Regional Chemistry: 2015

How do we fit together?

Purpose:

Establish themes for collaborative Doctoral Training.
Make contacts for collaborative grants.
Help find and reward excellence in Chemistry.
Free Lunch.

Who Participated?

PhD students, PDRAs, young academics,
established academics, Heads of chemistry units
interested in Chemistry and Doctoral training and
regional collaboration in Chemistry.

16 December 2015

Where? Nottingham Trent University, Clifton Campus, Pavilion Building.

Cost to attend: Submission of an abstract for a Poster or short
presentation. If you are PhD or PDRA you may be asked to
chair/organise a session. The rest is on us.

What subject areas?

If it is chemistry and suitable for Doctoral level and above,
it is all good.

What was presented

Anything that could be a solid foundation for doctoral training and above.
Anything where you collaboration might give you a better competitiveness for grants.
Anything where interaction might make your case for REF2020 stronger.
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Agenda

9:30-10:00 Meet, Register, Set up posters, Welcome.

10:00-10:15 Welcome PAV123
   Quentin Hanley, NTU

10:15-11:15
   Session 1a: Big Molecules, Small Molecules and Biology, PAV123
   Chair: Lauren Turner, Hull University.
   Session 1b: Computations and Interactions, PAV122
   Chair: Alexander Hamilton, SHU

11:15-11:30 Break

11:30-12:30
   Session 2a: Labels and Photons PAV123
   Chair: Andrew Leach, LJMU (tentative)
   Session 2b: Sensors and Recognition PAV122
   Chair: Marion Limo (NTU)
   Session 2c: PAV121 (tentative)
   Chair:

12:30-13:15: Poster Session 1: Pavilion Lobby

13:15-14:15: Lunch
   Working Lunch/Discussion Senior Staff/Heads of Department (Rm 123)
   Facilitated by Ross W. Boyle, University of Hull

   Early Career Academics (<5yrs) Lunch/Discussion (Rm 122)
   Facilitated by Ryan Mewis, Manchester Metropolitan University.

   Established Academics (>5 yrs) Lunch/Discussion (Rm 121)
   Facilitated by Lindsey Munro, MMU

   PhD Student PDRA Lunch/Discussion (Downstairs)
   Facilitated by Guy Entract, University of Hull.

14:15-15:15
   Session 3a: Synthesis and NMR PAV123
   Chair: James Ryan, MMU
   Session 3b: Overviews and Adsorption PAV123
   Chair: Karen Davies, NTU
   Session 3c: PAV123 (tentative)
   Chair:

15:15-16:00 Break, posters, and discussion.

16:00-16:30 Full Group Discussion: Vote of Thanks.
   Neil Bricklebank, SHU.

16:30 Follow-up with Senior Staff/Heads of Department
Scientific Programme

Session 1a: Big Molecules, Small Molecules and Biology PAV123
Chair: Lauren Turner, Hull University.

10:15: Decoding the biosynthesis of hydrocarbons in ants, Sue J. Shemilt and Falko P. Drijfhout.


11:00: Defeating the Superbugs: Self-sterilising polymers to combat healthcare associated infections. Lauren C. Turner, Maria G. Francesconi, and Ross W. Boyle.

Session 1b: Computations and Interactions PAV122
Chair: Alexander Hamilton, SHU

10:15: Towards an Understanding of Peptide - Inorganic Interactions Marion J. Limo, Rajesh Ramasamy and Prof Carole C. Perry.

10:30: Exploring Structure & Reactivity through Computational Chemistry, Alex Hamilton.

10:45: The Development and Assesment of Computational Approaches to the Thermodynamics and Kinetics of Binding, Dr Andrew Leach, Iva Lukac, Dr Judith Madden, Dr Steve St-Gallay.

11:00: Computational Insights into Real Systems, Lindsey J. Munro.
Session 2a: Labels and Photons PAV123
Chair: Andrew Leach, LJMU (tentative)


12:00: Traversing the challenges of extended conjugation: Bacteriochlorins and aza-BODIPYs, a new era in photomedicine. Miffy. H. Y. Cheng, Ross W. Boyle

12:15: Energy Transfer, Fluorescence Anisotropy, Quenching, and Induced Assembly. Quentin S. Hanley.

Session 2b: Sensors and Recognition PAV122
Chair: Marion Limo (NTU)

11:30: Dissection of molecular recognition contributions using synthetic porphyrin systems. Philip Lane, Alex Hamilton and Simon Turega.

11:45: A surface chemistry approach to the study of cell-interface dissociation, and anoikis resistance mechanisms. Matthew Nicklin, Robert C. Rees, A. Graham Pockley, David Boocock, Clare Coveney and Carole C. Perry


**Session 3a: Synthesis and NMR** PAV123  
Chair: James Ryan, MMU


14:45: Divergent Approaches to Piperidine and Spiropiperidine Alkaloids. Sasha Blackshaw, James Ryan, Elaine O’Reilly, Beatriz Macià and Vittorio Caprio

15:00: Novel Synthetic Methodologies for the Construction of Challenging sp2-sp3 and sp3-sp3 Bonds. Daniel M. Allwood.

**Session 3b: Overviews and Adsorption** PAV122  
Chair: Karen Davies, NTU

14:15: Overview of the Chemical Sciences Research Centre at Keele University. Falko P. Drijfhout


15:00: Applications of Flux Response Technology in gas adsorption and catalysis. David J. Richardson
Getting to NTU Clifton Campus

Driving:

Clifton is about five miles from Nottingham city centre. The closest motorway junction is junction 24 on the M1. If you are using a sat nav to find us, the campus postcode is NG11 8NS, or you can get directions to NTU here.

From junction 24 follow the A453 for seven miles to the Clifton campus. If you are travelling from the east follow the A52 and signs to Nottingham, then join the A453, signposted ‘M1 South’. The Clifton entrance will be on your right hand side. Parking is available at Clifton campus for all visitors.

Download a map of Clifton campus

Rail and Bus:

Nottingham railway station is about five miles from Clifton campus. A taxi from the station will cost around £10, and there is taxi rank right outside the station entrance.

If you have sufficient time, the number 1 buses stop by the campus.

Timetable for the number 1: https://www.nctx.co.uk/timetables-tickets-maps/buses-lines/bus/1

Tickets cost £2 for a single trip or £3.50 for a day's pass.
Abstracts

Divergent Approaches to Piperidine and Spiropiperidine Alkaloids

Sasha Blackshaw, a James Ryan, a Elaine O’Reilly, b Beatriz Maciá a and Vittorio Caprio a

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b Department of Chemistry, University of Nottingham, University Park, Nottingham. NG7 2RD

Our research focusses on developing methods for the convenient access of core structures of piperidine and spiropiperidine-based alkaloids. Herein we discuss two approaches to both target types based on functionalisation of nitrone precursors or biocatalysed cyclisations of diketones.

Thus, we are involved in developing routes to analogues of the anti-inflammatory alkaloid pinnaic acid 2 1 via functionalisation of spironitrone 1,2 and towards the non-competitive nAChR antagonist histrionicotoxin 3 3 using 4, a recently prepared isomer of 1.

![Pinnac acid 2]  ![Histrionicotoxin 3]

Our biocatalysis methodology centres on the domino amination/conjugate addition of diketones 5 and 6, in the presence of transaminase enzymes, 4 providing enantioselective routes to 2,6-piperidines 7 or spiro-derivatives 8. This work has recently led to the development of a three-step route to the anti-feedant pinidinone 9.

![Enzymatic cyclisation]

Hyperpolarisation of small molecules by Signal Amplification By Reversible Exchange

David Ashworth, Lisa A. Clayton, Ryan E. Mewis*
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Hyperpolarisation techniques overcome the inherent sensitivity issues in MRI and NMR. Para-hydrogen based techniques utilise para-hydrogen, a spin isomer of hydrogen, as the source of polarisation. SABRE (Signal Amplification By Reversible Exchange) is a para-hydrogen based technique, which transfers polarisation (mediated by an iridium di-hydride complex) without incorporation of hydrogen into the analyte (unlike traditional based para-hydrogen techniques).¹ Some molecules that have been polarised are shown in Fig. 1; one of the main areas of investigation is the production of ubiquitous contrast agents for MRI (such as nicotinamide).

Fig 1. Chemical structures of molecules that have been hyperpolarised
There are a number of factors that have to be tuned to improve the efficiency of the catalyst used to facilitate transfer of polarisation. The exchange rates of both para-hydrogen derived hydrides and analyte molecules are crucial for efficient transfer; ultimately, the rates need to be commensurate. Temperature, solvent, number of proton acceptors in analyte, magnetic field in which polarisation transfer is conducted and the choice of carbene used in the construction of the catalyst are all important factors that need to be considered.² ³ Furthermore, the longevity of the hyperpolarised state can be measured via $T_1$ measurements; increasing the magnitude of this state results in a longer period to detect and manipulate the analyte molecule. It is envisaged that optimising these variables will aid in realising the potential of SABRE by facilitating the detection of hyperpolarised contrast agents in vivo.

Fig 2. $T_1$ relaxation of hyperpolarised pyridine at 60 MHz. $T_1$ values for the $^1$H resonances are 19.0, 21.0 and 21.8 s (ortho, meta and para sites respectively).

Energy Transfer, Fluorescence Anisotropy, Quenching, and Induced Assembly.

