We describe a manganese porphyrin-α-cyclodextrin conjugate as a catalyst for the epoxidation of cis-polybutadiene with trans-epoxide preference, which is a reverse stereoselectivity as compared to normal porphyrin catalysts. A clamp-like mechanism is proposed based on a combination of circular dichroism analysis, molecular modeling, and a series of epoxidation experiments.

In nature, clamp-like proteins tether enzymes to polymeric substrates, allowing them to perform stepwise reactions along the polymer chain in a processive mode. One of the most studied examples is the replication of DNA by the bacteriophage T4, which employs a clamp-shaped protein (gp45) to associate the replication polymerase (gp43) to DNA, thereby improving the efficiency and reliability of the replication process. Many enzymes contain metal centres as catalytically active sites, for instance iron porphyrin as in the mono-oxygenase Cytochrome P-450. This enzyme catalyzes the oxidation of many substrates, including the hydroxylation of alkanes, the epoxidation of alkenes, and the oxidation of DNA in aqueous media. In these enzymes the porphyrin acts as the first coordination sphere for the catalytically active metal ion, whereas the second coordination sphere, which is crucial for selectivity, is provided by the protein mantle. Mimicking this aspect of intricate biocatalysis is not easy but using metal porphyrins in combination with other macrocyclic compounds with well-defined structures may offer a possible approach to achieve selectivity. For this purpose manganese porphyrins in combination with a nitrogen donor ligand, e.g. pyridine, are particular useful as they are more active than the naturally occurring iron porphyrin derivatives.

In our previous work, we reported on a series of diphenylglycoluril-based macrocyclic manganese porphyrin ‘clips’ that are capable of threading onto a polymer chain, e.g. cis-polybutadiene, followed by gliding along it, while converting the C=C bonds of this polymer into epoxide functions (processive catalysis). In addition, we have described a biohybrid catalyst composed of the T4 sliding clamp protein, which was shown to cleave DNA chains at AAA sites in a clamping and processive fashion. In the past, cyclodextrins (CDs) have been widely used in catalysis in combination with metal-complexes including porphyrins. In these systems the CD moiety acts as the second coordination sphere for the metal centre, allowing the substrate to bind into it, bringing it in close proximity to the catalyst. However, in order to achieve selectivity, the substrate had to be modified with additional groups to thread inside the cavity of the CD.

Fig. 1 Schematic representations of (a) structures of the catalysts, and (b) proposed catalytic epoxidation by the clamp-like catalyst MnTPP-αCD following a distributive mechanism.
We here report on a manganese porphyrin-αCD conjugate (MnTPP-αCD), which catalyses the epoxidation of polybutadiene with trans-epoxide preference. Experimental evidence suggests that this catalyst may operate in a clamp-like mode, reminiscent of naturally occurring clamp-shaped enzymes (Fig. 1).

Circular dichroism has proven to be a useful technology to investigate the chiral properties of protein and supramolecular systems as it is sensitive to changes in the relative geometry of specific chromophores. In particular, porphyrins have been profoundly studied by circular dichroism in view of their intense extinction coefficients (especially of the Soret bands) and their characteristic induced circular dichroism (ICD) when bound to cyclodextrins. In order to establish the conformation of the target catalyst MnTPP-αCD and to compare it with the permethylated reference catalyst MnTPP-PMαCD (compound 3 in Fig. 1a), ICD measurements on these compounds were carried out.

Interestingly, a much stronger and distinct ICD signal was observed in the Soret region of MnTPP-αCD, revealing a bisignate Cotton effect centered at 480 nm (Fig. 2a). Similar split and unsymmetrical ICD signals have also been reported by Mizutani and Shinkai for metalloporphyrins that bind to chiral amino acids or carbohydrate derivatives in a two-point-interaction mode. They confirmed that a chiral molecule (CM) interacts with an achiral metalloporphyrin at two sites (one end of the CM binds to the porphyrin at the meso-phenyl site and the other coordinates to the central metal), resulting in an optically active “CM on porphyrin plane” complex. The bisignate ICD signal is rationalized by the immobilized chiral orientation of the two-site bounded complex. Hence, the resemblance of the characteristic bisignate Cotton effect in the ICD spectrum of MnTPP-αCD with that of the reported porphyrin-CM complexes, as well as the clear difference with the ICD of MnTPP-PMαCD (Fig. 2a), suggests that MnTPP-αCD has a folded (clamp-like) conformation (Fig. 2c). In this conformation αCD is the chiral molecule that dually binds to the porphyrin, i.e. via a covalent bond and via coordination to the metal centre.

