Heterogeneous Catalysis and Industrial Chemistry
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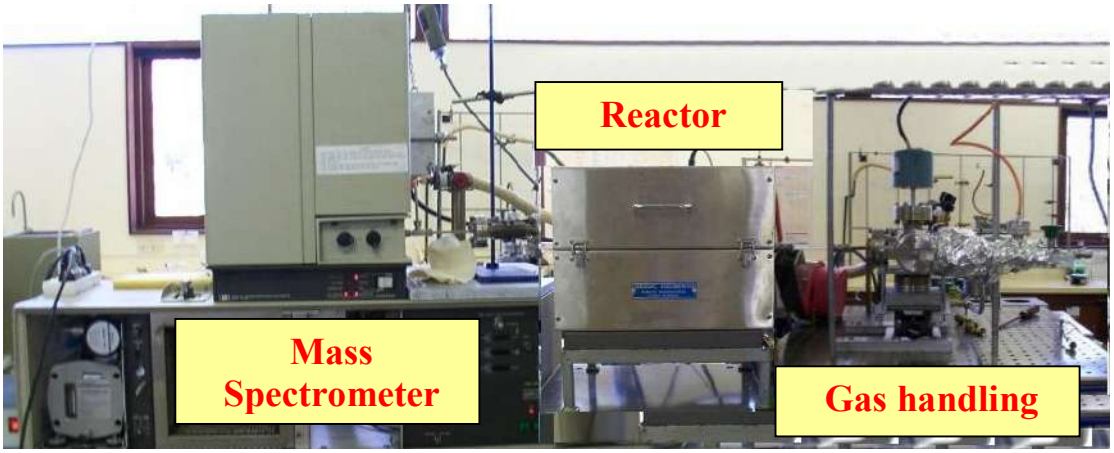
Kinetics of Heterogeneous Catalytic Reactions at Low Pressures

The major project to be undertaken in 2015 is the investigation of the catalytic oxidative dehydrogenation of isobutane to methyl methacrylate. We have designed and constructed a powerful technique for determining the kinetics of gas/solid catalytic reactions. The new technique involves monitoring the reactants, products and rates of catalyzed reactions at low pressures, with a quadrupole mass spectrometer. Investigations into acidic dehydrogenation and cracking of isobutane over zeolites and preliminary investigations of the oxidative dehydrogenation of isobutane over various metal oxides have been undertaken. For example,

$$CH(CH_3)_3 \xrightarrow{HZSM-5} H_2C=C(CH_3)_2 + H_2$$

$$CH(CH_3)_3 \xrightarrow{HZSM-5} H_2C=CH(CH_3) + CH_4$$

$$CH(CH_3)_3 \xrightarrow{3O} H_2C=C(CH_3)(CHO) + 2H_2O$$



Low-pressure reaction system for determining catalytic reaction kinetics

All catalytic reaction systems that we investigate are key industrial processes. The kinetic results allow an optimization of the catalysts and the conditions for maximum yield of required products.

During these projects skills will be acquired in the development and utilization of a broad range of experimental techniques. Such techniques include computer data control, acquisition and analysis, high temperature, gas flow and vacuum line methods, as well as a variety of characterization methods.

Free-Radical Polymerisation and its Applications

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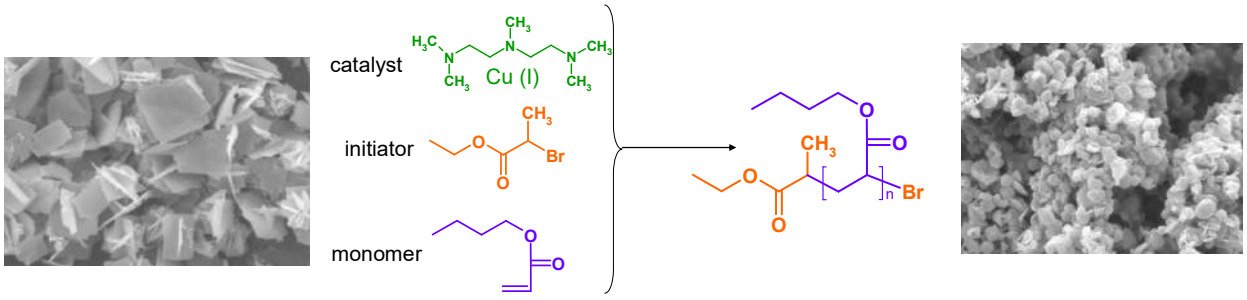
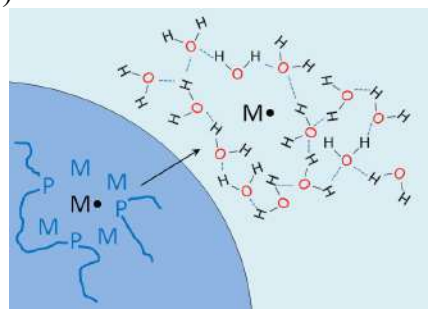
My main interests are in the fundamental mechanisms and kinetics of free-radical polymerisation, a reaction that has revolutionised the modern world. This field continues to be an inexhaustible source of new applications and exciting chemical problems.

