Controlling the length of porphyrin supramolecular polymers via coupled equilibria and dilution-induced supramolecular polymerization

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Multi-component systems often display convoluted behavior, pathway complexity and coupled equilibria. In recent years, several ways to control complex systems by manipulating the subtle balances of interaction energies between the individual components have been explored and thereby shifting the equilibrium between different aggregate states. Here we show the enantioselective chain-capping and dilution-induced supramolecular polymerization with a Zn2+ porphyrin-based supramolecular system when going from long, highly cooperative supramolecular polymers to short, disordered aggregates by adding a monotopic Mn3+ porphyrin monomer. When mixing the zinc and manganese centered monomers, the Mn3+ porphyrins act as chain-cappers for Zn2+ porphyrin supramolecular polymers, effectively hindering growth of the copolymer and reducing the length. Upon dilution, the interaction between chain-capper and monomers weakens as the equilibria shift and long supramolecular polymers form again. This dynamic modulation of aggregate morphology and length is achieved through enantioselectivity in the aggregation pathways and concentration-sensitive equilibria. All-atom and coarse-grained molecular simulations provide further insights into the mixing of the species and their exchange dynamics. Our combined experimental and theoretical approach allows for precise control of molecular self-assembly and chiral discrimination in complex systems.
Porphyrin-based supramolecular systems have received great attention in recent years, due to their intriguing and often complex stereoselective assembly behavior\(^1\). The extended π-system surrounding the core gives rise to high levels of absorptions in the ultra-violet and visible region, but it also causes a strong drive to aggregate through π-stacking and solvophobic interactions\(^2\). Small changes to the structure have significant influence on the assembly behavior, such as the amide connectivity of porphyrin supramolecular monomers\(^3\). While C-centered monomers assemble into highly cooperative supramolecular polymers, their N-centered counterparts only form short, non-helical J-aggregates due to a high rotation barrier around the amide groups preventing the formation of hydrogen bonds. In addition, porphyrins often exhibit pathway complexity, meaning that the monomers assemble into several types of aggregates via competing pathways and mechanisms\(^4,5\). The manipulation of the assembly equilibria under either kinetic or thermodynamic control has resulted in the discovery of exciting phenomena. Sugiyasu and others exploited the competition between different aggregate states in a living supramolecular polymerization to obtain fibers with controlled length and narrow dispersities\(^6-11\). Similar approaches have been employed for seeded growth of supramolecular polymers in one or two dimensions and the preparation of supramolecular block copolymers and polymorphs under kinetic control\(^12\).

The assembly behavior of porphyrins becomes even more challenging in multi-component systems. Here not only the homo-interactions between monomers must be considered, but also the hetero-interactions between all components over a wide range of conditions such as temperature, composition, solvent, and concentration. A number of elegant examples demonstrate selectivity of one pathway over the other by small changes in the solvent composition\(^16-19\). The group of Aida reported on thermally bisignate polymerization of porphyrin monomers by tuning the interactions between an alcohol associating with the monomers over a wide range of temperatures\(^20,21\). Our own group reported dilution-induced self-assembly of a monomer in the presence of pyridine by manipulating the coupled equilibria of complexed monomer versus polymer formation over a range of concentrations\(^22\). For all those reasons, one-dimensional porphyrin polymers are not only of interest for organic and polymer chemists, but also to close the gap to analogous complex aggregates, such as polymeric nanoscale fibers.

