Young Career Focus: Dr. Stephen J. Butler (Loughborough University, UK)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Stephen J. Butler (Loughborough University, UK).

Biographical Sketch

Dr. S. J. Butler

Stephen J. Butler completed his undergraduate degree at Warwick University, UK, before moving to Australia to study for a PhD at the University of Sydney, under the supervision of Prof. Katrina Jolliffe. His PhD focussed on synthesising cyclic peptide scaffolds as supramolecular receptors for anions. In 2010, he undertook postdoctoral research with Prof. Richard Payne, developing new methodology for the solid-phase synthesis of sulfated peptides, before returning to the UK to work with Prof. David Parker FRS at Durham University, synthesising highly emissive lanthanide complexes as cellular imaging probes. In 2013, Stephen was awarded a Ramsay Memorial Fellowship at Durham University, to develop molecular receptors for ATP. He began a Lectureship at Loughborough University (UK) in 2015, where his current position is Senior Lecturer. He leads an enthusiastic group developing molecular probes based on lanthanide complexes, for the purpose of sensing biological anions, probing enzyme activity and signalling biochemical events in living cells.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Dr. S. J. Butler We are studying molecular recognition and photophysical techniques. A major research focus in our lab is the design and synthesis of host molecules that bind selectively to biological anions in aqueous media. We are developing these molecules into bioassay tools and cellular imaging probes, which may be applied in a biomedical or clinical setting. Organic synthesis is at the core of our research, combined with photophysical studies of host–guest interactions. Our molecular hosts are based on macrocyclic lanthanide complexes, which offer unique optical properties that are very valuable for biological sensing and imaging. We are studying methods to tune host selectivity and affinity for target anions (e.g. ATP, ADP, AMP) through modifications in the structure and geometry of the macrocyclic ligand.

SYNFORM *When did you get interested in synthesis?*

Dr. S. J. Butler My interest in organic synthesis grew during the third year of my undergraduate degree at Warwick University – the enthusiasm of my lecturers around creating complex organic molecules was very motivating. I developed as a synthetic chemist during my PhD at Sydney University under the guidance of Prof. Kate Jolliffe, where I synthesised large cyclic peptides containing oxazole units that confer rigidity to the peptide macrocycle, and side chains functionalised with binding sites to recognise specific guests. I really enjoyed using organic synthesis to create molecules designed to perform a particular function. This theme continued in my postdoctoral work with Prof. David Parker, involving the construction of highly emissive lanthanide complexes with conjugated aromatic arms for use as optical imaging agents in live-cell imaging experiments. Synthesising a molecule and then testing its ability to achieve a specific task using a

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range of supramolecular experimental techniques was really rewarding.

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Dr. S. J. Butler From my perspective, organic chemistry allows us to create probes that may be applied at the chemistry/biology interface to advance our understanding of health and disease at a molecular level. In the context of molecular imaging probes, arguably the most important feature is selectivity; the biggest challenge is to create molecules that exhibit higher levels of selectivity, allowing a specific analyte to be distinguished within a complex biological environment. To this end, the modern role of organic synthesis is to develop new methods to integrate multiple recognition motifs within a molecular host structure, which engage their target to generate a distinct host–guest complex structure. The recognition of large biological guests demands new synthetic methodologies to access larger and more intricate host architectures. Synthetic receptors with increased selectivity will open the door to new and improved bioassays and imaging probes required for biomedical and clinical research.

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Dr. S. J. Butler I'd like to highlight three active research projects which all started out with a common goal to create new molecular structures designed to perform a specific task:

Supramolecular Anion Recognition (**Figure 1**). We have established key design principles to synthesise molecular hosts which bind a target nucleoside phosphate anion (e.g. ATP, ADP, AMP) with high selectivity in competitive biological media, avoiding interference from biomolecules and anions with similar charge and shape.[1–5] Nucleoside phosphate anions are critical to the maintenance of life and play crucial roles in energy transduction, cellular signalling and membrane transport.[6,7] We have developed a new class of emissive europium complexes bearing arms that bind selectively to ATP and ADP through a combination of electrostatic and hydrogen bonding interactions. Our lead molecule is capable of real-time analysis of kinase enzyme activity by monitoring the production of ADP, thereby providing a convenient luminescence assay for screening of potential kinase inhibitors.[2]

