Directional threading of a chiral porphyrin cage compound onto viologen guests

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We report on the face-selective threading of a chiral porphyrin cage compound onto viologen guests that are provided on both ends with substituents of different sizes. Depending on the types of terminal groups on the guest the cage compound orients itself in one of two possible directions.

One of the current challenges in science is to encode (write) information into single polymer chains and store it for later use.^{1,2} Efforts in this direction include the development of DNA-based systems, which make use of the four nucleotides to write a code (e.g. binary, tertiary, or quaternary) and the controlled synthesis of synthetic polymers composed of two different monomers, each representing the chemical equivalents of the digital codes 0 and 1. Until now these encoded (bio)polymers have been exclusively prepared by step-wise synthesis protocols.^{3,4} Nature on the other hand uses catalytic machines (e.g. DNA polymerases and ribosomes) to write and store information.⁵ We have started a program to write information on single polymer chains by catalytic machines inspired by the theoretical machine developed by the mathematician Alan Turing.⁶ This theoretical machine is composed of a tape-head that moves along a tape, while writing, storing, and erasing information on it. In previous papers we reported on a simple molecular equivalent of such a Turing machine, which is constructed from a toroidal-shaped porphyrin catalyst (**Mn1**) that can thread onto a polymer chain, e.g. polybutadiene, and glide along it while converting the polymer double bonds into epoxide functions (Fig. 1).^{7,8} Unfortunately, this previously developed system moves randomly along the polymer chain, nevertheless it achieves eventually full oxidation of the polymer. In order to be able to write a (chemical) code we have to construct a chiral machine that moves unidirectionally along a (chiral) polymer while writing chiral epoxides (*R,R*-epoxide = digital code 0, *S,S*-

epoxide = digital code 1). In a recent paper we reported on the direct and high yield synthesis of a chiral cage compound (**H₂2**) by the regioselective nitration of one of the side walls of the achiral compound **H₂1** (Fig. 1).⁹ Compound **H₂2** has a nitro handle that can be reduced to an amine function and in a later stage be connected to a light-switchable group that controls the chirality and catalytic activity of the cage compound. The presence of the handle in **H₂2** means that this compound has two faces allowing it to thread and bind in two ways onto a guest (low molecular weight or polymer chain), i.e. with its handle toward the guest end and, reversely, away from this end. Face-selective threading has been reported in the literature before, mainly involving studies on cyclodextrin host

Fig. 1 Top from left to right: structures of diphenylglycoluril-derived porphyrin cage compounds **H₂1**, **Mn1**, and (±)-**H₂2**. Bottom: cage catalyst **Mn1** provided with a 4-*tert*-butylpyridine ligand (blue) randomly moving along a polybutadiene chain, while converting the polymer double bonds into epoxide functions.

molecules.¹⁰⁻¹² The guest can thread in two ways as well, i.e. with each of its ends entering the host. In the past we studied the threading of **H₂1** onto oligomeric and polymeric chains that are open at one end and blocked at the other end by a bulky stopper group (see Scheme 1), forcing the threading process to be unidirectional, i.e. only from the open end.¹³ Close to this blocked end is a viologen function that binds inside the cage of

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H₂1 and acts as a trap. Unidirectional threading and motion has been studied in great detail in the literature.^{14–17} The threading and binding process of **H₂1** was followed by ¹H-NMR and fluorescence spectroscopy. In the latter case the fluorescence of the porphyrin of **H₂1** is quenched as soon as the cage compound binds to the viologen trap. In this paper we report on ¹H-NMR studies aimed at finding out how compound ($\pm$)-**H₂2** threads and orients itself onto guests that are blocked at one end and provided with substituents of varying sizes at the other end. This information is important for the further development of the above-mentioned chiral molecular Turing machine, in particular how this machine moves along a polymer chain.

