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Synthesis and characterization of squaramide-based supramolecular polymers

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CHAPTER 6

SUMMARY AND PERSPECTIVES

Supramolecular polymers are class of materials that are held together by non-covalent interactions such as hydrogen bonding, π-π interactions, electrostatic interactions and the hydrophobic effect. In the last decade, while most studies probed their assembly behaviour in organic solvents, the development of monomers that self-assemble in water is a rapidly growing area that provides opportunities to better understand the effects of this unique solvent on their formation and application. An often-used strategy for the formation of stable and well-defined aggregates in water, involves the coupling of the hydrophobic effect with hydrogen bonding interactions in the monomer design. The strength of the hydrogen bonds can be retained by their embedding within the hydrophobic domain of the monomer removing competition with water and further tuned by their number and arrangement of hydrogen bond donors and acceptors. In the case of squaramides, it was recently demonstrated they can be further affected by the aromatic character of the molecules strengthening the hydrogen bonds through an increased π delocalization on self-assembly. This effect in squaramides as demonstrated by the aromatic stabilization energy shows its significant contribution to the total interaction energy; in the range of 30%. Taking advantage of this minimalistic ditopic hydrogen bonding unit, the Kieltyka group has shown this unit play an active role in the formation of supramolecular materials taking them outside of the range of anion recognition and medicinal chemistry, and extending their application in the biomedical field. In their first publication, the capacity of the squaramide-based bolaamphiphiles to self-assemble into supramolecular polymers in water was investigated examining this process at several length scales. The synergy of very strong hydrogen bonding and aromatic gain was demonstrated to be the driving force for the formation of nanofibers. In a subsequent work, this effect was compared against its thiosquaramide counterpart, that displayed a distinct self-assembly mode that involves stacking rather than head-to-tail hydrogen bonding that also results in aromatic gain within the monomer unit showing the importance of this effect for this synthon. Additionally, it was demonstrated that by changing the monomer geometry from linear to tripodal, lateral aggregation is suppressed changing the morphology of the fibrillar aggregates from being rigid with a high persistence length and dimensions on the nanoscale to flexible with a low persistence length and on the micron scale. In this thesis, I examined the potential to use this panel of monomers to study the accessible range of formed polymers through modulating the monomer chemical structure, co-assembly and introduction of chemistries that are responsive to light to provide insight on how to design new materials at several length scales.

In **chapter 2,** the potential to control the microstructure of a squaramide supramolecular polymer was explored through copolymerization of oxo and thiosquaramide-based bolamphiphiles in water. In this chapter, the distinct modes of self-assembly of the two bolaamphiphiles were exploited; oxosquaramide bolaamphiphiles adopt a head-to-tail hydrogen-bonding configuration on aggregation, whereas thiosquaramide prefer a stacked configuration. This difference originates due to the less directional and weaker character of hydrogen bonds formed by sulfur, in comparison to oxosquaramide. In this chapter, the effect of O→S substitution in the squaramide bolaamphiphile on its supramolecular polymerization mechanism and its associated thermodynamics was first examined. NMR and DLS studies confirmed that HFIP (hexafluoroisopropanol) is a good solvent for oxosquaramide, and THF is a good solvent for thiosquaramide. This study was performed taking advantage of their solvent-induced depolymerization, where the self-assembled monomers were titrated with a good solvent to depolymerize the monomers and the solvent denaturation model was further applied to the data. Despite their different self-assembly modes, both of the monomers self-assemble according to a cooperative mechanism. To gain insight into the microstructure of the formed polymers and their dynamics fluorescently-labeled monomers with cyanine dyes (5/3) were prepared and their co-assembly experiment was examined through fluorescence studies. On co-assembly shorter fibers with a decreased persistence length were observed as compared to pure oxo-squaramide by cryoEM.

Since these results suggest co-assembly of the monomers, further insight in the microstructure of the final copolymers (alternating, random, block) should be investigated. Therefore, microscopy experiments such as SIM, STORM need to be performed. Moreover, since the individual monomers show different self-assembly modes, computational calculations can be a future route to better understand their interaction on co-assembly in the polymers. Additionally, since the co-assembly of oxo- and thiosquaramide was investigated only at 1:1 molar ratio, the effect of excess of one of the components could be investigated.

