 μmol) and 1,4-dibromobenzene (140 μmol) were diluted in 1 ml of dichloromethane. Commercial 30 wt.% solution of H_2O_2 (860 μmol) was added.

3. Results and discussion

3.1. Synthesis of meta-tetraglycosylated porphyrins

The *meta* substituted glycosylated porphyrins were synthesized by the method described by Maillard et al. [44]. This involves firstly the preparation of the appropriate substituted benzaldehyde bearing the acetyl sugar by the method described by Halazy [48]. This com-

pound was then condensed with pyrrole, using the Lindsey method [49–52], to give glycosylated porphyrins. They were purified by successive chromatography on a silica gel column and on preparative plates. Atropoisomers are not separable at room temperature.

3.2. Metallation of glycosylated porphyrins by manganese

The manganese complexes of porphyrins bearing acetylated sugar residues in *meta* position were prepared by a classical method [53]. For compounds substituted in *ortho* position by acetylated glucose or maltose, which are sensitive to atropoisomerization, the manganese complexes were prepared according to the Guilleux method [54] in THF containing $MnCl_2$ at 40°C under argon, in the presence of 4-nitrophenol.

3.3. Asymmetric epoxidation

Oxidation reactions of 4-chlorostyrene and 1,2-dihydronaphthalene were carried out with various catalytic systems. Depending on the solubility of the oxidant, the epoxidation of substrates was performed in either a biphasic medium CH_2Cl_2/H_2O when $KHSO_5$, H_2O_2 or LiOCl were used as oxidants, or in a biphasic medium CH_2Cl_2/solid with PhIO, which is sparingly soluble in CH_2Cl_2.

3.3.1. Epoxidation of 4-chlorostyrene

The results obtained with different catalysts and oxygen atom donors for epoxidation of 4-chlorostyrene are reported in Table 1.

3.3.1.1. Reactivity. With iodosylbenzene as oxygen atom donor, the nature of the coordinated sugar residues (glucose or maltose) and their substitution position (*ortho* or *meta*) on the *meso* phenyl rings did not significantly change the chemical yield of epoxidation. Conversely, when hydrogenpersulfate was used, noticeable differences in the reactivity of the catalytic system were observed. The epoxidation catalyzed by '*ortho*-Gluc' catalysts **1-Mn**, the $\alpha\alpha\alpha\beta$ atropoisomer **1c-Mn**, is by far more efficient than the two other isomers in the epoxidation of 4-chlorostyrene. Further, the '*meta*-Gluc' manganese complex **3-Mn** is more reactive than the *ortho* substituted analogues: in the latter case, with 0.26 mol% of catalyst, nearly complete conversion of 4-chlorostyrene, which is a rather unreactive terminal olefin, was obtained within 10 min.

Similar behavior was observed in the comparison of the catalytic activity of '*ortho*-Malt' and '*meta*-Malt' complexes, **2-Mn** and **4-Mn** respectively. This infers that, with these manganese porphyrin derivatives associated to $KHSO_5$, it is possible to modulate the activity of the catalytic system according to the steric hindrance of the active sites.

In the present reaction conditions, with **1c-Mn** as catalyst, LiOCl is as efficient oxygen donor as $KHSO_5$, the observed reaction rates being similar. (In 30 min, 83% conversion with LiOCl and 90% with $KHSO_5$). On the contrary, with the '*meta*-Gluc' **3-Mn**, $KHSO_5$ is by far, more reactive than LiOCl. This indicates that the steric hindrance of the active site due to *ortho*-substituents is able to diminish the influence of the intrinsic reactivity of the oxidant.

At 5°C, in spite of rather slow reaction rates, H_2O_2 is able to perform the epoxidation of the title terminal olefin.

3.3.1.2. Enantioselectivity. The environment of the metal-oxo species [2] generated by the chiral substituents influences the enantioselectivity of the epoxidation. With *ortho*-substituted porphyrins, regardless of the substitution (glucose or maltose) associated to iodosylbenzene, enantiomeric excess were in the range 21 to 29%. At 5°C, with H_2O_2 as the oxidant, similar ee values of 20 and 22% were obtained with **1c-Mn** and **2-Mn** respectively. It has to be emphasised that when the epoxidation was catalyzed by the '*ortho*-Malt' complex **2-Mn**, with all the oxidants used, the ee's were in the same range that

Table 1
Epoxidation of 4-chlorostyrene catalyzed by different glycosylated manganese porphyrins