Cage compound ($\pm$)-**H₂2** was prepared by a regio-selective aryl nitration of **H₂1** using excess of HNO₃ in chloroform at –40 °C, as reported previously (yield 75%).⁹ The substituted viologen guests (Scheme 1) that were used for the threading studies were synthesized according to published procedures (**V1–V3**, **V5**, **V6**).^{13,18} The synthesis of viologen guest **V4** is described in the SI.

Scheme 1 Structures of the non-symmetrically substituted viologen guests **V1–V5** and the symmetrical di-blocked viologen guest **V6**.

As mentioned above, cage compound ($\pm$)-**H₂2** may thread onto the non-symmetrical guests in two ways, i.e. with its nitro group toward the blocking group and with this group away from it, leading to mixtures of diastereomeric host-guest complexes. The directionality of the guest threading was studied by ¹H-NMR at 1 mM concentration in CDCl₃:CD₃CN 1:1 (v/v). Initial experiments were performed with **V1** revealing that pseudo-rotaxane complexes, in which the guest had two orientations, were formed. Unfortunately, the signals were broad due to a fast host-guest exchange process. Nevertheless, by lowering the temperature to –30 °C it could be established that the ratio of the two rotaxanes complexes was circa 1 to 0.75. Lowering the temperature of the solution further to –70 °C (CD₂Cl₂ was used as a solvent) did not sufficiently slow down the exchange process to allow for a detailed analysis of the spectrum and the establishment of the

orientation of the guest in each of the two rotaxane complexes (SI, Figs. S5–S6). Further experiments were therefore performed with guest **V2**, which possesses a bulky adamantane group, leading to a much slower host-guest exchange on the NMR time scale. Analysis of the ¹H-¹³C HSQC, and HMBC spectra revealed that the singlets found at 6.07 ppm and 5.86 ppm correspond to the sidewall protons attached to the same, unsubstituted benzene ring of ($\pm$)-**H₂2**, while the singlet at 6.37 ppm belongs to the sidewall proton of the nitrobenzene ring (Fig. 2, see also SI, Figs. S7–S12). The presence of only one set of sidewall protons indicated that the guest had threaded in a face-selective fashion through the host compound (Fig. 3). Binding of **V2** to ($\pm$)-**H₂2** also resulted in significant conformational changes in the porphyrin host, which was evident from the observed shifts in proton signals of ($\pm$)-**H₂2**.

Fig. 2 Summary of key ROEs that are important for the determination of the orientation of guest **V2** inside the cavity of ($\pm$)-**H₂2**.

Several ROE correlations between the host and guest were observed in the 2D spectrum, confirming the formation of a host-guest complex. The cross-peaks between the uniquely resolved sidewall protons and the protons of the pyridinium rings of the guest were critical for determining the directionality of the guest. By extracting 1D slices from the 2D spectrum, it was concluded that the two side-wall protons at 6.37 ppm and 5.86 ppm both had ROE correlations with protons at 8.03 ppm and 4.66 ppm (SI, Fig. S12). These protons were identified, via additional COSY and HSQC experiments, to be the *ortho* and *meta* protons, respectively, of the pyridinium ring connected to the adamantane group. Other ROE