In order to obtain more information about the precise conformation, the zinc derivative of TPP-αCD was synthesized. Unfortunately, this compound could not be studied by NMR because it was completely insoluble in all solvents, suggesting the presence of a polymeric coordination complex. We therefore had to resort to theoretical simulations, which were carried out on MnTPP-αCD with pyridine as the axial ligand using the PM7 quantum semi-empirical method. The result of this molecular modeling suggests that this compound may have a clamp-like structure, in which one of the primary hydroxyl groups of αCD coordinates to the manganese center (Fig. 3).

As shown in Fig. 2a, MnTPP-PMαCD shows weak and broad negative bands in the Soret region (478 nm) of the ICD spectrum as a result of dipole–dipole coupling of the porphyrin moiety with the CD. According to Kodaka’s rule, such a negative sign of the Cotton effect can be expected, when the transition dipole moments of porphyrin are located outside the CD cavity and the porphyrin plane is oriented more or less parallel to the symmetry axis of the CD (the extended conformation, Fig. 2d).
state, stronger interactions are present between the porphyrin moiety and the CD ring in MnTPP-αCD than in MnTPP-PMαCD. Such a red shift has also been observed previously in porphyrins to which benzoquinones or cyclodextrins were attached via flexible linkages. These shifts were ascribed to folded conformations in which the linked species interact with the porphyrin.\textsuperscript{15}

MnTPP-αCD was subsequently tested as a catalyst for the epoxidation of cis-polybutadiene (Poly-1) at room temperature in dichloromethane, using iodosylbenzene (PhIO) as the oxygen donor and pyridine as the axial ligand and co-solvent. Furthermore, to better understand the role of the appended cyclodextrin moiety on the stereo (cis/trans) selectivity of the epoxidation, a series of porphyrin catalysts with analogous structures (Fig. 1a) were synthesized and compared with MnTPP-αCD under the same experimental conditions. The epoxide yields and cis/trans stereoselectivities of six catalytic systems, i.e. MnTPP (1), MnTPP-αCD (2), MnTPP-PMαCD (3), MnTPP-βCD (4), MnTPP-PMβCD (5), and the 1:1 mixture of MnTPP and αCD in a 1:1 molar ratio (6), are presented in Fig. 4. Interestingly, although the catalysts display similar overall yields (ca. 80-85%), the stereoselectivities of the reactions are quite different. Starting from nearly 100% cis-polybutadiene, the epoxide product catalyzed by MnTPP-αCD (2) consisted of 72% trans-epoxide. This result is opposite to that of the epoxidation reaction catalyzed by the regular Mn-porphyrin catalyst (MnTPP, 1), which produced only 26% trans-epoxide under the same conditions. This difference in cis/trans selectivity demonstrates the effect of the appended α-CD. Evaluating all catalytic systems, it is evident that only two out of the six catalysts, namely MnTPP-αCD (2) and MnTPP-βCD (4), produced more trans- than cis-epoxide, while the other systems gave predominantly the cis-product (Fig. 4). A further comparison between catalysts 2 and 4 in Fig. 4, reveals that a porphyrin appended to a smaller-sized cyclodextrin (αCD) is a more selective catalyst than a porphyrin appended to a larger sized one (βCD). Based on the discussions on the structures of the catalytic systems above, we may reasonably conclude that MnTPP-βCD may also be in a similar clamp-like geometry as MnTPP-αCD. However, because of the increased size of βCD the interaction between the porphyrin and βCD may be weaker due to the larger distance between the hydroxyl groups and the metal center. Interestingly, catalytic system (6), in which the separate metalloporphyrin and αCD components were mixed in a 1:1 molar ratio, produced only 28% trans-epoxide. This result is almost identical to that obtained with the unlinked catalyst MnTPP, i.e. 26% trans-epoxide, while totally different from the result obtained with MnTPP-αCD. This comparison indicates that merely the presence of free αCD in the system does not affect the cis/trans selectivity of the epoxidation reaction, hence the covalent bond and the specific geometry and interactions between the porphyrin and CD are essential for achieving a high trans-selectivity.