Novel Polymers for Inhibition of Scale Formation (e.g., Al-Hamzah *et al*., *Industrial and Engineering Chemistry Research*, 53(21), 8793–8803 (2014))
Poly(electrolytes) such as poly(acrylic acid) are often used for inhibiting the formation of scale in various industrial applications where water is boiled. For example, precipitation of calcium oxalate (a common scale-forming mineral in sugar mills) is significantly delayed by addition of low molecular weight poly(acrylic acid), and the degree of effectiveness is sensitively dependent on both the molecular weight of the polymer and the end-group functionality of the polymer. This project will involve the preparation of new polymers of defined length and end-group functionality using Reversible Addition Fragmentation Chain Transfer Polymerisation and/or Atom Transfer Radical Polymerisation, then testing these polymers for effectiveness in inhibiting the formation of various scale-forming minerals under various conditions. This work will be carried out in collaboration with Dr Bill Doherty of the Queensland University of Technology and Dr Ali Al-Hamzah of the Saline Water Conversion Coroporation.



Exit Mechanisms in Emulsion Polymerisation (e.g., Fellows, Murison and Russell, *Macromolecular Theory and Simulations*, 20(6), 425-432 (2011)



In emulsion polymerisation, blobs of polymer and monomer tens or hundreds of nanometres across act as ‘minireactors’, and the kinetics of polymerisation is controlled by the rate of entry and exit of radicals from the aqueous phase to initiate and terminate polymerisation. While the mechanism of entry is well understood, there are two contradictory mechanisms for how exit is controlled. It has recently been suggested that an activation barrier to exit may arise from the need to structure water around an exiting hydrophobe and that the size of this barrier will depend on whether structure-breaking or structure-making solutes are present on the surface of the polymer particles. Thus determination of exit data for identical particles with different surfactants should provide conclusive evidence for this mechanism. The project will involve collaboration with A/Prof Greg Russell of the University of Canterbury, New Zealand, researchers at the Key Centre for Polymers and Colloids at the University of Sydney, and the Australian Nuclear science and Technology Organisation.

Pharmaceutical Chemistry

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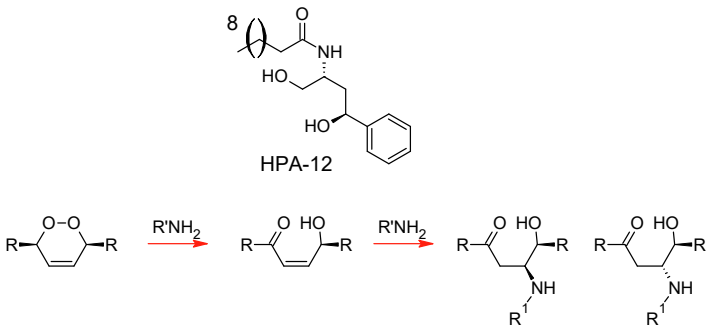
My research interests include synthetic organic chemistry, natural products chemistry and developing quantitative structure activity relationships to aid in the development of human therapeutics. Current synthetic targets include a series of naturally occurring glycosides with potent antiviral and immune stimulating activity. The goal of this research is to develop novel ways to construct complex carbohydrate containing molecules which will allow for the development of analogues which may display better activity and lower toxicity. The total synthesis of these molecules should help to develop new ways to construct glycosidic linkages and may yield new leads in the treatment of disease. I am also interested in the chemical and biological characterisation of triterpene and steroidal glycosides (saponins) in Australian native plant species. This class of compounds can have diverse biological activities such as calcium channel specificity, anti-bacterial, anti-fungal and immune stimulatory activity. We are currently engaged in the isolation of these molecules and they will be screened through collaboration and commercial agreements.

