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Highly Selective Bromination of Tetramesitylporphyrin: an Easy Access to Robust Metalloporphyrins, M-Br_8TMP and M-Br_8TMPS.

Examples of application in catalytic oxygenation and oxidation reactions.

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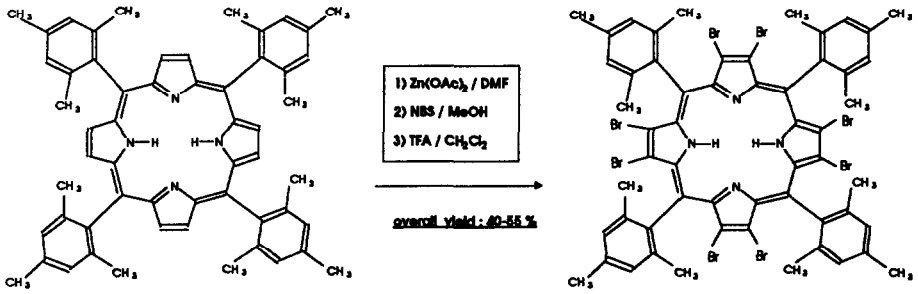
Summary: The N-bromosuccinimide bromination of the zinc derivative of *meso*-tetramesitylporphyrin, Zn(TMP), in methanol at reflux in air, gives the corresponding (β-pyrrole)octabromo derivative, *meso*-tetramesityl-β-octabromoporphyrinatozinc, Zn(Br_8TMP), in high yield (60-75%). Furthermore, the sulfonation by oleum of the metal-free ligand gives the persulfonated porphyrin, *meso*-tetrakis(3,5-disulfonatomesityl)-β-octabromoporphyrin, Br_8TMPSH_2 (70-75%). These robust manganese and iron derivatives are efficient catalysts in oxygen atom or electron transfer reactions.

Manganese and iron porphyrin complexes are efficient catalysts for oxygen atom transfer reactions.[1] Based on the modelling of oxygenation reactions known to occur in the hydrophobic pocket of cytochrome P-450, these studies have been performed with metalloporphyrins soluble in organic solvents. The favorite porphyrin ligands are currently molecules having substituents in *ortho* and *ortho'* positions of the *meso* phenyl groups to create a "cage effect" preventing (i) the formation of inert μ-oxo species and/or (ii) the oxidative degradation of catalyst molecules by an intermolecular process. Two of these ligands, namely *meso*-tetramesitylporphyrin, $TMPH_2$, and *meso*-tetrakis(2,6-dichlorophenyl)porphyrin, $TDCPPH_2$, are now available *via* an efficient two-step synthesis.[2] More recently, Traylor reported the synthesis of the brominated derivative of $TDCPPH_2$ at pyrrole positions, $Br_8TDCPPH_2$, and demonstrated its very high efficiency in catalytic oxygenation reactions.[3] In the course of a work on ligninase models,[4] we focused our attention on robust porphyrin ligands based on $TMPH_2$[5] and we found that this ligand is a valuable starting chemical for the syntheses of oxidation stable ligands. It can be easily fully brominated at the pyrrole β-positions with a very respectable yield leading to *meso*-tetramesityl-β-octabromoporphyrin, Br_8TMPH_2, which can also be sulfonated giving then access to a robust water-soluble ligand, tetrakis(3,5-disulfonatomesityl)-β-octabromoporphyrin or Br_8TMPSH_2. We report here the preparation of these ligands and the corresponding metalloporphyrins. The efficiency of these complexes in oxygenation or electron-transfer reactions is also illustrated.

In a typical experiment, $TMPH_2$ was first metallated with $Zn(OAc)_2$, $2H_2O$ in the presence of 2,4,6-collidine in refluxing DMF (82% yield).[6] The zinc derivative was then treated with a twenty-fold molar excess of N-bromosuccinimide,

NBS, in methanol for 1 hour at reflux. After neutralization by NaOH and evaporation, the residue was purified by chromatography on alumina. $Zn(Br_8TMP)$[6] was obtained in 60-65% yield. Demetallation by CF_3COOH gave the free ligand, Br_8TMPH_2 (85-90% yield after purification)[6,7]. The red-shift of its Soret band is 44 nm, corresponding to 5.5 nm per introduced bromine atom at the periphery of the macrocycle as previously observed (see Table 1 for UV-visible data).[3,8]



The most striking feature is the high selective bromination of pyrroles at β-positions, without noticeable bromination of the methyls of *meso*-mesityl groups, an alternative target for the halogenation reaction. As a working hypothesis one can note that NBS is a versatile reagent, leading to ionic or free-radical bromination.[9] Since the NBS reaction was performed without peroxides or radical initiators, in air (an inhibitor of free-radical bromination[10]), the main reaction at the pyrrole positions might be the result of a major ionic reaction pathway, opposed to a possible free-radical route leading to benzylic bromination.