Enantioselective interactions can reduce the level of complexity in multi-component systems by introducing specificity in the interactions of the components, which can be helpful to isolate effects in the aggregation pathways. Chiral recognition and exchange of chiral information are crucial in biological systems, but also in chemical catalysis\(^23-26\), host-guest complexes\(^27-29\) and supramolecular systems\(^30-35\). In the supramolecular polymerizations of homochiral monomers, M- or P-helical fibers are formed. For heterochiral monomer mixtures, the monomers either follow the majority rules and intercalate into a stack of majority-preferred helicity\(^36,37\), form alternating heterochiral polymers\(^38\), or the monomers narcissistically self-sort if the mismatch penalty for co-aggregate formation is too high. Nakashima et al. reported a method to tune aggregate length and morphology by balancing the enantiomeric excess (ee) of the components, leading to heterochiral dimers in racemic mixtures or homochiral polymers at high ee’s\(^39\). Another remarkable example reported the use of topological chirality to achieve narcissistic self-sorting into homochiral dimers, but social self-sorting into a heterochiral polymer with alternating microstructure\(^40\). Seminal work by George et al. demonstrated chirality driven self-sorting and stereoselective seeded supramolecular polymerizations with a series of naphthalene diimide (NDI) functionalized monomers\(^30,31,41,42\). Our group reported the self-sorting of zinc-centered porphyrin monomers into homochiral stacks in solution and selective depolymerization of the chiral monomers by addition of a Lewis base\(^15\). We propose that the chiral discrimination exhibited in self-sorting systems could be used as a tool to isolate the contributions of interactions and effects, allowing to control the aggregate microstructure in porphyrin-based multi-component systems.

In this study we focus on a zinc-centered porphyrin-based monomer (S-Zn), which in apolar solvents such as methylcyclohexane (MCH) forms highly cooperative, helical supramolecular polymers through fourfold hydrogen bonding interactions. The S-Zn monomers exhibit pathway complexity and form next to helical H-aggregates also non-helical weakly coupled J-aggregates via an isodesmic mechanism\(^19,22,43,44\). We use monotopic manganese\(^41\) porphyrin monomers (S/R-Mn) with an axially bound chloride ion as monotopic chain-cappers for zinc centered porphyrin monomers (Fig. 1)\(^15,46\). By adding homo- or heterochiral manganese chain-cappers we enantioselectively control the capping of H- or J-aggregates and reduce the length of the supramolecular polymers. Because of coupled equilibria, we can regain H-aggregates from depolymerized mixtures of manganese and zinc monomers by simply reducing the overall concentration of all components through dilution-induced supramolecular polymerization. With a combination of experiments and molecular modeling, we shed light on the complex interplay of interactions and how it is possible to exploit this knowledge to gain control over supramolecular aggregation in multi-component systems.

**Results**

**Supramolecular homopolymerization.** From previous studies the optical properties and polymerization mechanism of S-Zn in apolar solvents such as MCH are known\(^18,44\). Due to the difference in electronic coupling between monomers in the two (H- and J-type) aggregates, the H-aggregate exhibits an absorption band at \(\lambda = 392\) nm with a strong bisignate cotton effect in circular dichroism spectroscopy (CD), while the J-type aggregate has its maximum absorption band at 425 nm and is CD silent (Supplementary Figs. 2, 3). Due to the axially bound chloride counterion, the monomers of S/R-Mn can only be monomeric or

![Fig. 1 Molecular structure of R- or S-chiral porphyrin ligands](image-url)
Enantioselective chain-capping of porphyrin stacks. Porphyrin monomers are known to be highly narcissistic self-sorters, the energetic penalty for intercalating into an H-aggregated stack of the wrong helicity is high (~4 kJ/mol) at dilute concentrations of c = 50 µM (Supplementary Fig. 2c, d). In diffusion ordered spectroscopy (DOSY) NMR experiments at c = 2.0 mM solutions in deuterated MCH we find short species with a diffusion coefficient of 2.32 ± 10−10 m²s⁻¹ for S-Mn. This corresponds to a diameter of around 22.7 Å, which is in the range of dimers (Supplementary Fig. 8). Macroscopically, the formation of small monomeric or dimeric species for S-Mn is evidenced by excellent solubility and low viscosity in MCH as seen by tube inversion test of 2.0 mM solutions in MCH-d₆ (Supplementary Fig. 5). For S-Zn, on the other hand, we only observe the diffusion of the solvent in DOSY-NMR experiments, as the long supra-molecular fibers diffuse too slowly to be measured with this technique (Supplementary Fig. 9). Moreover, concentrated 2 mM solutions of S-Zn show high viscosity and gel-like properties due to the network formation of the supramolecular fibers (Supplementary Fig. 5). To further probe the ability of the two monomers to assemble, we conducted Fourier transform (FT)-IR measurements of 2.0 mM solutions of S-Zn and S-Mn in MCH. The amide NH stretch vibration for S-Mn is found at 3321 cm⁻¹ while for S-Zn this vibration is shifted to lower wavenumbers of 3289 cm⁻¹, indicating hydrogen bonded supramolecular organization for S-Zn (Supplementary Fig. 6) and only weak hydrogen bonding for S-Mn. Notably, S-Mn shows two vibrations in the carbonyl region at 1650 and 1675 cm⁻¹ in both bulk and solution spectra (Supplementary Figs. 6, 7). This hints to two different sets of carbonyl conformations in S-Mn, with one set as a free carbonyl in the monomeric state and the other being involved in the hydrogen bonding within the dimeric structures.