correlations between the above-mentioned sidewall protons and the *o*-xylylene and ethylene glycol moieties within the host molecule were also observed and were as expected quite strong. The sidewall proton of the benzene ring without a nitro function at 6.07 ppm also had several ROE correlations with the xylylene and ethylene glycol groups of the host, but more importantly also with the pyridinium ring of the guest connected to the stopper functionality. The 1D ROESY extract showed correlations between the sidewall proton at 6.07 ppm and two other protons at 5.25 ppm and 2.86 ppm, which were identified via COSY and HSQC and found to belong to the *ortho* and *meta* protons, respectively, of the pyridinium ring of the viologen molecule. These very large complexation-induced shifts (−3.68 and −5.37 ppm, respectively, with respect to the signals in uncomplexed **V2**) are attributed to the strong shielding by the porphyrin ring current and are further evidence of the close proximity of the bipyridinium moiety and the porphyrin of (±)-**H22** in the complex. Further ROEs from the *ortho* proton at 5.25 ppm to protons at 3.49 ppm and 3.18 ppm were found and the latter were identified as the diastereotopic CH₂ protons attached to the pyridinium nitrogen atom. This finding was substantiated by ¹H-¹³C HSQC and ¹H-¹H TOCSY experiments, which confirmed the CH multiplicity and revealed that these protons were part of the pentylene chain of the stopper. In principle, the two pyridinium rings mentioned above could be part of two separate guest molecules or belong to a single guest molecule. Several observations support the latter explanation, i.e. that these pyridinium rings belong to the same 1:1 host: guest adduct. Firstly, there are strong ROE correlations between the *meta* proton of the stopper pyridinium ring at 2.86 ppm and the *meta* proton of the adamantyl pyridinium ring at 4.66 ppm, which means that these protons lie in very close proximity to each other in a way that would be difficult to achieve for an intermolecular interaction between two guests. Secondly, there is only one set of ¹H resonances belonging to the host, which strongly supports a well-defined 1:1 host:guest complex. Further confirmation of the covalent attachment of the pyridinium rings via ¹H-¹³C HMBC experiments was unsuccessful, likely due to the relaxation of the nuclei, given the broad ¹H resonances, during the evolution of the long-range ¹H-¹³C *J*-coupling.

The above presented NMR results provide several key insights into the way **V2** is threaded through (±)-**H22**. The presence of ROEs between the two sidewall protons at 6.37 ppm and 5.86 ppm to a single pyridinium ring reveals that these protons are *syn*-facial to each other and sit on the opposite face of the cavity as the nitro group (Fig. 2). Additionally, this pyridinium ring was identified as the one connected to the adamantane group. Therefore, it can be concluded that the adamantyl group is positioned near the cavity entrance that is opposite to the nitro group. This is further supported by the ROEs between the opposite side wall proton at 6.07 ppm, which is *syn*-facial to the nitro group, and the pyridinium ring that is connected to the stopper linker (Fig. 2). Taken together these observations paint a clear picture about the directionality of the threading of **V2** through (±)-**H22**.

The adamantyl group of the guest molecule is located at the unsubstituted face of (±)-**H22**. The fact that the guest is threaded through the host from the most hindered side, i.e. the nitro side, apparently is needed in order to allow the host-guest system to form the most stable complex.

To further investigate what the role of the adamantyl group in **V2** is during threading, we also performed threading experiments with guest **V4**, in which a spacer is present between the viologen and adamantane group. In sharp contrast to the complex of (±)-**H22** with **V2**, **V4** preferentially oriented itself in the cavity of (±)-**H22** with the blocking group at the least hindered face of the cavity. Extensive 1D and 2D NMR experiments (SI, Figs. S18-S25) revealed that two pseudorotaxane complexes were formed in a ratio of 0.25:1 (Fig. 3)

Fig. 3 Computer-modelled structures based on ¹H-NMR data of the host-guest complexes formed between (±)-**H22** and **V2**, **V4**, and **V5**. Yellow: 3,5-di-*tert*-butylphenyl blocking group; blue: terminal group (**V2** and **V4**: adamantyl; **V5**: 1-(2-butylhexyl)).

The complexation-induced shifts of the aromatic protons of the viologen moiety, and ROE contacts between these protons and specifically the cavity sidewall protons at the unsubstituted face of (±)-**H22**, revealed that in both of the (±)-**H22**/**V4** isomeric complexes the viologen moiety is slightly shifted away from the nitro-substituted face of the cavity. The observation that the major product is now the complex in which the blocking group is located at the non-substituted face of (±)-**H22** reveals that the directionality in the complex formation is not based on kinetic face-selectivity processes between the cage and the terminal group of the viologen. Instead, it shows that the directionality is determined by which of the host-guest complexes is thermodynamically the most stable one.