Quentin S. Hanley
School of Science and Technology, Clifton Campus, Nottingham Trent University, Nottingham NG11 8NS.

Fluorescence resonance energy transfer (FRET) remains one of the few methods for assessing proximity on the nm scale, particularly inside living cells. Energy transfer occurs via a non-radiative process from a donor to an acceptor. FRET can occur between like molecules (homo-FRET) and different molecules (hetero-FRET) provided the conditions of proximity, overlap, and orientation are met.

FRET processes are widely used to study proximity relationships between labelled proteins using a wide range of measurement techniques. The mostly widely used experimental paradigm is hetero-FRET in a single donor-acceptor pair. The alternative homo-FRET experiment presents useful features making it attractive for observing cluster formation. However, fluorophores in clusters exhibit a range of behaviours dictated by the stochastics of labelling, the size of the cluster, and the characteristics of the fluorophore. Partially labelled species present both a challenge and an opportunity due to the distribution of fluorophores in clusters.

When interpreting anisotropy, an assumption of equal fluorescence intensity has widely applied. This assumption predicts, for example, that 3 fluorophores in a cluster have the same fluorescence intensity as the same three fluorophores outside of a cluster. This assumption will give incorrect predictions in cases where either quenching or enhancement of fluorescence occurs. Additionally, existing theory typically assumes that all positions within a cluster are equivalent.

To study anisotropy in clusters, the behaviour of fluorophores in variably labelled proteins and fluorophores assembled on DNA:DNA and DNA:PNA templates was studied. This revealed a range of paradigms depending on: the mechanism of assembly, the extent of quenching of dyes, and the distance between fluorophores.

This work provides opportunities for collaborative work ranging from synthesis of new fluorophores, revisiting existing systems and application to the study of receptors and plaques.

Attacking mass spectrometry from both sides – new sources and algorithm development

David P. A. Kilgour1, Benjamin Oyler2, Alison Scott2, Robert K. Ernst2, David R. R. Goodlett3, David C Clarke3

Mass spectrometry is a technique that offers tremendous capabilities in the modern chemical or biomedical laboratory. Over the past 25 years the performance of mass spectrometry systems has developed enormously. In particular, the design and performance of the mass analysers themselves has been improved dramatically. Alongside the development of the mass analysers, new ionisation sources have been developed and these have opened up new fields of ‘omics’ analysis. Despite the many advances in mass spectrometers, there remain many areas where MS system performance lags behind user expectations and generates a bottle-neck in research and development.

Here we present research to address some key areas where mass spectrometry system performance in practise could most usefully be improved; ionisation sources/interfaces and mass spectral data processing.

Nanospray is a common technique in many laboratories, providing high sensitivity and soft ionisation of bio-macromolecules. However, researchers are trying to both push the mass range of analytes higher, to investigate huge native state proteins and protein complexes; and to increase the numbers of samples analysed. In these areas, nanospray can often be frustratingly slow and difficult to tune. Revisiting ultrasonic assisted electrospray and other ultrasonic/acoustic methods is providing new and improved methods of ionising analytes from solutions, requiring less user tuning and providing higher throughput. Examples of the benefits of these new sources are presented.

Data processing of mass spectrometry data often takes much longer than the initial data collection. It is common for users to resort to manual data processing methods because of the difficulties of trying to use the available tools for automated processing. New instrumentation and techniques such as high field FT-ICR MS and mass spectrometry imaging are producing mass spectral datasets that are so complex or so enormous that manual interpretation is impossible. Furthermore, manual processing even of more traditional data-sets, is slow and also introduces an unwelcome degree of subjectivity that can complicate results interpretation, particularly in large and multisite studies. Therefore there is pressing a need to develop new, more robust, data analysis techniques.

New improved data processing and presentation techniques are presented. These include new algorithms and methods for absorption mode processing of FT-MS data (a technique that provides improved resolution, signal-to-noise and mass accuracy) for both orbitrap and ICR mass spectra. A new, high sensitivity, high confidence approach to peak detection is presented that is more reliable than common methods and can be applied to all isotopically resolved mass spectra. Even such simple tools as unsupervised automated recalibration methods and widgets for producing protein fragmentation maps provide a significant performance enhancement and an improved user experience.

We are keen to develop these tools further, discover new areas for improvement and find new partners with whom to test and develop tools and applications.
Development of PDT/PET Theranostics: Synthesis and Biological Evaluation of a 18F-Radiolabeled Water Soluble Porphyrin

Guy M. Entract*, Francesca Bryden†‡, Juozas Domarkas†‡, Huguette Savoie†, Louis Allott§, Stephen J. Archibald†‡, Chris Cawthorne‡∥, and Ross W. Boyle†

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Fig 1. – Schematic showing theranostic agent comprised of photosensitiser and positron emission tomography radionuclide.

Theranostics is a newly emerged field, born from the concept of combining therapeutic and diagnostic modalities with a focus to provide a more personalized cancer treatment which recognizes the heterogeneity of tumours in different patients. Therapeutic strategies exploited to date include nucleic acid delivery, chemotherapy, hyperthermia (photo-thermal ablation), photodynamic and radiation therapy, coupled with imaging strategies including MRI, fluorescent markers, SPECT and PET.¹

Porphyrrins offer excellent potential as theranostic agents for personalised medicine; their potent cytotoxic activity within the field of photodynamic therapy has been well documented, with published water-solubilisation and tumour targeting strategies demonstrating the increasing clinical relevance of these treatment modalities. In addition, porphyrins demonstrate potential as imaging agents; while they have clearly emerged as field-leaders in fluorescence imaging, they also allow chelation of a host of metals suitable for PET, SPECT and MRI (see Boyle et al for a comprehensive review).²

Fluorine-18 is often referred to as the “radionuclide of choice” for PET imaging agents. The 110 minute half-life allows for multistep synthesis, and allows ample time for imaging neoplastic tissue, including time for transportation to the clinic, while the short positron linear range within tissue (2.3 mm) gives it the highest resolution PET
images of all the positron emitters.

Following our current interest in porphyrin bioconjugation using the Copper (I) – Catalysed Alkyne-Azide Cycloaddition (CuAAC) reaction\(^{5-7}\), it was rationalised that a click conjugation methodology could be utilised to radiolabel a porphyrin under mild reaction conditions to a prosthetic radioalkyne-bearing PEG chain that would provide a facile and high yielding method for radiolabelling water-soluble porphyrin with minimal impurities. We have demonstrated that a single theranostic agent in the form of a novel fluorine-18 radiolabeled water-soluble porphyrin can be synthesized from an alkyne-bearing \(^{18}\)F PEG carrier chain and an azide functionalised porphyrin. This is the first demonstration of an \(^{18}\)F radiolabeled porphyrin retaining photodynamic toxicity following radiolabeling; with the synthesised compound showing cellular uptake, good photodynamic toxicity and minimal dark toxicity in a relevant human cancer cell line, as well as **confirmed uptake of the conjugate into neoplastic tissue and demonstrated potential as a radiotracer by *in vivo***. All restriction required for the synthesis of PET imaging agents in terms of time and radiochemical yield have been met, offering exciting possibilities for the simultaneous imaging and photodynamic treatment of tumours.

Defeating the Superbugs: Self-sterilising polymers to combat healthcare associated infections.

Lauren C. Turner*, Maria G. Francesconi and Ross W. Boyle.
Department of Chemistry, University of Hull, Hull, HU6 7RX.

Healthcare Associated Infections (HAI) in hospitals are a growing issue for both the public and scientists alike, with media coverage fuelling general unease regarding the safety and cleanliness of hospitals. While only *S. Aureus* has entered the public sphere of consciousness in the form of MRSA, there are many known HAI caused by a range of organisms including *C. difficile* and *E. coli* which can have wide-ranging consequences, from minor discomfort to serious disability and death. The impact of HAI is both widespread and costly; Department of Health figures confirmed that in 2004 there were 300,000 cases of HAI, with an estimated yearly cost to the NHS in England alone in excess of £1 billion. While HAI can be combated to some extent by implementation of good hygiene practices, increasing time and cost pressures on NHS Trusts mean that a radical paradigm shift towards the development of low cost solutions requiring minimal manual labour is required. An innovative solution to this problem is the use of polymeric materials which convert atmospheric oxygen into Reactive Oxygen Species (ROS) lethal to the pathogens that cause HAI.

This particular project looks firstly at the use of UV light and designing a prototype in which PVs are fine tuned for optimal anti-HAI activity. Correlation between ROS production and bacterial inactivation will be evaluated, allowing the optimisation of antibacterial activity. We are also investigating alternative co-reductants that use visible, rather than UV, light to maintain the PVs in their active form, thus ensuring a steady state sterility at the polymer surface driven by ambient light.

A library of polyviologen compounds have been generated with varying counter-ions, allowing fine tuning of system solubility. Systems using ultra-violet light have been synthesised using the viologen molecules attached to titanium dioxide. Shifting from the UV region to the visible region is a crucial part of this project as it allows normal hospital lighting conditions to be utilised. Porphyrins have been synthesised to help aid the shift to the visible region. The synthesis of porphyrin-viologen hybrids has been carried out using coupling reactions and click chemistry, with the porphyrins having halogenated or azide substituents and the viologens having boronic acid or alkyne substituents. The conjugation of porphyrin-viologens will be carried out along with the study of the electron transfer occurring at the surface.
Traversing the challenges of extended conjugation: Bacteriochlorins and aza-BODIPYs, a new era in photomedicine.