Coarse-grained molecular modeling of chain-capping events. To help understanding the experimental findings, we developed a molecular model to describe the system. We initially built an all-atom (AA) model of the monomers (computational details in the Supplementary Information). However, the size and the timescales involved in the self-assembly and dynamic behavior of these supramolecular systems exceed the possibilities for AA models. As recently done for similar structures 14,50, we thus developed coarse-grained (CG) models for the monomers which, based on the Martini CG force field 51, have been further optimized to be consistent with the behavior of the AA models. The limited resolution of these CG models (3 heavy atoms per CG-bead) does not allow to distinguish between S- and R- chirality. Nonetheless, such CG model can safely be used to qualitatively compare the dynamics of two (Mn and Zn) porphyrin-based supramolecular building blocks, and to shed light on the complex mechanism of monomer exchange and of interaction between cappers15,52–54. The model for Zn monomers was based on
previous work on zinc centered porphyrin polymer fibers. For the Mn monomers, we started from an AA model and we subsequently tuned the CG model in order to reproduce the porphyrin core–core dimerization free energy using a well-tested metadynamics (MetaD) protocol. We used these CG models to study and compare via MetaD simulations the Zn-Zn, Mn-Mn and Zn-Mn interactions. Our MetaD simulations provided a dimerization ΔG for Mn-Mn cores of ~18.0 kJ/mol. In previous work, the ΔG for Zn-Zn was found a higher values of ~45.2 kJ/mol. The Zn-Mn core interaction...
of Zn fibers by binding of Mn monomers to the fiber tips is a likely event. Next, we simulated two different model systems, (i) starting from free Mn/Zn monomers in solution that can freely interact and self-assemble (Fig. 5a) or (ii) starting from pre-formed Zn fibers surrounded by free/disassembled Mn monomers (Fig. 5b). We compare the behaviors of both systems by means of CG-MD simulations in explicit solvent. Based on the results on the exchange dynamics of the respective aggregate types, we would expect both sequestration and chain-capping to occur for the first case, while for the second case chain-capping should be most common as the Zn fibers exchange monomers very slowly. After 5 µs of CG-MD simulation time for the first scenario, short aggregated species are observed as spontaneously appearing in the system: these are homo- or hetero-dimers of the two monomers, sandwich type Mn-Zn-Mn complexes or short, chain-capped stacks of Zn (Fig. 5a). The occurrence of sandwich-type species in the simulations supports the previously mentioned probability that also longer stacks of S-Zn could be end-capped by two S/R-Mn monomers. For the second case, since the spontaneous chain-capping event could not be observed within the timescale accessible via classical/unbiased CG-MD simulations, for explorative purpose we used WT-MetaD to accelerate the sampling of the system (a detailed description of the WT-MetaD setup is available in the Supplementary Information). This allowed us to qualitatively observe that Zn chain-capping by Mn is indeed possible in the system (Fig. 5b). Interestingly, we could observe that over the course of this simulation the Mn monomer first starts to interact with the surface of the Zn stack. After some time, it finally binds and chain-caps the preexisting supramolecular Zn fiber. Such a complex adsorbing-sliding-stacking mechanism is in line with what recently observed also for other types of supramolecular polymers.