The synthesis of HPA-12, a small molecule inhibitor of ceramide transport protein which inhibits the hepatitis-C virus.

The aim of this project is to develop a new method to synthesise the molecule (1*R*,3*S*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecamide (commonly known as HPA-12), which is a potent binder of the CERT protein which mediates the transport of ceramide to the Golgi apparatus.[1] HPA-12 was recently identified as a sphingomyelin synthesis inhibitor in mammalian cells and HPA-12 has been shown to inhibit the replication of some forms of the hepatitis C virus by limiting sphingomyelin content in the viral structure.[2] The synthesis of HPA-12, will be made using a newly discovered transformation of 1,2-dioxines promoted by primary and secondary amines made here at UNE, Scheme 1. The reaction involves a Kornblum-DeLaMare reaction in tandem with an Aza-Michael reaction giving 4-hydroxy-3-aminoketones in a one-pot procedure. This exciting new chemistry will allow us to make derivatives of the lead compound that may show higher affinity or different selectivity towards the transport protein.



Scheme 1. HPA-12 and the new amine promoted transformation of 1,2-dioxines.

The synthesis of CP05, a natural product saponins from *Calliandra Pulcherrima.*

The biological properties of the class of complex secondary metabolites known as saponins are well known. These compounds have unique potential in treating and preventing human disease in prophylactic vaccination, therapeutic vaccination and as chemotherapeutics in their own right. The carbohydrate portions of saponins make them ideal for influencing cellular events through carbohydrate recognition proteins such as DC-SIGN and the TOLL like receptors.

The aim of this project is to work towards the total synthesis of the complex saponin adjuvant CP05 which was isolated from the South American plant Calliandra Pulcherrima. This molecule is known to have potent immune stimulating effects yet little is understood about the structural features of the molecule that lead to the observed activity.

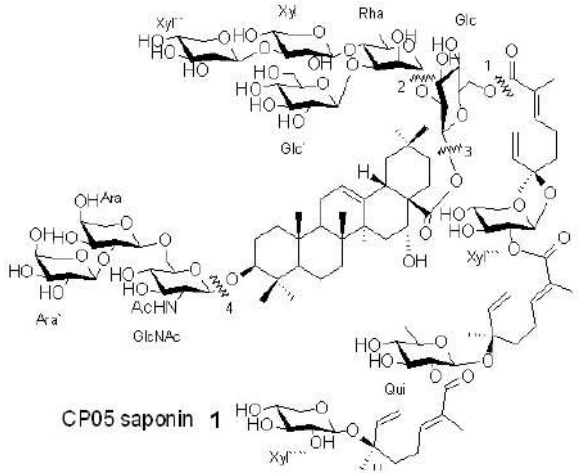


Figure 1. The saponin adjuvant CP05 showing the triterpene core and appended carbohydrates.

The students involved in these projects, in addition to the problem solving skills will gain important skills such as NMR structure assignment, synthetic design, reverse phase HPLC and the purification of organic compounds. They will be exposed to a variety of reactions which will assist them as they move towards a PhD or to find employment in the chemical industry.

Macrocyclic and Applied Chemistry

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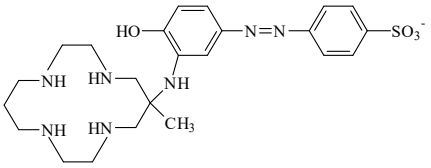
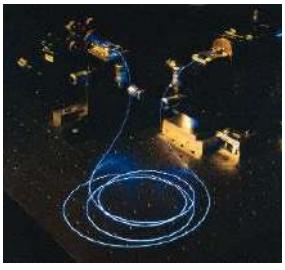
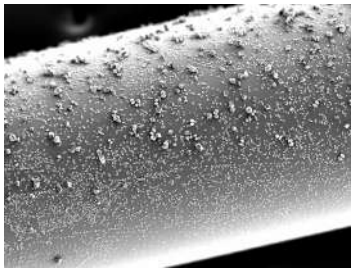
My broad area of research interest covers macrocyclic chemistry, with particular emphasis on the formation kinetics and thermodynamics of macrocyclic complexes, and the use of optical fibres for chemical sensing application. The following are areas of specific interest:



