PhD PROJECT PROPOSAL

PhD Project Title

Topological Design of Novel Metallo Foldamer-Protein Hybrids for Applications in Light Harvesting and Luminescent Imaging

PhD Supervisory Team

Principal Supervisor: Dr. Sarah Pike, School of Chemistry, Pike Research Group (synthetic supramolecular group), s.j.pike@bham.ac.uk

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Project Abstract

Foldamers have been explored as mimics of biological helices, wherein this topology has been shown to dramatically modify various physical properties (including photophysical) compared to alternative topologies. Foldamers are constructed from non-biological building blocks/components, and as such present an opportunity to readily introduce non-biological features into the design including optical, electronic and magnetic properties. However, there are no reports of attempts of using foldamers to construct higher order structures inspired by Nature. This is despite Nature utilising higher order topology for almost all functions. One example is the generation of metal ion sites which are essential to the correct function of ~50% of proteins.

This PhD will design, prepare and evaluate higher order foldamer structures, based on the coiled coil assembly (i.e., the supercoiling of multiple helices). Light harvesting and medical diagnostic function, through the introduction of metal binding and the associated physical properties, is entirely dependent on the resulting topology of these higher order structures. Accordingly, structure-function relationships will be explored so as to establish the key design rules that govern the construction of increasingly complex topologies based on an entirely new class of foldamer-protein hybrid scaffolds.

How does the project utilise topology or topological design?

Topological design plays a crucial role in this PhD project as the shape that these foldamer molecules adopts is integral in dictating correct function (e.g., as effective light harvesters or medical diagnostic tools).

The new structures that will be designed and synthesised in this project will exploit well-established biological topological principles and system design, to generate new coiled coil assemblies based on hybrid metallofoldamer-protein scaffolds. These novel higher order foldamer scaffolds signify an elevated level of topology compared to existing foldamers systems and represent a significant advance in the topological design of foldamers to obtain simple synthetic systems that can replicate the sophisticated tertiary and quaternary topological structures (essential for function in biology) found in biological systems.

This interdisciplinary PhD project aligns with the Soft Matter and Chemistry theme of the CDT programme and has additional applications in the Health and Life Science theme.

Detailed Project Description

Project Aim: This project will **design and produce new molecules** that self-assemble to create novel hybrid metallofoldamer-protein scaffolds capable of a diverse range of topologies by generating biomimetic coiled-coil structures from the assembly of stable synthetic foldamer-helices. These **new higher order hybrid structures will possess tuneable (photo)physical properties** and find **wide-reaching applications as light harvesting constructs and as luminescent and magnetic probes for potential sensing and medical imaging purposes.**

Background: Foldamers are synthetic helical oligomers that adopt stable secondary structures through mimicking the folding patterns of biological systems to generate structures of well-defined size and shape (Figure 1).[1,2] Foldamers have been the subject of great interest due to their diverse range of applications in materials chemistry and supramolecular chemistry. However, despite the importance of biomimetic foldamers and their known ability to mimic the simple natural helical topologies, there are no reports on the development of higher order foldamer scaffolds that can mimic the sophisticated tertiary and quaternary topological structures found in biological systems. Given that the topology of the foldamer scaffold controls their (photo)physical properties and, in turn their function, accessing new to higher order topologies has the exciting potential to open up the field towards optimising existing applications or generating new applications with these novel structures (e.g., as light harvesters or medical diagnostics).

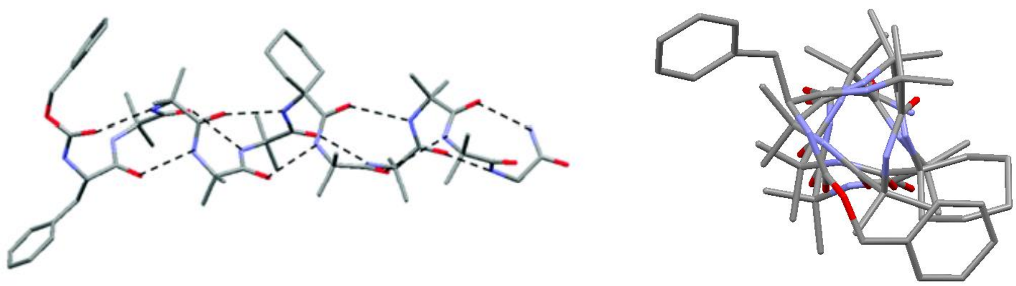

Figure 1. Stable folded conformation of synthetic organic helical oligomer (foldamer) in the solid state. a) viewed side on, b) viewed from the N terminus.[2]