Oxidant	PhIO			$KHSO_5$			LiOCl			H_2O_2 [f]		
Catalyst	r [a]	Yield [b] %	ee %	r [a]	Conversion [c] % (time, min)	ee %	r [a]	Conversion [c] % (time, min)	ee %	r [a]	Conversion [c] % (time, h)	ee %
1a-Mn	0.2	5	24	0.13	31 (60)	12	0.22	92 (60)	17		nd	
1b-Mn	0.2	49	20	0.24	50 (120)	nd		nd			nd	
1c-Mn	0.26	42	29	0.25	90 (30)	10	0.24	83 (30)	17	0.9 [e]	53 (21)	20
2-Mn	0.15	45	21	0.17	45 (90)	nd		nd		0.9[e]	36 (18)	22
				0.20 [d]	96 (90)							
3-Mn	0.25	36	0	0.26	97 (10)	3	0.57	35 (15)	0	0.8[e]	12 (3.5)	3
								81 (60)				
4-Mn	0.17	33	0	0.19	72 (30)	2		nd		0.8	22(2.3)	2
5-Mn	0.10	31	3	0.22	99 (30)	0		nd			nd	

[a] r = mol catalyst/mol substrate × 100 at t_0.
[b] Yield = mol produced epoxide/mol produced PhI at 30 min of reaction time.
[c] Conversions are based on the initial amount of olefin.
[d] 4-*t*-Butylpyridine was used as co-catalyst instead of 4-methylpyridine.
[e] A new fraction of H_2O_2 (860 μmol) was added after 3.5 h of reaction time.
[f] Reactions performed at 5°C.

those obtained with the '*ortho*-Gluc' catalyst, in spite of the fact that **2-Mn** was a mixture of atropoisomers. Further, the different atropoisomers of the '*ortho*-Glu' complexes **1-Mn** exhibit rather similar enantioselectivities.

During the epoxidation of 4-chlorostyrene with LiOCl or $KHSO_5$ catalyzed by *ortho* substituted glycosylated manganese porphyrins, the enantiomeric excesses obtained were lower (9–17%). With all the *meta* substituted catalysts, regardless of oxidant, the obtained ee's were lower than 3%. This feature indicates that the distance between chiral groups and active site of the catalyst in this case is too large to induce significant enantioselectivity.

3.3.2. Epoxidation of 1,2-dihydronaphthalene

The main results are reported in Table 2. The major trends in the epoxidation of this *cis*-disubstituted olefin, catalyzed by manganese glycosylated porphyrins associated with different single oxygen atom donors, were the same as observed in reaction of the terminal olefin 4-chlorostyrene. With iodosylbenzene as oxidant, the differences in reactivity due to the different porphyrin complexes are minimal. When epoxidation was performed with $KHSO_5$, the reactions were significantly more rapid when catalyzed by *meta* substituted compounds rather than the *ortho* isomers.

Regardless of the sugar, when it is in a *meta* substitution pattern on the phenyl ring, the conversion of 1,2-dihydronaphthalene was almost complete in under 10 min. In this case, with **3-Mn** as catalyst, the system exhibits similar reactivity with LiOCl (95% conv. in 10 min) and $KHSO_5$ (100% in 10 min).

In spite of the excellent catalytic activity, the enantioselectivity of this reaction was observed to be low. All of the observed enantiomeric excesses were generally below 5%. The highest obtained values were 8% with **4-Mn** associated with PhIO and 10% with H_2O_2 associated with the '*meta*-Gluc' catalyst **3-Mn** (in this latter case, the ee's were 2% when $KHSO_5$ and LiOCl were used as oxidant, and 0% with PhIO).

3.3.3. Stability of the catalysts

When the enantiomeric excesses were measured by chiral GC (all runs except for epoxidations with PhIO), ee's were monitored as a function of reaction time. No significant change in measured ee's was observed with time. This indicates that *no* non-chiral catalytically active species was generated under the reaction conditions (glycosyl cleavage could be envisaged

Table 2
Epoxidation of 1,2-dihydronaphthalene catalyzed by different glycosylated manganese porphyrins

Oxidant	PhIO			$KHSO_5$		
Catalyst	r [a]	Yield [b] %	ee %	r [a]	Conversion [c] % (time, min)	ee %
1a-Mn	1.0	51	2	0.44	97 (60)	0
1b-Mn	0.67	65	1	0.54	100 (40)	0
1c-Mn	0.60	59	0	0.27	96 (60)	0
2-Mn	0.38	56	0	0.21 [d]	53 (30) 100 (90)	5
3-Mn [e]	0.77	48	0	0.28 [d]	100 (10)	2
4-Mn	0.37	62	8	0.20 [d]	91 (10)	2
5-Mn	0.54	52	0	0.18	99 (10)	0