Miffy. H. Y. Cheng, Ross W. Boyle
University of Hull, Department of Chemistry

Surgery is one of the four main methods for treatment of cancers, in particular solid tumours; but the surgical margins are often indistinctive and in most cases, this can result in re-excision due to the difficulty of residual cancer tissue identification. Surgical molecular contrast agents have been in development recently for use in a real time intra-operative imaging technique known as near infrared (NIR) fluorescence-guided surgery.

Currently, contrast agents lack selectively and also suffer from poor absorbance at longer wavelengths, limiting light transmission to more advanced tumours.¹ This shorter absorbance wavelength limits the use in NIR fluorescence-guided surgery. In addition, the current contrast agents have poor chemical stability, limited water-solubility and lack active targeting to neoplastic tissue, again limiting their clinical application.²

The scope of this project encompasses the provision of novel theranostic agents, containing functionalised extended-wavelength chromophores for use in NIR fluorescence guided surgery, but which can also have potential as photodynamic therapeutics to treat as well as image solid tumours.

Throughout the project a series of water-soluble bacteriochlorins and aza-BODIPYs are being synthesised and a library of compounds has been developed for both diagnostic and therapeutic application. They have shown promising result as NIR fluorophores (λ\text{em} ≈760 nm), and methods are being development to include functionalisation suitable for bioconjugation, including alkyne and azide moieties for use in click chemistry. This will allow attachment of the functionalised photosensitisers to delivery platforms under mild biocompatible conditions.³ Further biological evaluation is progressing with the eventual aim of developing a pre-clinical model for NIR fluorescence guided surgery in colorectal cancer.

Decoding the biosynthesis of hydrocarbons in ants

Sue J. Shemilt and Falko P. Drijfhout*
Chemical Ecology Group, Keele University, Keele, UK

Within social insect species colony signatures are required so that altruistic behaviour can be appropriately directed. It is widely accepted that within ant species nest-mate discrimination is down to a chemical signature determined by the cuticular hydrocarbons present. Previous work involving Formica exsecta looked at the incorporation of labelled hydrocarbons within a very simple hydrocarbon profile of just alkenes and alkanes. Using such species as F. lugubris we hope to be able to replicate this work and investigate the incorporation of labelled hydrocarbons into the many methyl branched hydrocarbons that this species exhibits.

Preliminary studies involved feeding small groups of different species of British ants ad libitum a diet containing sodium acetate labelled with a single carbon-13 atom. The cuticular hydrocarbons were extracted with hexane and these extracts were analysed using gas chromatography coupled to mass spectrometry. By studying the level of incorporation of the labelled substrate into the hydrocarbon profile it is hoped that more information on the biosynthetic pathways that are employed can be determined.

This poster will introduce the results from the first preliminary experiments and the analytical techniques, equipment and methods used for work of this kind.
Optical oxygen sensing in collagen scaffold with porphyrin-based polyacrylamide nanosensors.

Francesca Giuntini1, Veeren Chauhan2, Jonathan W. Aylott2, Geri A. Rosser3, Alexander J. MacRobert4, Robert A. Brown4 and Ross W. Boyle5
1John Moores University, Liverpool, United Kingdom; 2University of Nottingham, Nottingham, United Kingdom; 3Durham University, Durham, United Kingdom; 4University College of London, London, United Kingdom; 5University of Hull, Hull, United Kingdom

Recent advancements in the fields of scaffold-supported tissue engineering have fuelled a renewed interest in the development of strategies for oxygen measurement and detection.1 The successful repopulation of cell-seeded matrices/scaffolds and subsequent regeneration of functional tissue depends on the ability to create a favourable environment for cell growth and differentiation, which relies on the constant supply of oxygen and nutrients. The non-uniform regeneration of the extracellular matrix (ECM) can prevent adequate oxygen supply to cells and lead to the formation of hypoxic zones in the supporting scaffold, a relatively common cause for the failure of engineered tissues: the measurement of the oxygen diffusivity of a given material is therefore pivotal to assess its suitability to sustain cell growth.2

We recently undertook a project aimed at the development of novel porphyrin-based oxygen nanosensors for incorporation in tissue regeneration scaffolds matrices.3 The possibility of monitoring the global distribution of oxygen within the scaffold during cell growth and migration represents the main advantage of such an approach. Indeed, while the more commonly used fibre optics and electrodes only permit localised measurements, the uniform distribution of an optical probe throughout the matrix of the scaffold allows real-time investigations of the behaviour of the device during the process of recellularisation. We report the synthesis and the oxygen-sensing behaviour of such species, in solution and within doubly-compressed collagen scaffolds, as models for tissue regeneration supports.

2 Streeter, I.; Cheema, U. *Analyst* 2011, 136, 4013
Novel Synthetic Methodologies for the Construction of Challenging sp$^2$-sp$^3$ and sp$^3$-sp$^3$ Bonds

Dr Daniel M. Allwood  
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Biomolecular Sciences Research Centre  
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The formation of strategically important bonds allows rapid and efficient preparation of a wide variety of useful molecules including pharmaceuticals, functionalised materials, agrochemicals and natural products. In turn, increased efficiency in chemical synthesis shortens synthetic sequences, lowers costs, reduces waste and passes on these benefits to the end-user.

However, many procedures for the formation of challenging bonds are not practically useful for a variety of reasons. They may require specialised equipment; preparation and use of complex, unstable, expensive or toxic starting materials or catalysts; require rigorous exclusion of air, require a large stoichiometric excess of one or more reagents; have poor substrate scope; be irreproducible or perform poorly on scale. By recognising and avoiding these issues in the development process, we can design more powerful chemical transformations and improve uptake of new synthetic procedures.

My research is focused on the development of novel synthetic and catalytic methodologies for the construction of challenging sp$^2$-sp$^3$ and sp$^3$-sp$^3$ bonds with a focus on robustness, procedural simplicity and reproducibility.
Overview of the Chemical Sciences Research Centre at Keele University

Falko P. Drijfhout*
Chemical Sciences Research Centre, Keele University, Keele, ST5 5BG

The Chemical Sciences Research Centre at Keele University was formed about a year ago, after restructuring of the research within the university. The research centre sits within the Faculty of Natural Sciences and is part of the School of Physical and Geographical Sciences.

Current research done with the research centre varies from synthetic chemistry, to analytical chemistry but also from materials chemistry to medical chemistry. Within this range each of the typical areas of research, organic, inorganic and physical chemistry is present. Whereas some staff is active in synthesizing new catalyst for fuel cells, others are analysing hydrocarbons on the cuticle of insects to help in forensic investigations. The breadth of research within the centre makes it ideal to collaborate both internally as well as externally.

In this presentation on overview of the research carried out within the research centre will be presented, as well as the facilities available.

Research of the Keele Synthesis & Medicinal Chemistry Cluster

Keele Synthesis and Medicinal Chemistry Cluster, Lennard-Jones Laboratories, School of Geographical and Physical Sciences, Keele University, Staffordshire, ST5 5BG

This presentation gives an overview of the active research within the cluster and the funding and research facilities available at Keele:

- Automation and Continuous-Flow methods in Chemical Synthesis (Matt O'Brien)
- Delivery Mechanisms and Drug release technology (Mike Edwards, Tessa Phillips)
- Synthesis of large oligosaccharides and carbohydrate mimetics for use as inhibitors and potential drug therapies (Gavin Miller)
- Novel synthetic methodology for the preparation of organic molecules (Mike Edwards Matt O'Brien)
- Synthesis of small molecule medicinal agents (Mike Edwards, Tessa Phillips, Gavin Miller)
- Autotaxin a potential target for drug resistant ovarian cancer (Mike Edwards)
- Synthesis of biologically active natural products (Matt O'Brien, Tessa Phillips, Graeme Jones)

More details can be found at www.keele.ac.uk/ksmc/
Controlling and exploiting C-H bond activation: strategies for the rapid construction and modification of functional molecules

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Over the past decade a number of highly-efficient synthetic strategies have been developed that involve the use of a transition metal catalyst to directly cleave non-acidic C-H bonds, a process known as C-H activation.\(^1\) These reactions are revolutionizing organic synthesis because they enable a more direct synthesis with fewer steps and because they enable unconventional synthetic strategies.

Our research in this area has focused both on fundamental investigations to gain more understanding of how to control C-H activation, and on investigations exploiting C-H activation in synthesis.

For example, we have demonstrated control of the site-selectivity in the C-H activation of naphthalene molecules, by using an appropriate bidentate directing group.\(^2\) In addition, for C-H activation reactions without a covalent directing group, we have demonstrated a rare example of metal-ligand control of site-selectivity, Scheme 1.\(^3\) Our research in these areas has also involved computational investigations, employing density functional theory (DFT) to rationalize our experimental findings.

![Scheme 1. Metal-ligand control of site-selectivity in C-H activation.\(^3\)](image)

Recently, we have been investigating the application of C-H functionalization as a new approach for the post-synthetic modification of peptides, Scheme 2. We are keen to establish new collaborations to pursue applications of this chemistry.

![Scheme 2. C-H functionalization for the post-synthetic modification of peptides.](image)

Our future plans include exploiting C-H functionalization as a late-stage and divergent synthetic strategy, for example for the facile investigation of structure-activity or structure-property relationships in medicinal chemistry or materials science; we are especially keen to collaborate in order to pursue these goals.