In **chapter 3**, a novel method for the synthesis of tripodal monomers for supramolecular polymerization by the Ugi reaction was developed. The Ugi reaction is a multicomponent reaction involving an isocyanide, amine, carboxylic acid and aldehyde or ketone that generates compounds with a

peptide-like bonds that are widely used in the chemical structures of supramolecular biomaterials. Trisquaric and nitriloacetic acid were used as the acidic component of this four component reaction along with modified amine, isocyanide and an aldehyde or ketone to construct tripodal scaffolds. As the synthesis of supramolecular monomers can be laborious, the multicomponent approach can be considered as a valid approach to find gelators in an efficient way with minimal synthetic effort. The success of the Ugi reaction is determined by parameters such as temperature, concentration and the choice of acidic component, thus these variables were examined to guide the distribution of mono- and disubstituted compounds to the trisubsituted product. To obtain a peptide-functionalized monomer, nitrilotriacetic acid was also examined as a core with benzaldehyde, oligoethylene glycol-isocyanide and ammonium carbonate. The low yield of the reaction was overcome using nitrilotrisquaric acid and replacing the ammonium carbonate with 2,4-dimethoxybenzylamine to overcome the unstable imine, and subsequently was deprotected under acidic conditions. Using this optimized protocol, a small family of compounds with different aliphatic spacers was synthesized. These compounds were found to form spherical aggregates likely due to the presence of three stereocenters that preclude their stacking in to fibrous aggregates.

Despite the lack of self-assembly, this optimized Ugi reaction could be exploited as source of inspiration for the synthesis of tripodal compounds using squaric acid. Moreover, to surmount the inability of the monomer to self-assemble, the Ugi reaction could be pursued using symmetrical ketones such as acetone, diethyl ketone or a chiral acid catalyst to prevent the formation of diastereomers. Provided that the Ugi reaction can be harnessed to prepare tripodal compounds based on squaramides, new opportunities will arise to prepare modules for supramolecular assembly that can result in discrete structures or materials.

In **chapter 4**, the self-assembly of small family of tripodal squaramide-based supramolecular polymers with respect to various structural substitutions including modulation of the hydrophilic and hydrophobic domains, the number of squaramide units and covalent linkages (e.g. carbamate, ether) for connection to the core of the monomer was examined. The self-assembly of the monomers was characterized at the molecular level through spectroscopic techniques such as UV-vis and fluorescence spectroscopy, at the nanoscale through AFM and at the macroscale using oscillatory rheology. The monomer

containing three squaramide moieties has the ability to self-assemble in nanometer fibers and to hydrogelate at a concentration of 5 mM. When the number of squaramides is reduced, the monomers with three aliphatic spacers still have the ability to self-assemble in fibers but no hydrogelation was observed. Conversely, the most hydrophilic monomer results in the formation of spherical aggregates. These studies supported the strong relationship between the monomer chemical structure and their self-assembly into supramolecular polymers. More specifically, the difference in the observed morphologies and ability for the monomers to self-assemble point to the importance of a certain ratio between the hydrophilic and hydrophobic domains, as a reduction of squaramides still results in self-assembly.

Further insight into the polymerization of the monomers can be gained by examining the supramolecular polymerization mechanism to understand how structural modifications affects their self-assembly behaviour and if any changes in mechanism is observed. Thoroughly investigating the self-assembly behaviour of this library of squaramide monomers, especially the extent to which various structural modifications influence their properties, will provide a framework for the design of new squaramide monomers that can be used in the biomedical area.

In **chapter 5**, a visible light-mediated strategy to modulate the self-assembly a tyrosine-dipeptide outfitted supramolecular monomer in water was examined. Since the tyrosine dipeptide has been shown to self-assemble into nanofibers and tyrosines have been used to cross-link polymer materials, the tyrosine dipeptide was conjugated to the tripodal core with two squaramide arms appended to a hydrophobic decyl spacer and hydrophilic tetraethylene glycol chain with either a carbamate or ether linkages between the segments. Self-assembly of the squaramide in a head-to-tail hydrogen bonding arrangement was observed in the case of the carbamate derivative in a concentration-dependent manner, but not in the case of the ether molecule. Further irradiation of the monomer with visible light at 440 nm in the presence of either FMN or $Ru(bpy)^{3+/}$SPS photoinitiators, did not yield formation of the tyrosine dimer as expected. These results suggest either a lack of exposure of the tyrosine moieties to the photoinitiator or a distance too large between them in the assembly for crosslinking.

In the future design of this type of monomers, the reduction of the chain length of the oligoethylene glycol or its exchange for a hydrophobic linker should be

considered. Moreover, the type of photoinitiator and photocrosslinking conditions should be probed further to understand their effect on self-assembly. Achieving this rapid, visible light mediated polymerization on supramolecular polymers will provide new opportunities for controlling supramolecular polymerization in the presence of cells either as nanoparticles or material