[a] r = mol catalyst/mol substrate × 100 at t_0.
[b] Yield = mol produced epoxide/mol produced PhI at 30 min of reaction time.
[c] Conversions are based on the initial amount of olefin.
[d] 4-*t*-Butylpyridine was used as co-catalyst instead of 4-methylpyridine.
[e] In similar conditions but LiOCl as oxidant, the conversion of olefin was 95% at 10 min of reaction time (ee = 2%). With H_2O_2 as oxygen atom donor (0.5% mol catalyst), the conversion of olefin was 19% after 6 h (ee = 10%).

leading to a non-chiral catalyst). Incomplete conversion of olefinic substrates are due to a chemical modification leading to the catalyst inactivation or to a bleaching of the porphyrin chromophore.

When the acetylated sugars are in *ortho* position, close to the center of the macrocycle, they generate steric hindrance which is able to protect the catalyst against intramolecular degradation. After oxidation of 4-chlorostyrene by PhIO, $KHSO_5$ or LiOCl catalyzed by each of the three atropoisomers of *ortho*-glucosylated catalyst **1a-Mn**, **1b-Mn**, **1c-Mn**, the UV–Visible spectra of the recovered catalysts were almost identical to the starting compounds, the Soret band being decreased by less than 10% over the course of the reaction. Further, after repurification, these '*ortho*-Gluc' catalysts were reused in further epoxidation runs of 4-chlorostyrene by PhIO or $KHSO_5$. The conversions and enantiomeric excesses obtained were similar to the first run. This would suggest that the catalytic efficiency and the chiral integrity of these compounds remained intact.

When the acetylated sugars are in *meta* position (**3-Mn**, **4-Mn** and **5-Mn** for '*m*-Gluc', '*m*-Malt', and '*m*-Lact' derivatives, respectively), the steric hindrance is not sufficient to protect both faces of the porphyrin core against oxidative degradation. Indeed, the chromophore was completely bleached during the oxidation of 4-chlorostyrene by $KHSO_5$ (the degradation was less than 30% with PhIO or LiOCl in similar conditions).

During the epoxidation of 4-chlorostyrene with H_2O_2 at 5°C, the bleaching of '*m*-Malt' catalyst (**4-Mn**) was complete. On the contrary, '*m*-Gluc' (**3-Mn**), '*o*-Malt' (**2-Mn**), and '*o*-Gluc' (**1c-Mn**) were more stable, a decrease of the Soret band of 70%, less than 40% and 30%, was observed after 21 h of reaction time, respectively.

It is also noteworthy that the degradation of the catalyst varied significantly with the olefin employed as substrate, the terminal olefin 4-chlorostyrene inducing a more drastic bleaching of the Soret band than the *cis*-disubstituted olefin 1,2-dihydronaphthalene. For instance, during epoxidation with the system **3-Mn**/$KHSO_5$, the catalyst was completely destroyed when 4-chlorostyrene was the substrate and the decrease in the Soret band was only 30% with 1,2-dihydronaphthalene.

4. Conclusion

This article describes the synthesis of new chiral metalloporphyrins and their evaluation in enantioselective epoxidation of a poorly reactive terminal olefin, 4-chlorostyrene. The chirality of these compounds is due to glycosylated residues (glucose, maltose or lactose) linked at the *ortho* or *meta* positions of the *meso*-phenyl substituents. The acetylated derivatives of natural D-saccharides represent a wide and easily accessible source of natural occurring chiral compounds. These porphyrin ligands can be obtained by direct condensation of pyrrole with glycosylated benzaldehydes in yields which can be considered as rather high compared to the multistep synthesis of other chiral porphyrin derivatives.

The manganese(III) complexes of these glycosylated porphyrins were found to be efficient and stable enough for the epoxidation of 4-chlorostyrene with different oxygen atom donors (PhIO, LiOCl, $KHSO_5$, and H_2O_2).

The enantioselectivity of this epoxidation reaction was moderate and strongly dependent on the glycosyl residue position. The *meta*-glycosylated catalysts are not able to induce significant ee's. In contrast, when the chiral moieties are in *ortho* positions, closer to the active center of the macrocycle, they generate an environment able to induce higher enantioselectivity. In that case, using H_2O_2 at low temperature, enantiomeric excess of 20% was obtained.

In conclusion, the use of natural sugar derivatives as chiral motives on metalloporphyrins appears to be an attractive possibility to perform enantioselective epoxidations of poorly reactive

olefins with easily accessible oxidants such as H_2O_2.

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