Taking into account the above presented results for all the catalytic systems and keeping in mind the structures of the polymer and various catalysts, we propose that the MnTPP-αCD catalyst dynamically and temporarily catches the polymeric substrate, allowing the reaction to take place in the restricted space between the porphyrin ring and the CD via a clamping mode. The catalytically active species in the epoxidation reaction most likely is a Mn(V)-oxo species, which reacts with the alkene double bond to generate a radical or cationic intermediate.\textsuperscript{3} In this intermediate rotation around the C-C bond of the alkene is possible. The steric effects and the interactions within the clamp structure may result in a trans-preference in the transition state of the reaction, because this trans-orientation requires less space.\textsuperscript{5} For the catalysts with an extended structure, i.e. MnTPP-PMαCD and MnTPP-PMβCD, the interactions between the porphyrin and CD are weak, and there is sufficient space between the porphyrin and CD to allow both cis- and trans-epoxide to be formed during catalysis. Therefore, no differences in stereoselectivity are found compared to the unlinked porphyrin MnTPP.

As outlined above, a plausible mechanism for the catalytic action of MnTPP-αCD and MnTPP-βCD is a temporarily binding of these catalysts to the polybutadiene chain during which epoxidation takes place (distributive catalysis\textsuperscript{25}). However, one may still wonder whether a processive catalytic mechanism\textsuperscript{25} is possible, in which the end of the polymer chain binds into the cavity of CD and threads through it, eventually leading to processive catalysis and the observed stereoselectivity. To answer this question, we synthesized a reference polymer, i.e.
3,5-ditert-butylphenyl-terminated cis-polybutadiene (Poly-2) from Poly-1 (Fig. 5, synthesis is detailed in SI). Because of the presence of two bulky terminal stoppers, threading into the cavity of αCD is impossible for Poly-2. The catalytic effects of MnTPP-αCD, MnTPP-PMαCD, and MnTPP on the epoxidation of Poly-2 were investigated under the same conditions as mentioned for the previous experiments with Poly-1. As shown in Fig. S2 in SI, the cis/trans selectivity obtained for the dumbbell-like polymer (Poly-2) was almost the same as that for Poly-1. That is, both the unlinked MnTPP and the extended MnTPP-PMαCD catalysts displayed similar cis/trans selectivities in the epoxidation reaction, with the trans-epoxide being the minor product (12% for MnTPP and 20% for MnTPP-PMαCD). On the contrary, 72% trans-epoxide was produced with the catalytic system MnTPP-αCD, which means that this catalyst still displays good trans-stereoselectivity, even when the polymer is terminated by bulky stoppers. These experiments undoubtedly exclude the possibility that a threading mechanism is the origin of the observed trans-stereoselectivity, as was the case for the glycoluril-based catalytic systems.5 As discussed above and shown in Fig.1b, we deduce that the epoxidation reaction takes place in the confined space between the porphyrin ring and the CD rim in a clamp-like fashion. This clamp structure may remain during the reaction because of the various enhanced synergetic interactions that are possible between the hydroxyl groups of the cyclodextrin and the double bonds of the alkene functions (-O-H-π interactions), the oxygen atom of the intermediate species (Mn(V)O−HO−), and the products (-OH−O of epoxide functions), eventually resulting in the observed trans-stereoselectivity.

A final comment is required on the possible binding of pyridine in the cavity of the MnTPP-αCD, which might also have an effect on the cis/trans ratio, at least in principle. Pyridine derivatives are known to bind only weakly in cyclodextrins in water and they can be expected to bind even more weakly in organic solvents.16 If such a binding occurs, the pyridine will coordinate to the manganese center from the side of the cycloextrin. In that case the epoxidation reaction must take place at the open opposite side, which will lead to a cis/trans-ratio that is more similar to that displayed by MnTPP (1) itself, which is not the case.

In summary, we have developed a porphyrin-cyclodextrin conjugated catalyst (MnTPP-αCD) as a simple mimic of a clamp-like enzyme, catalyzing the epoxidation of cis-polybutadiene with trans-epoxide preference, which is a reverse selectivity as compared to normal Mn-porphyrin catalysts. Through a combination of spectroscopic, simulation, and a series of epoxidation studies, we conclude that a clamp-like mechanism is the mostly reasonable modus operandi for explaining the distinct trans-epoxide preference observed for MnTPP-αCD. A similar clamp-like architecture is found in nature for the proteins and enzymes that are involved in the copying and modification of DNA chains. Furthermore, this catalyst does not require any modifications of the substrate, providing it with a wide substrate-compatibility, at least in principle.

This work was supported by the following grants: ERC Advanced Grants ALPROS-290886 and ENCAPOL-74092 and the Gravitation program 024.015.035 of the Dutch National Science Organization NWO. Mr. Wenqi Liu is thanked for assistance with the molecular modelling.

Conflicts of interest
There are no conflicts to declare.

Notes and references
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