The metallation of Br_8TMPH_2 with manganese or iron salts by conventional methods gave Mn(Br_8TMP)Cl and Fe(Br_8TMP)Cl (65-75% yield).[6] Furthermore, Br_8TMPH_2 was sulfonated with oleum (H_2SO_4, 20% SO_3) at 120 °C for 4-5 hours giving the water-soluble *meso*-tetrakis(3,5-disulfonatomesityl)-β-octabromoporphyrin, Br_8TMPSH_2 (75% yield).[11,13] The manganese and iron derivatives of this ligand, $Mn^{III}(Br_8TMPS)$ and $Fe^{III}(Br_8TMPS)$,[14] were prepared in 76% and 60% yield, respectively.[6]

Table 1. UV-visible spectra data of derivatives of Br_8TMPH_2 and Br_8TMPSH_2.

	solvent (conc. in μM)	λ nm (ε, M^{-1} cm^{-1} x 10^{-3})
$TMPH_2$	$CHCl_3$	419 (524), 514 (21.9), 548 (6.5), 590 (6.5) and 646 (2.9)
$TMPSH_2$	H_2O (2.0)	418 (330), 520 (13), 545 (1.7), 585 (3.4) and 640 (1.7)
Zn^{II}TMP	CH_2Cl_2 (16)	420 (450), 514 (4.6), 549 (15) and 588 (2.5)
$Zn^{II}Br_8$TMP	CH_2Cl_2 (6.9)	468 (230) and 600 (10)
Br_8TMPH_2	CH_2Cl_2 (8.9)	464 (190), 560 (1.1) and 609 (8.0)
$Mn^{III}(Br_8TMP)Cl$	CH_2Cl_2 (28.6)	506 (71), 616 (8.4) and 660 (8.4)
$Fe^{III}(Br_8TMP)Cl$	CH_2Cl_2 (8.9)	456 (51), 530 (13) and 570 (8.8)
Br_8TMPSH_2	H_2O (23.4)	468 (68), 568 (4.6) and 530 (5.7)
$Mn^{III}Br_8TMPS$	H_2O (11)	493 (56.4), 400 (23), 376 (22), 565 (5.9) and 600 (3.7)
$Fe^{III}Br_8TMPS$	H_2O (1.0)	397 (220) and 520 (44)

The efficiency and the robustness of two complexes from the first series of non water-soluble metalloporphyrins,

$Mn(Br_8TMP)Cl$ and $Fe(Br_8TMP)Cl$, have been tested in the epoxidation of various olefins and the hydroxylation of alkanes using $KHSO_5$ (potassium monopersulfate) or MMPP (magnesium monoperoxyphthalate[15]) as oxygen donor in experimental conditions indicated in reference 16. Using $Mn(Br_8TMP)Cl$ as catalyst, the reaction time is divided by a factor of 10 in the $KHSO_5$ olefin epoxidations as compared to Mn(TMP)Cl (see Table 2). Furthermore with MMPP as oxidant, almost complete olefin conversion was reached within 1 minute for disubstituted olefins, and within 10 minutes for 1-octene (terminal olefins are known to be unreactive with respect to epoxidation). In this latter case, Mn(TMP)Cl is mostly destroyed during the catalytic reaction, whereas $Mn(Br_8TMP)Cl$ is sufficiently robust to allow a complete conversion of the substrate. For such an inert olefin, the catalytic activity is 1 turnover per second, based on 90% of substrate conversion. However, we observed only an inhibition of the catalytic activity with H_2O_2 in the presence of imidazole in epoxidation reactions.[17]

Table 2. $Mn(Br_8TMP)Cl$ compared to Mn(TMP)Cl as catalyst in the $KHSO_5$ or MMPP epoxidation of olefins[a].

	$KHSO_5$		MMPP	
Olefin	Mn(TMP)Cl	$Mn(Br_8TMP)Cl$	Mn(TMP)Cl	$Mn(Br_8TMP)Cl$
Cyclohexene	98 (120)[b]	100 (10)	100 (1)	100 (1)
Cyclooctene	100 (60)	100 (10)	100 (1)	100 (1)
Styrene	100 (45)	100 (6)	100 (1)	100 (1)
1-Octene	80 (150)	80 (25)	75 (10)[c]	100 (10)[d]

[a] Data corresponding to olefin conversions. For experimental conditions see reference 16. All the data of this Table were obtained with 2 µmoles of catalyst, *i.e.* a catalyst/substrate ratio = 4/1000.
[b] These data represent the olefin conversion in % and the corresponding time in minute is indicated in parentheses. For all cases with this same system, the epoxidation selectivity is >95%.
[c] In the case of a terminal olefin, Mn(TMP)Cl is completely bleached within 10 minutes and consequently full olefin conversion can not be reached. [d] Even in the case of an inert substrate like a terminal olefin, the catalytic activity of the MMPP/$Mn(Br_8TMP)Cl$ system is as high as 1 turnover per second.