To further study the effect of the terminal group of the viologen guest on the direction of the pseudo-rotaxane formation, we also investigated the threading of (±)-**H22** onto viologens **V3** and **V5** (Table 1). In the case of **V3** as guest, we observed the formation of complexes in which the orientation of the guest inside the host was such that entry from the nitro side versus the open side had occurred in a ratio of 1:0.55. The complex formation reached an equilibrium state immediately after the addition of (±)-**H22** to **V3** (SI, Fig. S13). This indicates that **V3** with its methylcyclohexyl terminal group can pass the cavity easily.

Table 1 Ratio of the two pseudorotaxane isomers formed in the binding of guests **V1**–**V5** in (±)-**H₂2**.^[a]

Viologen guest	Orientation of guest in host-guest complex (entry from nitro : opposite nitro side)
V1	1:0.75 or 0.75:1 ^[b]
V2	1:0
V3	1:0.55
V4	0.25:1 ^[c]
V5	1:0 ^[d]

^[a] Determined by ¹H-NMR (CHCl₃:CH₃CN (1:1, v/v)). ^[b] It was not possible to identify the precise orientations of guest binding by ¹H NMR. ^[c] Complexes prepared at 80 °C ^[d] Complexes prepared at 45°C or 100 h at room temperature.

When the sizes of the terminal groups in **V3** (methylcyclohexyl) and **V5** (1-(2-butylhexyl)) are compared¹¹ no facile threading is expected for the latter guest at room temperature. Indeed, threading only occurred when the host-guest mixture was kept at room temperature for extended periods of time (100 h) or when the temperature was raised to 45 °C (SI, Fig. S31). Interestingly, **V5** was also found to thread into (±)-**H₂2** in a face-selective fashion under these conditions. It forms the host-guest complex with the blocking group located at the nitro side of the host, similar to (±)-**H₂2/V2** (Fig. 3). It should be noted that the nitro side of (±)-**H₂2** is flexible enough to eventually accommodate **V5** at higher temperatures, as can be concluded from VT experiments (SI, Fig. S33). The above results clearly reveal that the direction of the threading of the guest through (±)-**H₂2** does not simply depend on the size of the terminal end of the guest molecule, but more on the local bulkiness of the guest near the nitro group of (±)-**H₂2** in the final host-guest complex. As a control, we also performed threading studies with guest **V6**, which has two bulky blocking groups (Scheme 1). As expected, in this case no pseudo-rotaxane complex was observed with (±)-**H₂2** (SI, Fig. S32 and Fig. S33), in line with our previous observations on cage compound **H₂1**.¹³

Controlling the direction of threading of macrocyclic cages onto (polymeric) substrate molecules is important for the development of a molecular Turing machine that can write information on a polymeric chain, as explained in the introduction section. Our present study reveals that the non-symmetric host compound (±)-**H₂2** does not always thread onto one-side blocked guest molecules in the same manner, i.e. with either the open side (without handle) or with the side containing the nitro handle approaching the guest. Our data suggests that in the case of the sterically bulky threads (**V2** and **V5**) the thermodynamically most favored product is formed. On the contrary, a mixture of kinetic and thermodynamic stereoisomers is observed when the threads have a medium to small size (**V1**, **V3**, **V4**). These results have to be confirmed in future studies, which are underway. For the further development of a molecular Turing machine and (as part of this) for a more detailed analysis of the threading of a chiral cage compound onto a chiral polymeric substrate it may be better to use a macrocyclic compound with a functional handle that is more bulky than a nitro group. This may increase the

face-selectivity of the threading process.. Alternatively, one may consider to use a chiral porphyrin cage compound with two handles on opposite sides of the host (a C₂ symmetric host), in which case face-selectivity does not play a role. Work along this line is in progress.

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Conflicts of interest

There are no conflicts to declare.

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