De novo designed metallopeptide scaffolds that adopt topologically well-defined coiled-coil motifs (Figure 2) can be accessed through combining the fields of inorganic chemistry with synthetic biology (i.e. by incorporating metals into folded biological building blocks (peptides) to create new metallopeptide scaffolds).[3,4] In recent years, *de novo* metallopeptide coiled-coil scaffolds, have found impressive applications as potential light harvesting constructs and MRI contrast agents.[5-7] However, the fact that these existing metallopeptide coiled-coil scaffolds are made from biological building blocks, means that they are based on, and therefore limited, to biological topologies. Accordingly, existing systems are restricted to exhibiting a range of topologies, that historically have been limited by evolutionary-imposed constraints, and this severely hinders the optimisation of their performance and the accessibility of new topologies for innovative applications.

As it is necessary to tune and improve the photophysical properties of these scaffolds in order to optimise their performance for applications beyond biology, including as light harvesters and luminescent or magnetic probes for medical purposes, it is vital that we are able to access new topologies that are not restricted to biomimetic systems with evolution-imposed constraints. Accordingly, we will create new hybrid metallofoldamer-protein systems that adopt higher order coiled coil assemblies which are able to adopt a range of novel topologies for generating new applications as highly efficient light harvesters or effective medical diagnostics tools.

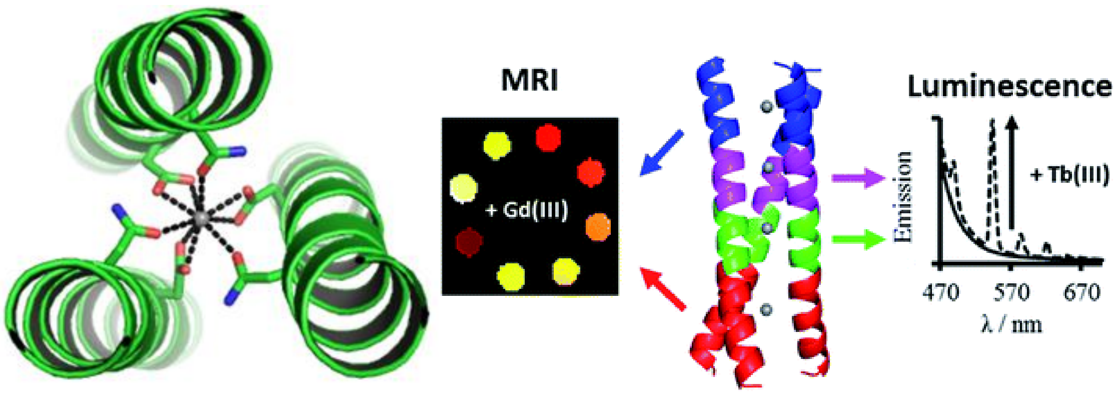

Figure 2. a) Coiled-coil scaffold incorporating lanthanide ions,[5] b) *de novo* coiled-coil lanthanide design for potential MRI imaging and luminescence purposes.[7]

Project Outline: In this project, we will address the current limitations associated with the lack of higher order foldamer scaffolds and the biologically restricted topologies of existing *de novo* metallopeptide scaffolds by creating a new class of hybrid metallofoldamer-protein systems that adopt the coiled coil motif which have the potential to adopt non-natural topologies. These hybrid metallofoldamer-protein scaffolds will be made from synthetic building blocks (foldamers and metals) and will be able to be readily modified, at the molecular level, so that the (photo)physical and magnetic properties of the system can be easily tuned in order to optimise their performance as light harvesting constructs and luminescent or magnetic probes and sensors for medical diagnostics.

Through systematic variation of the molecular structure of the synthetic building blocks (i.e., type of metal) we will systematically tune the size and shape of the coiled-coil scaffold. In this way, we will access new topologies in order to achieve molecular control over the (photo)physical and magnetic properties of the system. Accordingly, during the course of the project, a diverse range of libraries of metallofoldamer-protein coiled-coil whose novel topologies will permit optimization of their performance as a new class of light harvesting system and luminescent or magnetic probe for medical diagnostic purposes.