In order to obtain more robust evidence, we also conducted WT-MetaD simulations for the exchange of a single Mn monomer in a single Zn fiber (see Supplementary Fig. 12a). From WT-MetaD, we could obtain a free energy surface for the Mn exchange process, which confirms such exchange pathway (Supplementary Fig. 12b). Kinetic analyses obtained from multiple infrequent WT-MetaD simulations (using the same approach used to calculate the exchange timescales of Fig. 4b, c) also demonstrate that, in this system, the interaction of Mn with the surface of a Zn fiber is relatively weak, while the directional interaction between the Mn and the Zn cores that is established upon Mn capping is considerably stronger (rate limiting step—

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Dilution-induced supramolecular polymerization. To visualize changes in aggregate morphology and length by the addition of S-Mn, we conducted a series of atomic force microscopy (AFM) experiments (Fig. 6c, d). At identical concentrations as in the spectroscopic experiments (c_{S/Zn} = 25 \mu M), the surface is densely covered in long fibrous aggregates for S-Zn solutions but only small, non-fibrous deposits were observed for S-Mn (Supplementary Fig. 14). For mixtures thereof, a gradual transition from fibers to disordered material can be observed in the images (Fig. 6c), which supports that S-Mn causes the depolymerization and transformation of H- into J-aggregates of S-Zn. Intriguingly, when diluting the mixtures and repeating the AFM measurements at lower concentration (c = 5 \mu M, Fig. 6d), we witnessed the reformation of H-aggregates from the J-aggregates. At 5 \mu M, all samples show long fibrous structures with some exposed chain-ends. This is most apparent for the 1:1 mixture where we observed short bundles of fibers. For heterochiral mixtures of [S-Zn]:[R-Mn] at same concentrations, this effect is not as pronounced (Supplementary Fig. 15). At high molar ratios of R-Mn at 25 \mu M, the morphology found on the surface resembles the organization of J-aggregates on a surface as reported previously for a sequestered mixture of N- and C-centered porphyrins. At 5 \mu M of S-Zn with 0 equivalents of chain-capper, we observe fibrous aggregates but without the exposed chain-ends as for the homochiral mixture. This counterintuitive repolymerization with decreased total concentration is a consequence of coupled equilibria and pathway complexity and has previously only been described in the dilution-induced self-assembly of S-Zn with a 40-fold excess of pyridine (Fig. 6a). Solutions of S-Zn/S-Mn at 25 \mu M show significant amounts of J-aggregates for the 1:1 mixture, which upon dilution to 5 \mu M transform into H-aggregates. In supramolecular polymerizations, dilution causes a decrease in chain length scaling with the square root of the concentration until ultimately below the critical aggregation concentration monomeric species form. Here, by lowering the concentration and shifting of the equilibria, the S-Mn/S-Zn interaction becomes less favorable than S-Zn homo-interaction. This in turn causes a release of the S-Mn chain-capper from the chain ends and thereby reformation of the supramolecular polymers. For the dilution-induced supramolecular polymerizations the rate of sample equilibration was essential to avoid kinetic effects. Slow equilibration resulted in the formation of thermodynamically more stable H-aggregates, while for fast cooling rates kinetic trapping into J-aggregates was observed (Supplementary Fig. 16). So far, only two examples of this dilution-induced polymerization effect have been reported in supramolecular chemistry. Here we reported a highly sensitive multi-component system, that is responsive to both dilution and the chirality of additives due to pathway complexity and coupled equilibria. By tailoring the specific interactions between S-Zn and homochiral additive S-Mn, we could significantly increase the sensitivity and effect on the chain-length compared to the S-Zn/pyridine system.