Computational Insights into Real Systems

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Computational chemistry techniques can be used to investigate a wide range of systems providing an insight into the processes occurring at an atomic and electronic level.

This can be used to:
- find lowest-energy structures,
- explain reaction mechanisms (by calculating the thermodynamics of different pathways for organic / inorganic synthesis),
- simulate processes (using molecular dynamics),
- analyse the electron density distribution (in frontier orbitals),
- highlight regions susceptible to attack by electrophiles, nucleophiles or radicals
- investigate novel inhibitors for protein targets
- predict spectra.

Current areas of interest include investigating the pathway of odorant molecules from the air to the olfactory receptors – using protein-ligand docking calculations and molecular dynamics. In addition, we are designing a series of molecules that self-assemble and probing their thermodynamic stability, electronic and optical properties. Furthermore, we regularly collaborate with experimental colleagues to model graphene, fullerenes, inorganic complexes and inhibitor design in order to interpret experimental data and provide direction on subsequent experiments.
The Development and Assessment of Computational Approaches to the Thermodynamics and Kinetics of Binding

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Over recent decades there have been many improvements in the techniques available for predicting the pharmaceutically relevant properties of a compound. However, predicting the binding strength between a compound and a protein target remains an unsolved problem. The challenge of predicting this binding strength has been complicated in recent years by the insights provided from the measurements of thermodynamics and kinetics. Those attempting to design drugs now have more parameters, rather than less to worry about! [1,2]

At John Moores University, we are undertaking a program of work to design and evaluate computational tools to predict the thermodynamics and kinetics of binding. These tools will help drug designers to navigate this complex array of interdependent properties.

The project presents a novel approach in which QM (quantum mechanics) is used to calculate binding energies: by constructing ‘theoceptors’- theoretical receptors constructed by computing the optimal geometry. QM calculations on LDHA (Lactate Dehydrogenase A) have been performed: previous work has shown that for iNOS (inducible nitric oxide synthases) a QM model system was able to provide binding energies that correlate well with LLE (ligand lipophilic efficiency) [3]. LLE as a property resembles enthalpy of binding; hydrophobic binding is associated with entropic forces [4].

Figure 1  a. Crystal structure of the LDHA and the ligand. Key residues are shown as stick. b. Theoceptor LDHA with ligand in binding site. c. LLE vs ΔE plot

The aim of this work, besides explaining the link between the structure and thermodynamic/kinetic signatures, is to address some of the issues and uncertainties associated with two biophysical techniques:- Surface Plasmon Resonance (SPR) and Isothermal Titration Calorimetry (ITC).

In this presentation, we will disclose the insights available for a congeneric series of PHGDH (3-Phosphoglycerate dehydrogenase) inhibitors that has been studied using ITC and SPR and the observations rationalized with experimental structures and computational modeling.

These findings contribute beneficially to the development of computational methods for interpreting potency in terms of thermodynamic or kinetic parameters. This will reduce the time and cost of making and testing compounds that are unlikely to become drugs.
References:
Applications of Flux Response Technology in gas adsorption and catalysis

David J. Richardson
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Flux Response is a simple concept based on fundamental ideas of physical chemistry, it consists of ultra-precise measurement of gas molar flow rates by means of a specially designed differential capillary flow meter\cite{1} shown in Figure 1 where the reactor contains the adsorbent and the dummy reactor contains non-adsorbing material of similar porosity and flow resistance.

![Figure 1: Simplified flow diagram for a Flux Response Apparatus. Abbreviations BPR – Back Pressure Regulator, MFC – Mass Flow Controller, DPT – Differential Pressure Transducer.](image)

For a gas flowing through an adsorption column, the difference between the flow rate entering and leaving the column gives a measure of the rate of adsorption or desorption. When the flow rate measurements are combined with composition measurements of the gas it is possible to determine binary or multicomponent adsorption isotherms\cite{2}.

When a reaction takes place, the Flux Response gives a measurement of the net rate of production of gas molecules. Since the response time is fast (ca. 10ms) Flux Response can be considered an \textit{in situ} technique and analysis of the shape of the Flux Response graph can give details of the kinetics of the reaction\cite{3}.

![Figure 2: Flux response output. For a reaction with known stoichiometry (e.g. decomposition of ammonia) the ratio of the area of the reaction peak to the injection peak can be used to determine the percentage yield achieved.](image)

Preliminary unpublished work has been carried out in several areas:
Some modifications to the published model\cite{1} have been made enabling a better fit of experimental data; adsorption measurements have been made at pressures below 1 bar by adding a vacuum pump to the system and a mass spectrometer has been integrated into a flux response adsorption system.

\textbf{References}

Exploring Structure & Reactivity through Computational Chemistry

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The application of computational chemistry methods, predominately density functional theory (DFT), has dramatically enhanced our understanding of the relationship between molecular structure and reactivity. Elucidating the steric and electronic parameters which control desired properties is the first (and some may say most important) step towards rational molecule design.

The focus of this talk will be a general overview of the types of chemistry that interest the computational chemistry group at Sheffield Hallam University; from small molecule catalysts to non-covalent interactions in supramolecular systems. Highlighted will be the synergistic relationship between experimental and theoretical collaborations, which when productive can lead to internationally recognised research. The question question will be posed; what can computational chemistry do for you?
Silica is one of the most common materials in nature and is the second most common biogenic mineral after carbonates, and it is deposited in living organisms, including animals, plants and diatoms. Horsetail (Equisetum spp.) is classified as one of the most ancient species of living vascular plants. A remarkable characteristic of Equisetum species is their ability to take up and accumulate silica in their tissues giving the epidermis a rough texture. This natural silica, often referred to as biogenic silica, is present in the form of amorphous silica and for some plants seems to be an essential mineral for growth. The ability of plants to produce biogenic silica with a wide range of morphologies (Figure 1) under mild physiological conditions is of great interest to scientists (and industry); as it gives the material exceptional properties, such as ordered hierarchical porous structures applicable for catalysis, biosensing and biomedical applications. Biogenic silica in plants is present together with the organic matrix, including polymers (i.e. cellulose), proteins, other carbohydrates, lipids, metal ions (such as Ca, K, S, Cl, Na and P), and phenolic compounds, which also play an important role for the hierarchical structures of biosilica. Numerous methods have been developed for elimination of the organic material and/or metal ions present in plant material to isolate biogenic silica. However, depending on the chemical and/or physical treatment applied to branch or stem from Equisetum Arvense; other mineral forms such glass-type materials (i.e. CaSiO₃), salts (i.e. KCl) or luminescent materials can also be isolated from the plant material. In the current work, it is shown the chemical and/or thermal routes that leads to the formation of a number of different mineral types in addition to biogenic silica.

![Figure 1. SEM images from Equisetum Arvense plant. All scale bars are 100 μm.](image-url)
A surface chemistry approach to the study of cell-interface dissociation, and anoikis resistance mechanisms

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Almost all cancer related death and suffering is associated with metastasis, a complex multi-step process resulting in the dissemination of cancer cells from the primary tumour to surrounding/distant tissues. In order for metastasis to occur, tumour cells must first detach from their extra cellular matrix (ECM) and adapt to survive in its absence through the dysregulation of several regulatory systems including the anoikis pathway. Gaining a better understanding of cell detachment processes may prove instrumental in the design of anti-metastasis therapy. However, research in this area is hindered by the absence of an in-vitro platform which supports active cellular detachment under traditional culture conditions. We have previously reported on a Fluoro-Silica (FS) surface used for studying cancer cell aggregation-disaggregation, a process attributed to a differential adsorption profile of factors from serum. Here the FS surface has been utilised to study the cell-interface association in serum free conditions during TGF-β1 stimulation, where an upregulation of cellular FN was shown to coincide with a progressive cell-surface disassociation process. Mass spectrometry/pathway analysis has highlighted Oxidative Phosphorylation (OP) alongside other metabolic factors to be upregulated during FS surface culture and cell-interface dissociation, linking metabolic state to the anoikis pathway. Herein, we present the FS surface as a potential platform for focused study into cell-interface dissociation mechanisms, anoikis resistance and for better characterisation of the role ECM factors, such as FN hold in the process.
Towards an Understanding of Peptide - Inorganic Interactions

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Material binding peptides are proving to have great potential in improving material synthesis and advancing device fabrication; however, their specificity and interaction mechanisms with target surfaces remain largely elusive. This study contributes to the developing understanding of fundamental principles through which ZnO binding peptides (ZnO-BPs) interact with and modify ZnO growth/morphology. The ZnO-BPs used were the reported phage display (PD) identified sequence (G-12 (GLHVMHKVAPPR) and its derivative, GT-16 (GLHVMHKVAPPR-GGGC))1,2 as well as novel sequences generated from postselection modifications including alanine mutants of G-12 (G-12A6, G-12A11, and G-12A12) chosen on the basis of peptide stability calculated in silico.3 Two approaches were used to study interaction of ZnO-BPs with ZnO. Firstly ZnO growth was monitored in the absence and presence of ZnO-BPs during solution synthesis using two different growth routes; the Zn(NO₃)₂·6H₂O-HMTA system and the ZnAc₂-NH₃ system.3,4 Secondly, isothermal titration calorimetry (ITC) was used to characterize thermodynamic changes during interaction of ZnO with ZnO-BPs.5