This same octabromo-TMP manganese catalyst is very efficient in alkane hydroxylation. In the $KHSO_5$ oxidation of adamantane, the conversion is 21% within 5 minutes, with a ratio catalyst/substrate of 1/1000 (at this stage of the reaction, the selectivity in alcohols, adamantan-1-ol plus adamantan-2-ol, is as high as 77% and the selectivity in ketone is only 3%). An even higher efficiency is observed with MMPP. With this oxidant and the same catalyst/substrate ratio, we observed 40% of adamantane conversion within 1 minute *(corresponding to a turnover rate of 6 cycles/sec, i.e. 40 times more active than for cytochrome P-450 itself)* and nearly complete adamantane conversion is reached before 1 hour. For cyclohexane, the conversion is 14% within 5 minutes when the ratio catalyst/substrate is 4/1000 (7 cycles/min). In these cases, there is no degradation of the catalyst during the hydroxylation reaction, and the reactivity of the system is about the same as observed with Mn(TDCPP)Cl, another robust metalloporphyrin.[18]

$Mn^{III}(Br_8TMPS)$ and $Fe^{III}(Br_8TMPS)$ complexes are efficient catalysts for the oxidation of lignin model molecules.[4] In the same experimental conditions used for $Mn^{III}(TPPS)$ and $Fe^{III}(TPPS)$ in the $KHSO_5$ oxidation of veratryl alcohol or 1-(3,4-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol, 100% conversions are observed for both substrates

within one minute (up to 40 cycles per seconde can be reached) without noticeable decomposition of catalysts.

In conclusion, the easy perbromination of β-positions of $TMPH_2$ pyrroles made possible the access to a new series of very robust catalysts for oxygen transfer reactions in organic medium or electron transfers in aqueous solutions. The presence of electron attracting substituents at the periphery of the macrocycle tends to enhance the reactivity of the metal-oxo species generated during these catalytic oxidations.

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5. This porphyrin ligand is obtained in higher yields than for $TDCPPH_2$. In our laboratory, $TMPH_2$ is usually obtained in 25-30% yield, instead of 15-20% for $TDCPPH_2$.
6. See Table 1 for UV-visible data.
7. NMR and mass data are in agreement with the per-bromination of the pyrrole β-positions. No pyrrolic protons are detectable in the 8.40 - 8.80 ppm region. *o*-Me and *p*-Me groups are observed (in ^1H NMR) at 2.00 ppm and 2.57 ppm, respectively and *m*-aromatic protons at 7.23 ppm in CD_2Cl_2.
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11. The same procedure applied to $TMPH_2$ gave the *meso*-tetrakis(3,5-disulfonatomesityl)porphyrin, $TMPSH_2$. Details on preparation and characterization will be published in a subsequent full article. The sulfonation conditions used for the *meso*-tetrakis(2,6-dimethylphenyl)porphyrin led to one sulfonato group per phenyl ring.[12]
12. M. F. Zipplies, W. A. Lee and T. C. Bruice, *J. Am. Chem. Soc.*, **1987**, *109*, 7865 and references therein.
13. ^1H NMR data: *o*-Me and *p*-Me groups are at 2.04 and 2.46 ppm, respectively, in CD_3COD. The simplicity of the NMR spectrum is an additional argument for a centro-symmetric structure.
14. $Mn^{III}(Br_8TMPS)$ and $Fe^{III}(Br_8TMPS)$ stand for the octasodium salt of the manganese and iron derivatives of Br_8TMPSH_2.
15. MMPP is another water-soluble oxidant used in olefin epoxidations (C. Querci and M. Ricci, *J. Chem. Soc., Chem. Commun.*, **1989**, 889) or manganeseporphyrin-mediated DNA cleavage (G. Pratviel, J. Bernadou, M. Ricci and B. Meunier, *Biochem. Biophys. Res. Commun.*, **1989**, *160*, 121).
16. All reactions have been performed in air at room temperature. CH_2Cl_2 (2mL), olefin or alkane (0.5 mmol, final concentration: 0.25 M), internal standard (octane or nonane in epoxidations or chlorobenzene or 1,2-dibromobenzene in hydroxylations, 0.25 mmol) and 4-*t*-butylpyridine (0.050 mmol, *i.e.* 25 equiv./catalyst) were successively added to catalyst (2 µmol, 0.4%/substrate or 0.5 µmol, 0.1%/substrate) and benzyldimethyltetradecylammonium chloride (0.075 mmol) and then 1 mmol of oxidant was added ($KHSO_5$ being diluted in 10 mL of 0.25M phosphate buffer, pH = 7; MMPP in 10 mL of water). For additional experimental data and GC analyses, see reference 18. It has to be noted that the concentration of phase tranfer agent, PTA, is three times that one used previously.[18]
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