Discussion

In this study we demonstrate how from coupled equilibria and complex pathways, intriguing and counterintuitive assembly behaviors can arise. We combine two monomers, a zinc centered porphyrin monomer (S-Zn) which assembles into H-aggregates or J-aggregates, and a monotopic manganese porphyrin (S/R-Mn) with an axially bound chloride ion that forms monomers or dimers and can act as a chain-capper for S-Zn stacks. We exploit the narcissistic self-sorting behavior of porphyrin monomers to enantioselectively discriminate between capping the helical H-aggregates or the achiral J-aggregates depending on the chirality of the chain-cappers. With increasing amounts of...
homochiral S-Mn chain-capper, both H- and J-aggregate of S-Zn get chain-capped. At equimolar ratios of [S-Zn]:[S-Mn], the H-aggregates become short and destabilized, resulting in conversion to J-aggregates. If R-Mn, a chain-capper of opposite chirality, is mixed with S-Zn this effect is much weaker as R-Mn can only interact with the achiral J-aggregates or monomers. Using coarse-grained molecular simulations, we observe the underlaying dynamics of co-assembly and chain-capping events, revealing that multi-step processes (absorb-slide-stack) are likely involved in the exchange phenomena. AFM microscopy images show the transformation from long fibrous H-aggregates to short, disordered J-aggregates with increasing amount of homochiral chain-capper S-Mn. However, upon dilution this process can be reversed with the dilution-induced supramolecular polymerization effect. The two-component system of an either manganese (dichloromethane or chloroform) was added to break up aggregates and re-evaporated. Then the flask was filled up to the meniscus with methyl cyclohexane (MCH), heated and sonicated until complete dissolution. Samples for measurements were prepared by diluting the stock solution to the respective concentration. Before measuring mixed samples of Mn- and Zn-porphyrins the samples were thermally equilibrated by heating the sample solutions in a thermally equilibrated by heating the sample solutions in a

**Methods**

**Sample preparation.** Stock solutions (100 μM) were prepared by weighing the compound and transferring it in a volumetric flask. One milliliter of a polar solvent (dichloromethane or chloroform) was added to break up aggregates and re-evaporated. Then the flask was filled up to the meniscus with methyl cyclohexane (MCH), heated and sonicated until complete dissolution. Samples for measurements were prepared by diluting the stock solution to the respective concentration.

**Spectroscopy.** UV/Vis and circular dichroism (CD) spectra were recorded on a Jasco J-815 spectropolarimeter with a Jasco PFD-425S/15 Peltier. The measurement parameters for sensitivity, scanning rates and ranges were chosen appropriately for each experiment. Cuvette cells with an optical path length of 1 mm were used for all experiments.

**Atomic force microscopy.** The sample solutions used in the spectroscopic experiments were also used for the AFM experiments by dropcasting 20 μL of solution onto a 1 × 1 cm mica sheet (V1 quality). After complete evaporation of the solvent, the samples were measured on an Asylum MFP3 system with soft NanoWorld NCSTR50 tips in non-contact tapping mode.

**Molecular modeling and simulations.** All simulations have been performed with GROMACS 2018.6.61, patched with the PLUMED plugin 2.5.061,62. The CG model for the Zn porphyrin monomer was adapted from our previous work on a similar system15. The AA and CG models for the Mn porphyrin monomer were developed, based on the GAFF force fields and the MARTINI force fields, respectively, following the same procedure14 (see Supplementary Information for complete details).
The free energy surface (Supplementary Fig. 12b) was obtained from a well-converged WT-MetaD simulation, using the distance between the central Mn bead and the central Zn bead of the closest neighbor monomer in the Zn-fiber as the CV1, and the number of contacts between the core of the Mn monomer and the core of all the Zn fiber as CV2. During the WT-MetaD simulation, the system successfully diffuses in the entire CV space, recrossing between the visited relevant states, reaching a satisfactory convergence.

The kinetics of the monomer exchange events have been estimated following a validated procedure, by running multiple infrequent WT-MetaD simulations. The collected transition times were proven to fit well the typical Poisson distribution expected for a rare exchange event, validating the adopted setup. From the fits, we estimated the characteristic transition times expected for monomer exchange in the various cases.

**Data availability**

The authors declare that the experimental data supporting the findings of this study are available within the paper and its Supplementary Information file. Complete details of the procedures for the parametrization of the molecular models and of the simulations’ setup, along with additional simulation data, are provided in the Supplementary Information file. Complete data and materials pertaining to the molecular simulations conducted herein (input, model files, raw data, simulation trajectories, etc.) are available at: [https://doi.org/10.5281/zenodo.5717968]. All other information is available from the corresponding author upon reasonable request.

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