The outcomes of the ZnO synthesis studies demonstrate that a single ZnO-BP can utilize different sequence and concentration dependent mechanisms to control ZnO growth and generate different morphologies. The specific synthesis system used dictated the species present in solution and the solid phases formed, some of which ZnO-BPs could interact with and consequently modify ZnO growth and resultant morphologies. The role of histidine within ZnO-BPs in interaction with ZnO and stabilization of LBZs is also demonstrated.4 Analysis of the thermodynamics of ZnO-BP-ZnO crystal interactions using ITC yielded biphasic isotherms comprising both an endothermic and an exothermic event. Measured ΔG values were between -6 and -8.5 kcal/mol and high adsorption affinity values indicated the occurrence of favourable interactions between the peptides and the mineral phase.5 Predictive control of material formation processes by peptides can be achieved through a clear understanding of the growth process and interaction mechanisms.4,5

Key words: peptide, inorganic structure, interfacial interaction

REFERENCES
Dissection of molecular recognition contributions using synthetic porphyrin systems

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Interest in molecular recognition encompasses the recognition of both rigid guests, drugs or steroids and more flexible guests, glycan chains or histone proteins. Individual elements work together to form strong and selective binding events which result in the molecular transport, conformational change and chemical or biochemical modification of the systems involved. Investigating the makeup of important molecular recognition invents in nature can be complicated through the functional nature of the molecules involved, this makes the study of the individual motifs contribute to a molecular recognition event a useful strategy in improving our understanding of these essential processes.

The use of porphyrin host–guest systems is a rapid and productive method for the dissection of individual contributions to more complex molecular recognition interfaces. This strategy has previously allowed the investigation of the additivity, variation of hydrogen bond acceptor strength and effect of removing a rotor in the formation of cooperative hydrogen bonds.

A porphyrin host–guest system has been designed and synthesised that allows the evaluation of an intramolecular O-Zn interaction (Fig. 1). This has been tested using several systems containing differing linker lengths. Further synthetic and measurement work will allow the comparison of this interaction using both esters and carboxylates. This can provide the in-depth analysis of fundamental molecular recognition that is used in the design of biologically functional molecules and medicinal chemistry.

The Nature of the Silicaphilic Fluorescence of PDMPO

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PDMPO (2-(4-pyridyl)-5-((4-(2 dimethylaminoethylaminocarbamoyl) methoxy)phenyl) oxazole), has unique silica specific fluorescence and is used in biology to understand biosilicification. This ‘silicaphilic’ fluorescence is not well understood nor is the response to local environmental variables like solvent and pH. We investigated PDMPO in a range of environments: using UV-vis and fluorescence spectroscopy supported by computational data, dynamic light scattering and zeta potential measurements to understand the PDMPO-silica interaction. From absorption data, PDMPO exhibited a pKₐ of 4.20 for (PDMPOH₂²⁺ to PDMPOH⁺). Fluorescence emission measurements revealed large shifts in excited state pKₐ* values with different behaviour when bound to silica (pKₐ* of 10.4).

PDMPO bound to silica particles is located in the Stern layer with the dye exhibiting pH dependent depolarising motion. In aqueous solution, PDMPO showed strong chromaticity with correlation between the maximum emission wavelength for PDMPOH⁺ and dielectric constant (4.8-80). Chromatic effects were also observed for silica bound dye which allow its use as a direct probe of bulk pH over a range far in excess of what is possible for the dye alone (3-5.2). The unique combination of chromaticity and excited state dynamics allows PDMPO to monitor pH from 3 to 13 while also reporting on surface environment opening a new frontier in the quantitative understanding of (bio)silicification.
Novel material binding peptides via phage display and their adsorption studies

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With increasing use of phage display technology to display material specific peptides it is very important to understand the interactions between (bio)molecules such as peptides, proteins and materials and to identify ‘rules’ or ‘guiding principles’ that could explain and further more predict structure and properties.\(^1\,2\) The use of 7mer peptides to identify tightly bounded hydrophilic or hydrophobic silica nanoparticles, their peptide sequence similarity scores with different elution and washing strategies is limited and needs to be further explored. The goal of the project is to develop a new approach to elute and identify and understand their molecular behaviour material binding peptides onto material surfaces using phage display technology.

The process used for synthesizing the silica nanoparticles show monodisperse silica nanoparticles although they slightly differ in their sizes for different methods. The novel silica binding peptides isolated from biopanning process were synthesized and characterised for studying the peptide-inorganic material interactions. The initial results on peptides (LPVRLDW, NDLMNRA, GQSEKHL and GASESYL) binding to silica surfaces showed that the peptide adsorption to silica surfaces will have more than one type of interaction and will be influenced by the experimental conditions. Quantitative analysis of silica binding peptides, including the presence or absence of a soft corona has helped to understand more about their binding patterns. Initial experiments using Raman spectroscopy show that this method can be used to identify specific amino acids (aromatics) and use them as markers to assess the local environment in silica-peptide composites.

References
Simple, small, and cheap yet ultra-sensitive chemical sensors

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Ionophore-based sensors (IBSs) are one of the most sensitive chemical sensors. Their typical targets are small ions including both cations and anions although there are reports describing IBSs for multicharged ions such as heparin. Limits of detection (LOD) in part-per-billion (ppb) are routinely achieved thus allowing IBSs to sometimes rival the most sensitive instrumental techniques including ICPMS. Such detection limits are obtained with sensors utilizing very simple experimental setup and platforms that can be produced on a mass scale for example using screen-and-ink-jet printing. This makes IBSs excellent candidates for routine monitoring and as early warning systems.

Our research balances between fundamental and applied. In the former we work towards understanding mechanisms of response of IBSs thus allowing us to address some of the main issues that IBSs inherently have. This is done by collaborating with material scientists and statisticians. In collaboration with the former we work towards the development of new materials while with the latter we collaborate in the development of modern statistical methodologies. This multidisciplinary combination of skills and expertise allowed us to prepare ultra-sensitive carbonate-selective sensor that was used on an expedition to Antarctica to among other goals study the effect of climate change on ocean acidification. Applied aspect of our work often involves collaborating with engineers in order to integrate sensing films into very simple hand-held platforms that utilize wireless data transmission and enable using mobile communication devices for data acquisition and processing.

Some of the main recent achievements will be present here and few ideas for further work will be put forward. Hopefully this will initiate/stimulate discussion and identify potential for training of PhD students.
Palladium-stibine complexes: unprecedented triply bridging coordination of trimethylantimony

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Palladium phosphine complexes are widely used as catalysts in organic cross coupling reactions, and the electronic and steric characteristics of the phosphine ligands can be varied in order to tune catalyst activity and selectivity. Palladium complexes with stibines, SbR3, the heavier congeners of phosphines, have been much less explored. Stibine ligands exhibit a number of unusual coordination behaviours which are distinct from their lighter analogues, such as redox activity and formation of acceptor interactions with anions and other electron donors both intra- and intermolecularly.1,2 Both phosphines and stibines are found almost exclusively in the terminal coordination mode; a handful of examples of doubly bridging behaviour for these ligands were reported in Rh carbene systems.3

Investigation of the coordination chemistry of stibine ligands with Pd(II) has led to the isolation of a number of dimeric or cluster complexes, featuring short Pd-Pd distances and several unusual ligand behaviours. The Lewis acidity of coordinated halostibines is demonstrated by the formation of intermolecular secondary interactions between stibine and halide ligands. A [Pd(0)]4 tetrahedron incorporating μ3-SbMe3 ligands has been prepared. The triply-bridging behaviour of a monodentate organopnictine is unprecedented, and the electronic structure and bonding in this complex is being examined using ADF calculations.

The effect of vessel wettability on the foamability of ‘ideal’ surfactants and ‘real-world’ beer heads

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The ability to tailor the foaming properties of a solution by controlling its chemical composition is highly desirable and has been the subject of extensive research driven by a range of applications. However, the control of foams by varying the wettability of the foaming vessel has been less widely reported. This work investigates the effect of the wettability of the side walls of vessels used for the in situ generation of foam by shaking aqueous solutions of three different types of model surfactant systems (non-ionic, anionic and cationic surfactants) along with four different beers (Guinness Original, Banks’s Bitter, Bass No 1 and Harvest Pale). We found that hydrophilic vials increased the foamability only for the three model systems but increased foam stability for all foams except the model cationic system. We then compared stability of beer foams produced by shaking and pouring and demonstrated weak qualitative agreement between both foam methods. We also showed how wettability of the glass controls bubble nucleation for beers and champagne and used this effect to control where bubbles form using simple wettability patterns.

Fig. 1. The effect on beer foam, and bubble formation at the beer / glass interface, in a glass exhibiting both hydrophilic and hydrophobic surfaces

Our research program sits at the chemistry/biology interface. We are interested in further understanding fundamental mammalian biological signaling processes and in exploring unchartered bacterial biosynthetic pathways; all encompassed within the field of *glycomics*.

As a means to achieve this, we are developing and applying new synthetic organic methodologies to construct *mimetic carbohydrate building blocks*. This technology will facilitate the application of such building blocks, both as individual biological tools/probes, and also for constructing more complex *mimetic oligosaccharide* and *sugar nucleotide* targets.