Reactivity-Based Probes (**Figure 2**). The reactivity of molecular probes with biomolecules and endogenous reactive

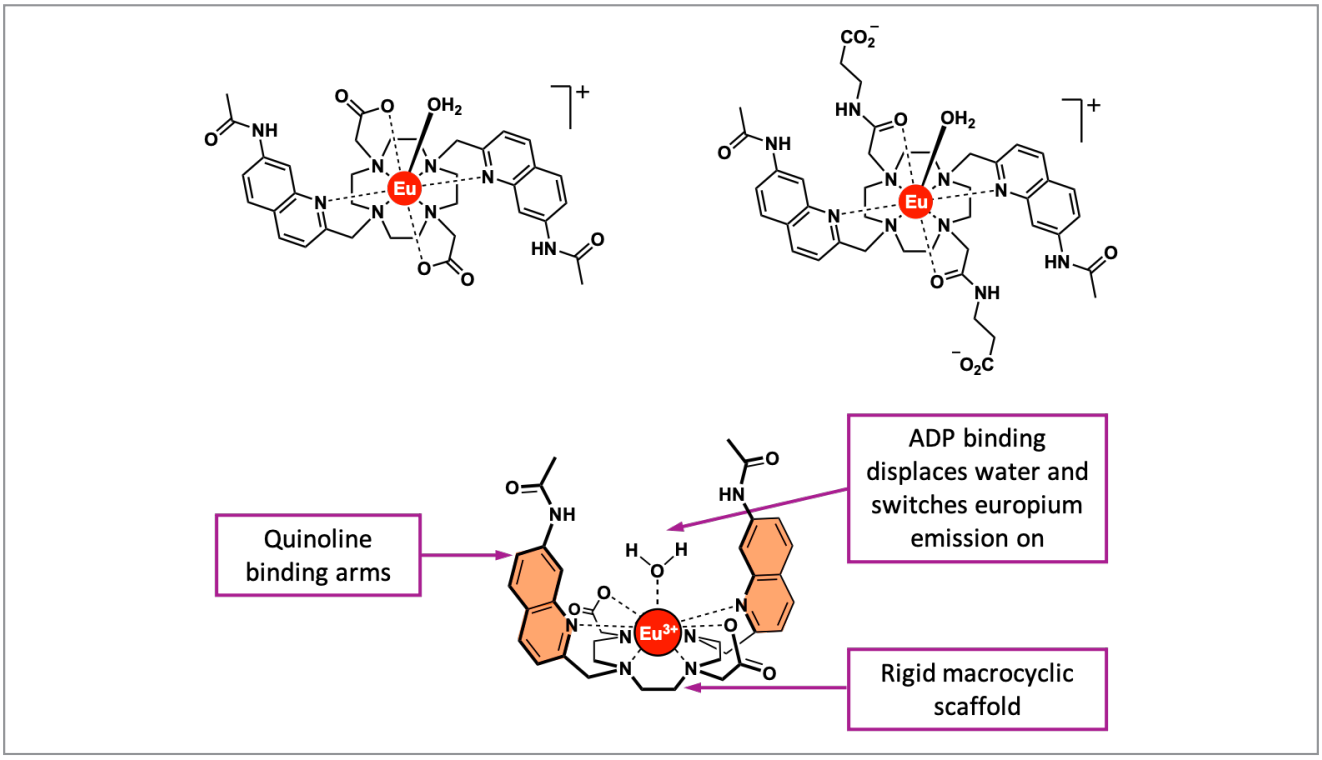

Figure 1 Europium-based host molecules for the recognition of ADP and ATP

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species is also being studied in our group. For example, we recently developed a europium-based probe that reacts selectively with peroxynitrite, a short-lived species that causes harmful oxidation of cells. Our probe can be used to visualise peroxynitrite levels in the mitochondria of living cells using fluorescence microscopy.[8] We are also developing new conjugation methods for the site-selective attachment of a paramagnetic probe to cysteine residues of proteins, providing a versatile tool to study the protein by multiple spectroscopic techniques, including NMR, EPR and time-resolved FRET experiments.

