Direct Synthesis of Chiral Porphyrin Macrocyclic Receptors via Regioselective Nitration

Shaji Varghese,*† Bram Spierenburg, Anne Swartjes, Paul B. White, Paul Tinnemans, Johannes A. A. W. Elemans, and Roeland J. M. Nolte*‡

Radboud University, Institute for Molecules and Materials, Heyendaalseweg 135, 6525 AJ, Nijmegen, The Netherlands

Supporting Information

ABSTRACT: Nitrations of tetraphenylporphyrin cage compound 1, at −40 °C, leads to the regioselective formation of the chiral mononitro compound 2 (75% isolated yield) and, at −30 °C, to the achiral syn-dinitro-derivative 3 and the chiral anti-dinitro derivative 4 in a diastereomeric ratio of 5:2, which were separated by chromatography (46 and 20% yields, respectively). The structures of the compounds were confirmed by X-ray crystallography.

The work described in this paper is part of a larger project aimed at developing techniques to encode single polymer chains with information.1 It is inspired by the hypothetical machine (called the Turing machine) developed by the mathematician Alan Turing in 1936.2 The Turing machine is composed of a tape head that, while moving along a tape, reads, writes, and erases symbols on this tape according to a table of rules (Figure 1a). The tape head can switch between different (instruction) states and controls what is written on the tape. The latter stores the information produced by the machine. In the past, we have constructed a simple molecular equivalent of such a Turing device, i.e. a catalytic cage compound composed of glycoluril with a manganese porphyrin roof (compound Mn1, Figure 1b). It can thread onto a polymer chain, e.g. polybutadiene and, while moving along it, convert the double bonds into epoxide functions (Figure 1c).3 Unfortunately, this “writing” process takes place randomly; i.e., the cage catalyst hops from site to site, although this eventually leads to full oxidation of the polymer tape. The next step in this project is the design of chiral cages of type 1, which when provided with a manganese(III) center can write chiral epoxides on a chiral polymer chain. In a later stage, these chiral cage catalysts will be further modified to systems that can write either (R,R)- or (S,S)-epoxides (digital codes 0 and 1) depending on the chirality of the cage. The introduction of chirality in the cavity-containing framework 1 may require extensive synthesis and tedious purification processes, which is challenging. Hence, the development of a new, simple route for the preparation of chiral derivatives of 1 is of great interest. In this paper, we report a facile and mild procedure to convert 1 into chiral derivatives, i.e. by a direct regioselective nitration reaction leading to chiral hosts 2 and 4 and achiral host 3. Both compounds 2 and 4 are potential candidates for the development of sequential processive catalysts that can be used to prepare optically active polyepoxides from polyolefins, as outlined above.