**Cortisol Determination**

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Due to globalization and competition in daily life, the rise of disease such as stock and depression gained serious attention for personalized health diagnostic and monitoring. Cortisol levels have been correlated to environmental stress not just in human but in animals such as fish being bred in fish farm. Cortisol secretion follows a circadian rhythm (all day cycle). As a result the need for construction of a device or a system for monitoring physical variables as daily basis, such as point-of-cure (POC) to provide valuable heath informatics. Immunoassays with chemiluminescence (CL) detection provide a selective and sensitive detection method for proteins such as cortisol and can be incorporated into a POC.

References:
Chemical Tools for Marine Ecology - Effects of pH on Marine Communication

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The oceans pH is predicted to decrease from its current level of 8.1 to a pH of 7.7 by the year 2100. This rapid acidification is unprecedented in evolutionary terms and numerous studies already reported possible severe effects on physiology and fitness of marine organisms and communities. In most marine animals chemical cues mediate a large variety of behavioural traits such as homing, habitat choice, mate selection or kin recognition, and are also important in food location, dominance interactions and predator avoidance. Reduced responsiveness of marine animals to chemical cues under reduced pH conditions has been shown in marine fish. We tested the hypothesis that signal disruption through modification of signalling compounds at reduced pH leads to altered behavioural responses. Many of the acid dissociation constants (pKₐ values) of signalling molecules fall within the pH range affected by ocean acidification. Therefore changes in charge and structure of these molecules are likely to occur. The present work focuses on the effect of reduced pH conditions on the chemical properties and functionality of different signalling peptides from marine invertebrates using NMR spectroscopy and quantum chemical calculations in combination with bioassays.

Biofortification of potatoes (Solanum tuberosum) with metal oxide nanoparticles.

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Work carried out in this project aims to biofortify potatoes with bioavailable minerals (including iron, calcium and zinc), towards commercially improving their nutritional value without the need for genetic modification or new breeds.

There are three strategies commonly adopted to improve plant fortification: enhanced fertilisers, breeding and nutritional genetic modification. While GM has produced some interesting results its commercialisation is hindered by public perception and legislation, therefore selective breeding programmes are now being developed to circumvent these issues and help address the hidden hunger in developing countries. This programme of work adopts a more holistic approach, whereby a plant food additive has been developed that can be fed to all varieties of potatoes without the need to develop new strains. The new feed contains benign mineral oxides formulated to be bioavailable by synthetising them on a nanometre scale and coating them with essential amino acids using a patented flow reactor technology.

Generally soils contain large amounts of iron but only small amounts are phytoavailable due to its low mobility in soil (FeSO₄ rapidly binds to soil and becomes unavailable). Current iron enhanced fertilisers contain an iron-chelate e.g. Fe-EDTA, which maintains a desirable level of iron in the soil, but prove costly and are therefore commercially prohibitive. By using the natural form of iron (magnetite) we produce a particulates that can penetrate through the epidermis allowing the iron to traverse into the plant without chelation, thereby significantly reducing the cost while at the same time increasing the nutrient content of the plant and improving yield.
New methodologies for the catalytic enantioselective addition of organometallic reagents to carbonyl compounds

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The titanium promoted addition of different organometallic reagents (i.e. organolithium, Grignard and organoaluminum reagents) to carbonyl compounds in the presence of catalytic amounts of chiral Ar-BINMOL ligands provides versatile optically active alcohols in good yields and enantioselectivities.¹

This methodology allows the preparation of methylcarbinol units (very interesting motifs for its abundance in natural products and biologically active compounds) from MeMgBr or MeLi with with unprecedented yields and enantioselectivities, in a simple one-pot procedure and under mild conditions. Moreover, the methodology is applicable to aliphatic substrates and, when aryl nucleophiles are employed, to ketones.

A Chemo-Enzymatic Route to Chiral 2,5-Disubstituted Piperidines.

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ω-Transaminases (TA) have been successfully applied to the synthesis of chiral 2,5-disubstituted pyrrolidines1 and 2,6-disubstituted piperidines,2 which represent versatile building blocks. Herein we propose an expansion of the TA catalytic scope to the synthesis of new 2,6-disubstituted piperidines scaffolds. This can be represented in the simple biocatalytic retrosynthesis (Scheme 1) of 2,6-disubstituted piperidines 1, which provides us with enone scaffold 3.

Scheme 1: Biocatalytic retrosynthesis of 2,6-disubstituted piperidine.

Traditional synthetic methods will be used to produce the required enone scaffolds 4. We then propose that these can undergo a selective transamination to insert the amine functionality which is expected to undergo a 1,4-addition reaction to generate a wide range of natural products and chiral building blocks (Scheme 2) that are of great interest to the pharmaceutical industry.3

Scheme 2: Natural 2,6-disubstituted piperidine products.

References:
Towards Isolating and Identifying Feeding Stimulants in Honey Bee Pollens

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One contributing factor to the decline of honey bees could be that reduced colony strength during the winter period, and in times of sparse natural forage, leaves bees more susceptible to parasites, disease, and starvation. Beekeepers may attempt to enhance colony health during such times by feeding high protein supplemental diets to colonies. Unfortunately, these tend not to be as readily consumed as pollen.

The addition of natural pollen to such diets can increase uptake by bees. It is therefore believed that pollens contain naturally occurring feeding stimulants to honey bees. Modern analytical techniques provide the best hope of being able to conclusively isolate and identify such stimulants. Current work is looking at the novel application of Counter-current Chromatography, within a process of bio-guided fractionation of mixed-species pollen extracts, to attempt to isolate and identify compounds within pollen that elicit an increased feeding response in pollen consuming bees. Results obtained through feeding trials indicate that the majority of the sugars and proteins present in pollens may have a limited effect on increasing consumption. Work to isolate compounds responsible for increasing the consumption of diets in feeding trials continues, with initial screening suggesting sterols may be present in the more active extracts.

If stimulant identification can be achieved it is hoped a future range of more palatable supplemental diets, which more effectively maintain colony strength, may be produced for use by beekeepers. Such diets could also be of significant benefit to commercial beekeeping and industrial pollination services.
Post-synthetic modification of phenylalanine containing peptides by C-H olefination

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The modification of peptides is rapidly becoming important in areas such as therapeutics and as drug delivery systems.¹ Post-synthetic modification of peptides is an exciting procedure in which peptides containing natural amino acids can be altered after the sequence has been set. Through sidechain modification, the conformation and physical properties of the peptide can be altered.

Palladium catalysed C-C coupling reactions are a relatively new approach to peptide modification; however, conventional cross-coupling reactions require either incorporation of a non-natural halogen containing amino acid into the peptide synthesis, or require pre-functionalization of the peptide with a halogen.² Direct C-H functionalization is emerging as a more efficient synthetic strategy for peptide modification, but this new chemistry has only been reported for tryptophan residues.³

Scheme 1: Palladium catalysed olefination of phenylalanine containing dipeptides

The focus of this research has been the as-yet unreported olefination of phenylalanine containing peptides. We have found that the reaction of styrene with appropriate peptides in the presence of catalytic Pd(OAc)₂ has given olefinated peptides in moderate yields, Scheme 1. Research into the optimisation of the reaction has been undertaken in order to maximise the yield and effectiveness of the procedure. Current investigations are targeted on the scope of the reaction, in terms of the nature of the alkene and the sequence and length of the peptide.

The ultimate aim of this research is to develop versatile new tools for the post-synthetic modification of peptides and proteins with applications in: (a) advancing understanding of biological function, (b) the diagnosis and treatment of disease, and (c) the manufacture of new materials. We are seeking new collaborations to pursue these goals.

Combining Chirality and Conductivity in Radical-Cation Salts with Novel Chiral Donor Molecules and Chiral Anions

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The organosulphur donors TTF and BEDT-TTF have produced a large number of radical-cation salts combining a variety of electrical properties, ranging from semiconductors to paramagnetic superconductors. The TTF based molecular conductors provide an excellent opportunity to explore the combination of chirality and conductivity in the same crystal lattice, which is of importance in understanding magnetochiral anisotropy as seen in carbon nanotubes.\textsuperscript{1} In order to explore the effect of handedness on a conducting material a number of approaches have been taken to introduce chirality into TTF based conductors. Chiral radical-cation salts have included a variety of chiral anions, chiral donors, or have been electrocrystallised from a chiral solvent.\textsuperscript{2-5} Using novel chiral donor molecules and chiral anions we have now synthesised and characterised several new families of radical-cation salts. Resistivity, magnetic and Raman data will be presented.


Photochemical Harpoons: Covalent labels for multi-protein complexes

Chris Garner and Thomas Pearson

NTU

The term Chemical Proteomics was coined to describe the use of chemically induced external stimulus to interrogate the function of proteins. In this paradigm small molecule probes which modulate biochemical activity are employed to identify the players in a biochemical response.

This project seeks to prepare new tools for chemical proteomics which will enable the identification of multi-component protein complexes in cells without the need for genetic perturbation the system. The conceptual model for the design of this chemical tool consists of a ‘bait’ component which is used to deliver a fluorescent tag to its target which allows its isolation and identification. It is envisaged that this tool can be applied to investigate a wide range of systems. This project is currently focused on the development of functional probes to identify protein targets of two biologically active small molecules: (i) organophosphate neurotoxin, saligenin and (ii) the putative targets of the cardioprotective drug, diazoxide.

The role of silica in composite materials for bioengineering applications including bone regeneration and cell based therapies.