Molecular Imaging (Figure 3). We are developing new synthetic approaches to polymeric MRI contrast agents. MRI is invaluable for imaging tumours and diagnosing disease. Contrast agents have been used in the clinic since the 1980s to enhance the image contrast by increasing relaxation of local water molecules. However, these contrast agents are far from optimal and the image contrast is nowhere near the theoretical maximum. We have prepared gadolinium complexes bearing two polymerisable arms, which can be readily polymerised in a single step to form macromolecules with different architectures, such as hyperbranched polymers.[9] By limiting the local motion of the gadolinium complex through crosslinking, we have produced contrast agents with 8-fold higher relaxivities compared to commercial agents (e.g. Gd-DOTA), which could enable lower and safer doses of the contrast agent to be used.

SYNFORM *What is your most important scientific achievement to date and why?*

Dr. S. J. Butler Perhaps the most significant contribution so far is in the area of supramolecular anion recognition – we have synthesised a new class of receptors that can discriminate between ATP and ADP for the purpose of monitoring kinase enzyme activity in real-time.[2,4] This could underpin new bioassay tools for high-throughput screening of potent kinase inhibitors for the treatment of cancer. I'm proud that some of our molecules are already being used in studies led by biochemists and biologists – I find collaboration with experts in different fields to be very rewarding and certainly the best