Porphyrin cage compound 1 is prepared in a multistep procedure starting from diphenylglycoluril and tetrakis(2-hydroxyphenyl)porphyrin; see Scheme S1 in Supporting Information (SI).4 While designing a chiral derivative of 1, we realized that the attachment of a substituent, e.g. a nitro-group, to one of its side walls would create a compound with a plane of chirality and two chiral centers (the carbon atoms marked with an asterisk in Scheme 1).5 Initially, we tried to synthesize such a compound by nitrating one of the intermediates in the synthesis of 1 (compound 5 in Scheme S1 in SI), but this reaction led to black reaction mixtures and unidentified products. We discovered that when 1 was treated with fuming nitric acid (10 equiv) in chloroform at −40 °C, compound 2 was directly formed in 90% yield (75% isolated yield), while no starting material remained, and only traces of dinitro-side products were present. Interestingly, when the reaction mixture was carried out with 20 equiv of nitric acid at −30 °C a mixture of dinitro-products 3 and 4 was isolated in a...
yield of 66% (Scheme 1). The latter compounds were generated in a 5:2 syn (3)-anti (4) ratio based on an analysis of the isolated products from the reaction mixture (see Figure S13 in SI). The remarkable regioselective outcome of the aromatic electrophilic substitution reaction was unexpected as cage compound 1 contains several phenyl rings, which could also react with nitric acid, at least in principle. It might be that the cage structure and the presence of the crown ether-like rings in 1 assist in the selective reaction of the reactive NO2+ species with the side walls. To gain more insight into this possibility, 5 equiv of [NO2]BF4 were added (at room temperature) to a solution of 1 in CDCl3. The 1H NMR spectrum of this mixture showed that particularly the signals of nearly all oxyethylene protons, as well as those of the β-pyrrrole protons directly above the entrance of the cavity, displayed significant downfield shifts compared to the spectrum of 1 (see Figure S27 of SI). These shifts indicate that the positively charged NO2+-species interacts with the cavity, possibly stabilized by ion–dipole interactions with the oxyethylene spacers. Similar interactions between crown ethers and NO2+ have been reported before, and in addition it is known that its positive charge can be stabilized by interactions with a porphyrin ring. The linear NO2+-species may form a host–guest complex with 1, in which the ion is located in the cavity, in close proximity to the cavity side walls. Since these are also the most electron-rich aromatic moieties of the cage molecule, and thus the ones that are most susceptible to electrophilic aromatic substitutions, we propose that a combination of the electronic and proximity factors governs the observed regioselectivity of the nitration reaction. The preferential formation of the syn-dinitro-compound 3 over the anti-dinitro-compound 4 is interesting from a stereochemical point of view. There is more steric hindrance between the nitro-functions in 3 than in 4; hence, the former compound is expected to be formed in smaller amounts than the latter compound, which is not the case. Furthermore, the dipoles of the nitro functions are oriented in a parallel orientation in 3, which is also less favorable than the antiparallel orientation in 4. It might be that the cavity also plays a role in directing the orientation of the second nitration reaction on 1. For example, the nitro group on the cavity side wall of mononitro-compound 2 may have a favorable electrostatic interaction with a NO2+-ion that also interacts with the cavity of the cage compound, thereby regioselectively directing its electrophilic attack at the syn-position of the opposite side wall.

All isomers could be separated by conventional column chromatography, revealing that the chromatographically more polar isomer of the dinitro-compounds is 3 and the less polar one is 4, as expected. The new compounds 2–4 were completely characterized by standard spectroscopic and analytical techniques (see SI). The proton signals in the 1H NMR spectrum of 2 at room temperature were sharp, and the increased number of resonances revealed the unsymmetrical nature of the macrocycle (see SI). The protons of the CH2 group of the oxyethylene side chain closest to the nitrogroup in 2 displayed a shift from 3.34 ppm in 1 to 2.40 ppm in 2. This indicates that this proton is oriented inside the cavity and, hence, shielded from the magnetic field, probably because of steric interactions with the nitro group. The presence of the nitro group and the inward orientation of the oxyethylene spacer indicate that the cavity portal of 2 is smaller than that of 1. The same conclusion can be drawn from the X-ray structure of 2, which also showed that the oxyethylene spacer is bent inward; see below. The 1H NMR spectra of the isolated isomers 3 and 4 in CDCl3 were different, as is expected for

Scheme 1. Synthesis of Mono- and Dinitro Cage Compounds 2–4

Figure 1. (a) Schematic representation of the hypothetical Turing machine. The tape-head can switch between n states and write m codes. (b) Manganese porphyrin cage compound Mn1 derived from diphenylglycoluril. (c) Catalyst Mn1 provided with a 4-tert-butylpyridine ligand (blue) gliding along a polybutadiene chain while converting the polymer double bonds into epoxide functions.
diastereomeric products. In particular, a significant difference in the shifts of the side wall benzene protons was observed, i.e. at 6.40 and 6.21 ppm for 3 and 4, respectively (see Figures S14 and S20 of SI). Furthermore, the occurrence of only one single resonance peak for the two side wall benzene protons indicates that molecules 3 and 4 have symmetrical features. The HRMS analysis of 3 and 4 confirmed the dinitro-substituted structure of the cage compounds as signals for the sodium adducts [M + Na]+ and for the protonated [M + H]+ cage compounds were found at m/z = 1457 and 1435 amu, respectively. Since cage compound 3 is achiral (meso-configuration) and compound 4 is chiral (and racemic), we used 13C NMR as a tool to assign (and differentiate) the meso and racemic structures. Careful inspection of the 13C NMR spectra revealed that 3 and 4 have a different set of peaks in the carbonyl region. Diastereomer 4 showed one resonance for the carbonyl functionality of the glycoluril part at 156.41 ppm as a result of the C2 symmetry of the molecule, and diastereomer 3 showed two peaks at 156.89 and 155.50 ppm (see Figure S25 of SI). This means that, in the case of the meso-compound 3, the carbonyl groups lie in the mirror plane of the molecule and are nonequivalent, whereas, in the racemate, they are identical via a rotation axis. This helped us assign the meso-structure to 3 and the racemic structure to 4. After we had assigned these stereochemistries, all the 1H NMR signals of hosts 3 and 4 were assigned on the basis of 2D NMR techniques, i.e. COSY, ROESY, HSQC, and HMBC (see SI).