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Silica forms a key component of many biomineralized structures found in nature, such as the skeletons of diatoms and primitive animals. Though the nature of these materials is greatly appreciated and can be observed in great detail, the formation of these materials is only partially understood.

The potential to fine-tune the chemical and physical properties of silica to a high degree combined with silica’s general biocompatibility holds great potential for the application of silica as a biomaterial. However what is less well understood is the effect(s) that silica and its constituent components can have on other cells. As part of our continued studies of the interactions of silica with a variety of biomolecules and complex biological system we present three case studies in which the influence of silica has been assessed on: (1) markers of bone regeneration with silk/ silk fusion protein/silica composites; (2) influence of silica on protein release/ mesenchymal cell maintenance characteristics of alginate composites and (3) influence of silica surface chemistry on cell sub populations and cellular adhesion.
Probing Chemical Bond Formation and Interactions in peri-Substituted Naphthalenes.

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The study of the charge densities of a series of peri-substituted naphthalenes bearing a dimethylamino group next to an electron deficient alkene are reported. The charge densities are derived from experimental X-ray diffraction data in most cases and analysed by the “Atoms in Molecules” approach. These structures represent a transition from pairs of groups which just interact through space, as in 1, to those where a considerable degree of covalent bond formation has taken place by Michael addition to give a zwitterion, as in 2. All structures show a critical point in the charge density between the peri-groups and are characterised by the charge density and Laplacian at that point. The bond formation in the zwitterions is not complete, as can be seen in the maps of the Laplacian and indicated by the long C-N bonds (1.61-1.65 Å).

Liquid-Liquid Extractions in Continuous-Flow Synthesis

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Incorporating several open-source software technologies (e.g. Python, OpenCV), a computer-vision system has been developed which allows real-time positional monitoring of the liquid-liquid interface in a continuous flow liquid-liquid extraction device. This has been used for several continuous flow reactions where the principle by-product is water soluble (hydrazone formation, epoxidation using m-CPBA, dithiane formation, bromination with NBS).
Chiral Organosulfur Donors for Preparing Chiral Conducting Materials.

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Crystalline chiral conducting materials has been a topic of considerable interest in recent years, due to the discovery of magnetochiral anisotropy by Rikken et al.\textsuperscript{1} In addition, enantiopure systems are less likely to suffer from disorder than racemic systems where the two enantiomers can in some case interchange locations in a crystal lattice. Magnetochiral anisotropy, the observation of different resistivities for two enantiomeric materials in a coaxial magnetic field, was recently observed in a molecular material for the first time.\textsuperscript{2} Some of the enantiopure organosulfur donors which we have prepared in recent years are presented including the synthetic schemes to prepare them. Furthermore, structures of radical cation salts which are prepared either by donor/acceptor chemistry or by electrocrystallisation are presented.

Molecular magnetism and single-molecule magnets

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Molecular magnetism is a new and extremely fascinating field on the borders of chemistry, physics and materials science. The design and synthesis of molecule-based magnets requires the chemist to exert considerable control over the molecules to arrange the constituent atoms appropriately. It also demands the development of new theories to explain the complex magneto-structural behaviour of these intriguing solids. Molecular magnetism is still at a very early stage of development and single-molecule magnetism is but one offshoot. Single-molecule magnets (SMMs) allow digital information to be stored on a single molecule by manipulating the orientation of its anisotropic ground state magnetic moment (Fig. 1, left).\(^1\) This class of material reveals some considerable advantages over conventional magnets: increased density of data storage (~40 TB/inch\(^2\)) and faster processing of information to name just a few. The current challenge however is to increase the blocking temperature at which digital data can be stored on a single molecule, which is currently at cryogenic temperatures (< 20 K). SMMs are synthesised using a bottom-up approach utilizing transition and lanthanide ion salts with various stabilizing organic bridging ligands (Fig. 1, right).\(^2\) The field relies heavily on single crystal x-ray diffraction and SQUID magnetometry. Utilization of these techniques allows the determination of the structural parameters that influence the magnetic behaviour, ultimately enabling the design of SMMs with improved properties. Current strategies include increasing the strength of the magnetic interactions between spin carriers in polynuclear lanthanide containing complexes and enforcing strict control of the coordination sphere around mononuclear transition or lanthanide ion complexes.\(^3\)

![Fig. 1](image-url)  
(Left) Magnetic bistability of a \{Cr\(_2\)Dy\(_2\}\) SMM; (right) \{Mn\(_{32}\}\}, \{Co\(_8\}\) and \{Dy\}\(_3\) SMMs.

TiO2 based hetero-structures for solar light technologies.

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TiO2 (titania) is the most studied photocatalyst, it is considered the benchmark material for the photodegradation of environmental pollutants and a promising material for a variety of emerging technologies including: photovoltaics, sensing, molecular fuels, photoreduction of CO2. TiO2 can only absorb UV light, and one of the major challenges is the development of materials that can absorb in a wider range of the solar spectrum.

The modification of TiO2 adsorption properties is typically achieved by doping or sensitization with dyes, narrow band-gap semiconductors, or plasmonic nanoparticles. The presenting author’s research interest focuses on the design of hetero structures, containing TiO2, with improved light harnessing properties, in particular towards the visible and near IR region of the spectrum. Our approach focuses on the development of hierarchical hybrid systems, containing TiO2 structures. As an example, perovskite/TiO2 photoanodes consisting of 1-D titania structures were prepared by electrospinning or hydrothermal methods, and uniformly coated with a thin film of organic-inorganic hybrid perovskites (e.g.: CH3NH3PbX3; X= I, Br or Cl). Organolead halide perovskite have allowed an unprecedented progress in solar cell conversion efficiency, reaching 16.8% when deposited on mesoporous TiO2 [1]. The use of 1-D TiO2 nanostructures (i.e.: nanofibers and nanorods) in the photoanode can potentially further increase the efficiencies reached to date. Other classes of sensitzers and morphological combinations are also currently investigated.

An overview of current chemistry research themes and ambitions at LJMU

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The School of Pharmacy and Biomolecular Sciences at Liverpool John Moores University is one of the oldest in the UK, with its origins dating back to 1849. The School has specific specialisms in Pharmaceutical, Medicinal and Natural Products Chemistry owing to the wider research interests within the School. With new MChem and BSc programmes in Applied Chemistry due to begin in October 2016 we will also be looking to expand into other relevant areas of chemistry. Our ambition to enhance our research reputation and productivity has been supported by a grant worth £12M awarded in part by HEFCE, which has been used for the refurbishment of chemistry teaching and research facilities. This has included new purpose-built state-of-the-art laboratories and significant investments in new equipment, including a 600 MHz NMR spectrometer.

Our staff collaborate with leaders in the healthcare and pharmaceutical sector, including AstraZeneca and Pfizer and with other university research groups across the world including China, France, Spain, Slovakia, Iran and Thailand. Funding sources are varied; to name just a few, our staff have received funding from: the British Council, Research Councils, Department of Health, European Commission and the Swiss government.

Specific research interests include, but are not limited to: (i) designing novel nanomaterials for targeted drug delivery e.g. pulmonary delivery; (ii) developing novel methods for preparing cyclic and stapled peptides with a focus on selective-targeting and treatment of disease; (iii) utilizing fluorine chemistry in chemical biology; (iv) isolation and characterization of natural products with anticancer, anti-inflammatory and antimalarial activity; (v) computational methods for predictive assessment of toxicity of pharmaceutical products and quantitative structure-activity relationships (QSARs); (vi) development of nanosensors and techniques for the analysis of chemicals and bioactive substances for pharmaceutical and forensic applications.

Here we will provide an overview of the range of current research projects being undertaken within the School of Pharmacy and Biomolecular Sciences, which will hopefully pave the way for future collaborations.
Neighbouring Group Direction in Asymmetric Glycosylation – Developing a Sacrificial Protective Group to Deliver the 1,2 cis Glycoside

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Glycoconjugates are among the most structurally diverse and densely functionalised natural products. They play essential roles in biomolecular processes as varied as neuronal development through to tumour growth and metastasis.\(^1\) The synthesis of complex carbohydrates has therefore become an area of active research and the last twenty years has seen major advances in synthetic methodology from protective group chemistry and anomeric activators to novel glycoside construct-strategies.\(^2\)

Approaches to stereocontrol in glycosylation have included neighbouring group participation (NGP), solvent effects and anomeric equilibration.\(^3\) More recent contributions include Boons’ refinement\(^4\) of neighbouring-group participation, using thioethers to deliver α-selectivity. Disposable tethers and palladium catalysis have also been used to effect β selectivity in a limited range of substrates\(^5\) and Fairbanks has also used chiral Bronsted acids to induce a diastereoselective coupling.\(^6\)

Arguably however, NGP still remains the most reliable method of generating the ‘1,2-trans’ geometry. We propose to combine NGP with the concept of disposable tethers to generate a ‘sacrificial protective group’ to effect asymmetric glycosylation through a mechanism we are calling ‘neighbouring group direction’ (NGD). This approach will deliver the 1,2 cis geometry and will be complementary to current NGP methodology.

We will develop a hydroxyl protective group based on the acetonide motif, which is well known within protection methodology. Our original concept was based on the notion that this acetal could be cleaved under the same conditions as glycosylation.

\[
\text{Scheme 1}
\]

Thus treatment of donor 1 with excess NIS would lead initially to oxonium ion 2 which would react with acceptor 3 to give the temporary tethered compound 4. Under the reaction conditions, a second equivalent of NIS would now activate the anomeric pentenyl glycoside and the reaction will then follow the standard pathway for ‘tether controlled’ glycosylation to produce disaccharide 5 as a single anomer.