Objectives

1) **To create a new class of topological molecules based on coiled-coil systems incorporating hybrid metallofoldamer-protein scaffolds and fully characterize them using standard and advanced analytical and spectroscopic techniques.**
2) **To generate libraries of these new topological metallofoldamer-peptide scaffolds wherein fundamental structural features (e.g. type of metal) are systematically varied to provide a broad scope of substrates and a vast library of hybrid scaffolds.**
3) **To optimise the photophysical or magnetic properties of the new class of topological molecules based on hybrid metallofoldamer-protein scaffolds and establish structure-activity and function relationships on the influence of key structural features (e.g. foldamer length, foldamer building block and/or type of metal) on their performance as light harvesting systems and as luminescent or magnetic probes for imaging applications.**

Methodology: Each of the objectives of the project require a combination of organic chemistry synthesis and advanced analytical study to generate the new hybrid metallofoldamer-protein scaffolds and to assess their stability and performance as light harvesting systems and as luminescent or magnetic probes. This work will be carried out under the supervision of Drs. Pike and Peacock in the Department of Chemistry.

Training and skills to be developed over the PhD: The candidate will develop a range of standard and advanced organic and biological chemistry synthetic skills. The candidate will also develop a wide-range of analytical skills and techniques over the course of the PhD including, UV/vis, circular dichroism (CD) spectroscopy, mass spectrometry, infrared spectroscopy, and NMR spectroscopy (including ^{1}H and ^{13}C NMR and 2D-correlation techniques) and single-crystal X-ray diffraction analysis. The candidate will develop a **multi-disciplinary skillset** with **expertise in organic, biological and inorganic chemistry design, synthesis and characterisation** (including crucially elucidating 3-dimensional structure), as well as cultivating important keys skills relating to science communication and developing the ability to tackle tasks through **problem-based thinking and analysis**. Upon completion of the PhD, the candidate will be equipped with the necessary skills to pursue a future career in academia or industry.

Suitability of the Project for the CDT in Topological Design

The topological design of these new hybrid scaffolds is central to the successful progression of this PhD project. The ability of these new hybrid scaffolds to exhibit important physical properties for light harvesting and luminescent imaging for medical diagnostic purposes is dependent on the scaffold adopting a precise topology. Therefore, the successful application of this methodology and rational design of the topological features of these new mimetic/bioinspired coiled-coil scaffolds will be critical in tuning and improving their photophysical properties in order to optimise their performance as light harvesting constructs and as imaging probes for medical applications.

Research Links of the Project with the Supervising Team: Dr. Pike has extensive experience in synthetic organic chemistry and is an expert at designing new supramolecular systems based on foldamers. Dr. Peacock is a world-leader in the field of bioinorganic chemistry and metallo coiled coil design and has extensive experience in the design and synthesis of new topological architectures with tuneable physical properties. This PhD projects complements and directly aligns with ongoing research in both groups and the PhD candidate will work closely with the friendly members of both the Pike and Peacock research teams.

Links with Research Strategies: This PhD project strongly links with the Materials Science and research strategic unit of the School of Chemistry at the University of Birmingham and continues the great tradition of the School in the development of exciting molecules with unique topologies in supramolecular chemistry (the 2016 Nobel Prize in Chemistry was awarded for the supramolecular chemistry conducted by Sir Fraser Stoddart at UoB). The PhD project directly aligns with the EPSRC Chemical Sciences and Engineering Grand Challenge: “Directed Assembly of Extended Structures with Targeted Properties” (for which Peacock is a Grand Challenge Leader for the “Controlling molecular self-assembly in biological and biomimetic systems”) and strongly fits the EPSRC research areas of synthetic supramolecular chemistry and energy storage.

Candidate Background and Interests: Candidates should have an interest in or experience of synthetic organic and/or inorganic chemistry. Candidates should hold or expect to receive a good (1st or 2.1 UK or equivalent) degree in chemistry or a chemical sciences related subject.

References:

[1] G. Guichard, I. Huc, *Chem. Commun.,* **2011**, *47*, 5933-5941.

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[5] Slope, L. N.; Daubney, O. J.; Campbell, H.; White, S. A.; Peacock, A. F. A. (2021) Location dependent lanthanide selectivity engineered into structurally characterized designed coiled coils, *Angew Chem.*, **2021**, *60*,24473-24477.