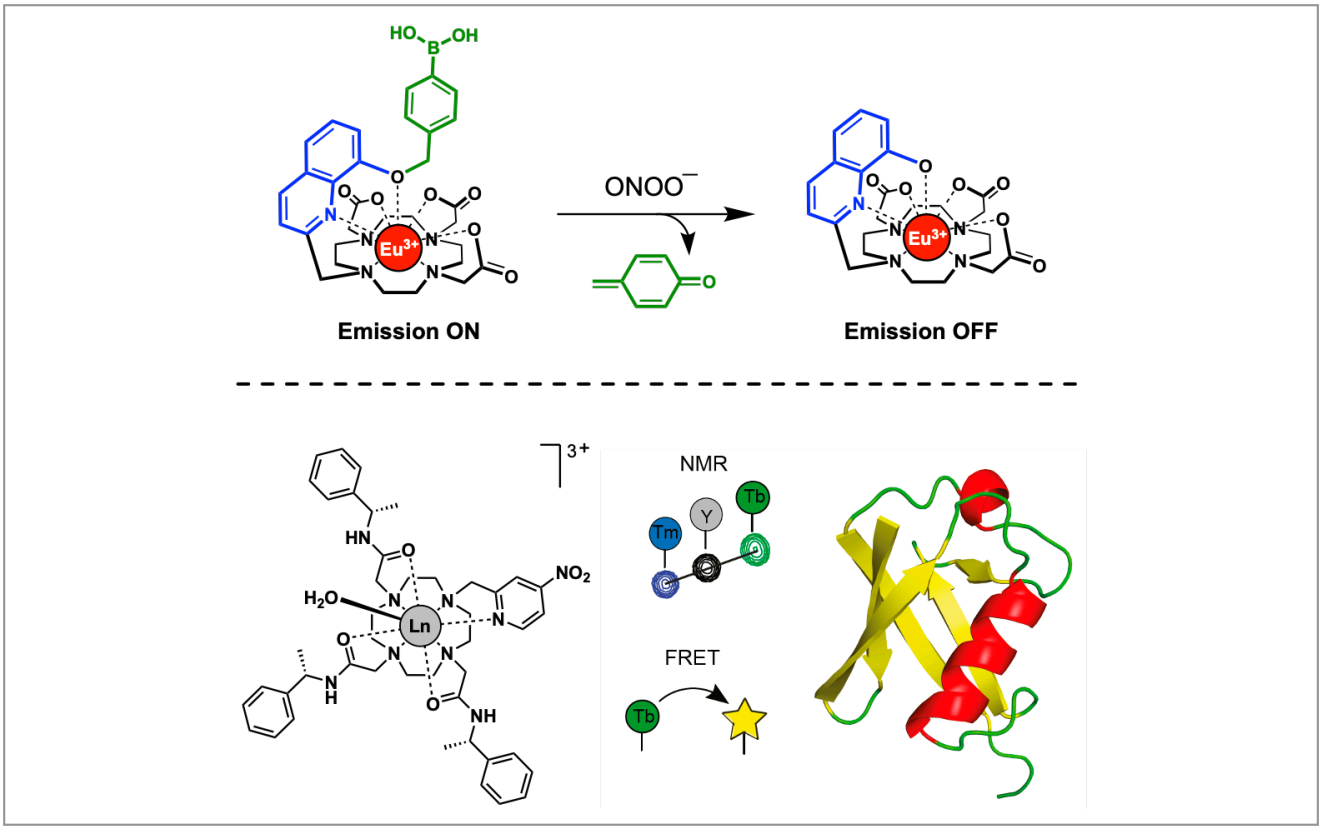

Figure 2 Reactivity-based probe for selective detection of peroxynitrite (top). Chiral paramagnetic tag for site-selective attachment to proteins (bottom).

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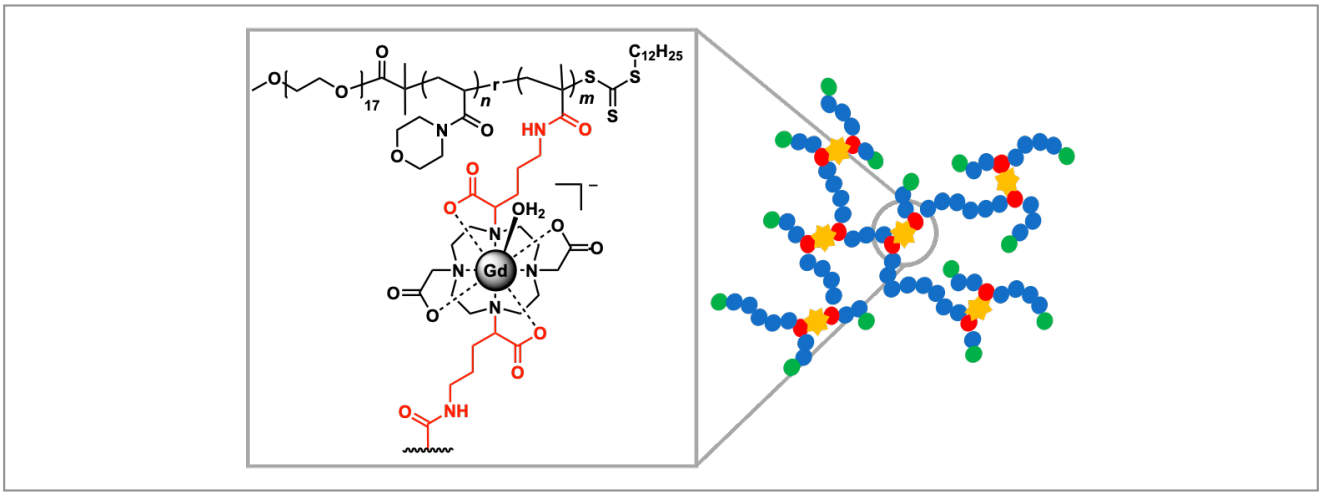

Figure 3 Gd(III) building blocks for macromolecular MRI contrast agents

way to optimise our supramolecular receptors for eventual 'real-world' applications. There is no doubt that my scientific achievements are only possible because of the talented and enthusiastic group of researchers that I've had the pleasure to work with in our lab over the past 5 years. Thanks to their drive and talent, we also have more exciting projects in the pipeline.

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