Macrocyclic chemistry & chemical sensors: Due to environmental and industrial applications there has been a surge in interest in the development of chemical sensors with optical detection. In optical sensors the concentration dependent signal is a direct result of the interaction of the carrier/receptor molecule (ligand) with cation or anion to be analysed. This can be achieved by using a ligand with a chromogenic group (intensely coloured) attached and close to the coordination site of the target molecule. The synthesis of macrocyclic ligands with pendant azo arms (such as that shown) is currently under investigation. Projects available include, macrocycle synthesis and characterization, the determination of binding constants and rates of complexation of macrocycles with a range of metal ions and the investigation of macrocycles with pendant fluorophores i.e fluorescent sensor, or appended macrocycles able to intercalate with DNA. Collaborative projects within and outside of Chemistry are possible.



Optical fibre sensors: Light rays, introduced into one end of an optical fibre, travel down the core *via* numerous total-internal reflections at the core cladding interface. If the cladding has been removed and the core immersed in a liquid medium, light can penetrate some distance into the sample. This is known as the *evanescent field*. The interaction between the evanescent field can take to different forms. The first involves the process of optical absorption, and results in attenuation of the intensity of the radiation along the fibre. The reduction in intensity may be measured and related to the concentration of the coloured species in contact with the fibre core in the same way as traditional optical absorption measurements. Secondly if crystals form on the fibre surface (scale formation, see picture) light can be lost from the fibre due to refraction. Projects are available investigating the use of fibre sensors to measure the anthocyanin content of red wine grapes and to monitor scale development. These projects may involve collaboration with A/Prof. David Lamb from Physics



Environmental Chemistry: The focus of projects in this area includes investigating contamination of soils with copper, arsenic and antimony and studying the bioavailability of these contaminants. Further projects investigating the adsorption of metal cyanide complexes to clays are also available. These projects may involve collaboration with Dr Susan Wilson from Soil Science.

Molecular Dynamics Simulations of Chemical and Biological Systems

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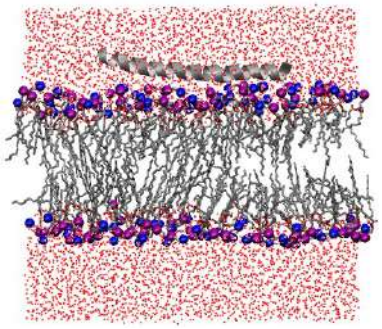
My research interest is in using computer simulation techniques to assist in the generation new hypotheses and models, and also in using computational methods for the analysis of experimental and simulated data. Computer simulation provides a direct route from microscopic details of a system to macroscopic properties and with the advent of more powerful and cheaper computing, the use of molecular simulation to gain atomic level understanding of important systems is rapidly increasing. Projects in this area will develop skills in molecular dynamics simulations, scientific programming, data analysis, high-performance parallel computing and applied statistical mechanics. Projects can focus on biological, chemical or materials problems wand typically focus on molecular behaviour at interfaces. Areas of specific interest are as follows:

Concentration Dependence of Partitioning of Hydrophilic Monomers in Aqueous Solution

The application of pulsed-laser polymerization size-exclusion chromatography (PLP-SEC) has made it possible to unambiguously determine propagation rate coefficients (k_p) in radical polymerization in a single experiment. Accurate Arrhenius parameters are now available for a wide range of monomers, where previously great uncertainty prevailed even for very common commodity monomers. While propagation rate coefficients are largely insensitive to solvent effects and to monomer concentration, water is a significant exception, and current models do not fit the experimental data. We hypothesise that partitioning arises for these monomers, although they are water soluble and have little interfacial interactivity, due to the robust ice-like structure of liquid water and that, prior to the total disruption of the water structure by dissolved monomer, aqueous solutions are effectively heterogeneous on the propagation timescale, with polymer and monomer excluded from regions where water displays medium range order (and restricted to regions of disordered water) at a much higher effective concentration for polymerisation. In this project, molecular dynamics simulations are used to study the extent of water structure disruption and the extent of clustering of monomer molecules in water/monomer mixtures and show that the trends obtained are consistent with experimental observations. This project is done in collaboration with Associate Professor Chris Fellows.