Novel Adrenergic Receptor Inhibitors as Potential Inhibitors of Cancer Metastasis.

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It is well known that survival rates of cancer patients decrease with metastasis formation. Laboratory cancer models^1^ reveal a biological role for the hormones epinephrine and norepinephrine in the stress-induced metastasis of breast, prostate and other cancers, mediated by adrenergic receptors. Epidemiological studies show a possible reduction in mortality in breast and prostate cancer patients coincidentally prescribed some types of beta-blockers.^2^ Furthermore, immunophenotyping studies^3^ suggest an association between tumour protein expression of beta and alpha adrenergic receptor subtypes and a poorer patient outcome. It is therefore hypothesised that blockers of these receptor types could improve survival outcome. Our research aims to explore this hypothesis through the design and synthesis of novel ligands which target appropriate alpha and beta adrenoceptors and to determine their effect on the inhibition of breast cancer. Approaches include the development of an in-house library as well as computer-aided design.

Synthesis of Novel Anti-malarials

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The current strategy for Malaria treatment involves Artemisinin based combination chemotherapies as a first line of treatment, this is to reduce the likelihood of resistance occurring.¹ However, due to resistance already being a prominent issue with antimalarial drugs there is a need for new antimalarial compounds that have novel modes of action. This research investigates structure-activity relationships of tetrahydro-β-carbolines, a class of compounds known for their biological activity against disease such as; antimicrobial, antiviral and anti-tumour compounds.² Our research into this area has been recently further validated by the inclusion of the related structure MMV008138 in a highlighted series of potential malaria leads by the medicine for malaria venture.³ MMV008138 displays several key features which have shown both potency and fast rate of kill against Plasmodium falciparum, attractive properties warranting further investigation.

![Chemical Structure of MMV008138](image)

Our initial synthetic strategy towards these molecules involves the use of stereocontrolled Pictet-Spengler reactions of derivatives of L-Tryptophan (Scheme 1). In this way, we have been able to prepare enantiopure versions of each of the possible stereoisomers for biological testing, the results of which will be incorporated into this presentation.

![Scheme 1: Pictet-Spengler reaction](image)

References
Exterior and interior modification of viral nanoparticles for tumour-targeting, dual functional detection and photodynamic therapy of tumours

Steven Y. Yap*, Graeme J. Stasiuk, David J. Evans, and Ross W. Boyle
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Photodynamic therapy (PDT) involves the administration of a photosensitising drug, which ideally will accumulate in tumorous tissues and upon irradiation of light, it will generate reactive oxygen species, inducing a toxic response to surrounding tissues, eventually culminating in cell death. Porphyrins are the molecules of choice due to their well-established photophysical properties and relative ease of synthesis and functionalization.

While PDT is a well-established cancer treatment technique, imaging using Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET) to locate and stage the tumour prior to treatment is still required. The combination of diagnostic and therapeutic modalities into a single entity is of particular interest and is a growing area of research¹, often referred to as theranostics. Not only will this approach negate the requirement for administering separate imaging agent and drug, for the case of PDT, which requires light activation in situ, the diagnostic modality of the drug will be able to provide information on the degree of accumulation in the target tissue, allowing optimal treatment of cancer.

In order to achieve this, capabilities for SPECT or PET, for pre-treatment imaging, and PDT for treatment of tumour will be incorporated into a single construct. Plant-derived viral nanoparticle (VNP) and their genome free counterpart, virus-like particles (VLP), have seen a growing interest as platforms for delivering large payloads of drugs². In this project cowpea mosaic virus (CPMV) are being functionalised internally with high affinity ligands for either $^{99m}$Tc (SPECT imaging radiotracer) or $^{68}$Ga (PET imaging radiotracer) and externally with porphyrins for PDT, to yield “next generation” theransotic agents for combined imaging and treatment of solid tumours.

Exterior surface of CPMV can be modified by lysine modification using N-hydroxysuccinimide (NHS) ester and carbodiimide-mediated amine coupling to solvent exposed carboxylates. Interior modification can be achieved via maleimide coupling to cysteine residues that are selectively expressed only on the interior surface.

1. Theranostics, 2012, 2, 916-966
2. Biomacromolecules, 2012, 13, 3990-4001
High levels of single and double diastereoselectivity via epimerisation of a furanyl ether on the tetrahydropyran scaffold.

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The tetrahydropyran moiety is seen in a number of biologically active and pharmaceutically interesting compounds and therefore stereoselective pathways that lead to their synthesis are of considerable interest.1 Previous work within the group has looked at utilising the rapid acid-catalysed epimerisation of furanyl ether chiral centres on conformationally well-defined scaffolds. This has been demonstrated in 2,6-disubstituted tetrahydropyrans,2,6-disubstituted piperidines,3 and also in spiroketals.4 In all cases high levels of stereocontrol were seen.

We have now investigated the stereoselective synthesis of 2,4-disubstituted and 2,4,5-trisubstituted tetrahydropyrans starting from ‘stereorandom’ precursors. In all cases we have seen high levels of stereocontrol, going from an approximately 1:1 ratio of the corresponding diol or triol starting materials to ratios exceeding 10:1 for the disubstituted tetrahydropyrans (see scheme 1) and ratios exceeding 15:1:0:0 for the trisubstituted tetrahydropyrans. This is presumably due to the rapid epimerisation of the furanyl chiral centre allowing the substituents to adopt the thermodynamically favoured equatorial position on a chair conformation.

Scheme 1

The trisubstituted tetrahydropyrans demonstrate very high levels of double diastereoselectivity (two of the four possible diastereoisomers are not observed at all). NMR data (including J-value analysis and NOESY/ROESY correlation) is consistent with our stereochemical assignment and this has been confirmed by x-ray diffraction on crystalline products. As the furanyl group is able to undergo a number of synthetically useful transformations (e.g. Diels Alder reaction, hydrogenation reactions, Achmatowicz oxidation,5 etc.) these reactions represent a highly useful stereoselective synthesis of this important moiety.

References:
Anion-Deficient Inorganic Compounds as Novel Materials for CO₂ Capture

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We propose to “turn something bad into something good” by exploiting gases harmful to the environment as reagents towards the preparation of innovative materials. Currently, flue gases such as CO₂ and SO₄ can be re-utilised to prepare construction materials like limestone and gypsum respectively. We aim to synthesize more complex, single-phase materials with advanced properties (e.g. magnetic, transport) and will achieve this by reacting appropriate classes of complex inorganic solids (oxides, nitrides, sulphides, halides) with gases such as CO₂, SO₄ and NO₃.

These gases will insert anionic groups into the starting materials ((CO₂)²⁻, (SO₄)²⁻ etc) changing their crystal structures and their properties and producing new inorganic materials (see for example, Figure 1). Crystal structure and physical properties of these new materials will be probed and compared to the same properties of the starting materials. A wealth of recent literature shows that anionic substitution/insertion in solids is acquiring a great deal of interest as it gives rise to interesting phenomena such as optical properties (pigments) and superconductivity. Our additional aim is to evaluate the suitability of these new materials to contribute to lowering flue gas emissions. The materials that will show gas insertion at a low temperature and pressure will have possible application in gas storage. Similarly, materials that will show gas de-insertion at low temperature and pressure will be of interest for usage as “catalysts” to provide the gas for practical uses.

Control of the temperature and pressure of the insertion and de-insertion of gases will be controlled at the synthesis stage, for example by using starting inorganic materials in the form of nanoparticles, functionalised nanoparticles and porous materials to react with the gases.

![Figure 1: The incorporation of CO₂ into the crystal structure of Sr₂CuO₃ produces Sr₂CuO₂(CO₃). The carbonate tetrahedral in Sr₂CuO₂(CO₃) are coloured in grey and red.](image)
Development and Synthesis of Molecules for Probing the Crosslinking of Proteins by the Dopamine Metabolite DOPAL

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Dopamine is oxidised via monoamine oxidase enzymes (MOA) to form the metabolite DOPAL. Oxidised sites on this metabolite are thought to crosslink alpha-synuclein proteins (fig 1) which are suspected of facilitating neuronal death in Parkinson's disease. Multiple derivatives of DOPAL will be synthesised, incorporating an acetylene tag, and then tested for protein crosslinking and aggregation. By reacting the acetylene group with an azide dye in a copper catalysed click chemistry reaction, visualisation of the crosslinking can occur using fluorescence microscopy. The results from these experiments will not only generate a better understanding of protein aggregation, but also provide scope for further research to develop ways of combatting the disease.

Fig 1: Potential crosslinking with lysine residues on alpha-synuclein proteins and DOPAL derivatives.
Elucidating the Structure of Povidone-Iodine - A Synthetic and DFT Study

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Povidone-Iodine (PVP-I2) is a widely used antiseptic solution applied topically for the prevention of post-operative wound infection. Produced by the complexation of polyvinylpyrrolidone and iodine and sold under the name Betadine, it finds preferential use over other iodine solutions owing to reduced toxicity and irritation.

The structure of PVP-I₂ has been accepted and widely cited for over 35 years. However, from our recent investigations we have highlighted issues with the accepted structure. The work herein attempts to better elucidate the structure of PVP-I₂ through synthetic and computational analysis.
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