The molecular structures of cage compounds 2–4 were confirmed by X-ray analysis (for details, see SI). The crystals of 2 were found to have a racemic space group. X-ray analysis also confirmed the structure of mononitro-compound 2 (Figure 2a) and revealed that in the crystal the cage molecules were packed as dimers (Figure 2d). The enantiomers of 2 were arranged in an alternate fashion in one crystal plane. The porphyrin rings are oriented opposite to each other and partially overlap. The distance between the side wall benzene rings of two adjacent cage molecules is 3.628 Å, indicating that the π–π interactions stabilize the structure. Interestingly, in the vertical direction, the enantiomeric molecules of 2 stack on top of each other, forming long chiral channels (Figure 2d). The X-ray structures of compounds 3 and 4 are presented in Figure 2b and c. Just as in the case of 2, the nitro groups in 3 and 4 are positioned approximately perpendicular to the benzene side walls of the cage compounds. This conformation seems to be induced by the strain created in the oxyethylene spacers and the o-xylene methylene groups next to the nitro groups. According to the X-ray structures (see SI), the distances between the oxygen atoms of the nitro groups and the first oxygen atoms of the oxyethylene spacers were found to be 2.93 and 2.5 Å for 3 and 4, respectively. This short distance leads to electrostatic repulsion forcing the CH2 group of the oxyethylene spacer next to the nitro group to move inward. A noticeable feature is the twist in the diphenylglycoluril part of compounds 3 and 4. In the case of host 3, the dihedral angle of C43–C36–C35–Nβ is 117.8° and the angle of C37–C35–C36–Nα is 125.27° (for atom numbering, see Scheme 1 and Figure S1 in SI). For host 4, the angle C43–C36–C35–Nβ is 142.11° and the angle C37–C35–C36–Nα is 102.81°. These twists are clearly visible in the 1H NMR spectra as well, showing distinctive features for the xylylene ring protons of the diphenylglycoluril parts of hosts 3 and 4 (see SI).

In summary, we have discovered a mild, single-step synthesis of a new family of chiral macrocyclic porphyrin receptors. The structures of the new compounds were proven by mass spectrometry, 1H and 13C NMR spectroscopy, and single crystal X-ray spectroscopy. We are currently resolving the chiral compounds into enantiomers, and their manganese complexes will be tested as catalysts for the enantioselective epoxidation of polybutadiene and related polymers.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b01055.

Experimental procedures and detailed characterization of all new compounds (PDF)

**Accession Codes**

CCDC 1834463–1834465 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: ++44 1223 336033.

**AUTHOR INFORMATION**

**Corresponding Authors**

*E-mail: S.Varghese1@tue.nl.*

*E-mail: R.Nolte@science.ru.nl.*
ORCID
Roeland J. M. Nolte: 0000-0002-5612-7815

Present Address
\textsuperscript{1}Department of Chemical Engineering and Chemistry, Stimuli-responsive Functional Materials and Devices Group, Department of Chemical Engineering etc., Eindhoven University of Technology, P.O. Box 513, 5600 MB, Eindhoven, The Netherlands.

Notes
The authors declare no competing financial interest.

\section*{ACKNOWLEDGMENTS}
This work was supported by the European Research Council (ERC Advanced Grants 290886 ALPROS and 740295 ENCOPOL to R.J.M.N.) and a grant from the Dutch Ministry of Education, Culture and Science (Gravity Program 024.001.035).

\section*{REFERENCES}
(9) For a theoretical analysis of the regioselective nitration of 1,2- and 1,4-dimethoxybenzene, see: Shopsowitz, K.; Lelj, F.; MacLachlan, M. J. \textit{J. Org. Chem.} \textbf{2011}, \textit{76}, 1285.