Stabilization and Disruption of Phospholipid Membranes by Antifreeze and Antimicrobial Peptides

Both these classes of peptides can disrupt and/or stabilize cell membranes; however the molecular mechanisms are not understood. A detailed molecular understanding of the interactions of these peptides with phospholipid membranes will give insight to their activity, ultimately allowing the engineering of "designer" peptides to target organisms for specific outcomes. Applications are cell preservation; agriculture and medicine, and cell destruction, most notably the use of antimicrobial peptides as novel therapeutic agents. This project would be done in collaboration with computational scientists at Duquesne University in the USA.



Specificity of the Adsorption/Desorption Behaviour of Polymers onto Crystal Faces

Inform the design of compounds to stop scale from forming in industrial systems which imposes costs of billions of dollars on the chemical and food industries. These projects would be done in collaboration with Associate Professor Chris Fellows.

Elucidating Cancer Signalling Pathways

The interaction of hypothesized clusters of phospholipids contained in cell membranes with a protein called profilin has been implicated in cancer signaling pathways. We are interested to know if the phospholipids aggregate and then sequester the profilin to the membrane, or does the binding of the profilin to the membrane cause the lipid aggregation. This project would be done in collaboration with researchers in Human Biology and Physiology at UNE.

Synthetic Inorganic and Organic Chemistry

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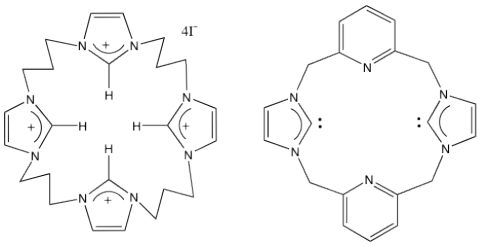
My research interests include synthetic inorganic and organic chemistry, specifically the development of transition metal based imaging agents for oxidative stress and the synthesis of fluorescent- and profluorescent-labelled drugs and the development of dual-acting drugs.

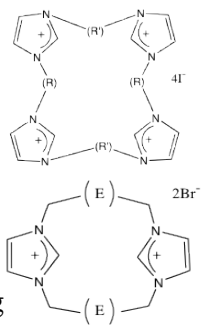
The design and synthesis of metal complexes for in-vivo detection of inflammatory based diseases.

Transition metal complexes have a vast array of applications from catalysis, sensors and optoelectronics to therapeutic compounds and medical imaging agents. The properties of these compounds are to a significant extent controlled by the ligands that complex the metal, and alterations to the ligand framework can impart considerable changes on the properties of the resulting metal complexes. As such, understanding the relationships between ligand features such as donor atoms, flexibility, substituent groups and (for macrocycles) cavity size with properties such as coordination geometry, redox potential and solubility are integral to designing a compound with specific properties. This project aims to delineate these relationships for the novel macrocyclic poly N-heterocyclic carbene (NHC) and mixed NHC-heteroatom donor ligands.



This knowledge will allow us to make informed decisions in the design of metal complexes that can be used in the detection of inflammatory based diseases in vivo. Inflammation involves the production of oxidants, excessive or inappropriate production of which results in damage to host tissue and is implicated in the pathology of numerous diseases. Using the knowledge gained in the early stages of the project complexes to design complexes that will interact with biologically relevant oxidants causing a change that will result in them being localised in afflicted tissues.

Specific projects available include:

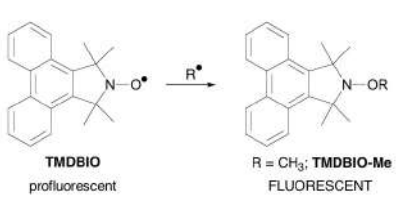


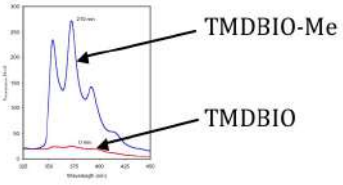
- Synthesis of novel macrocyclic polyNHC ligands of various ring size and their complexes with transition metals – examination of the effects of altering ring size on coordination geometry, oxidation state and redox potential.

- Synthesis of mixed NHC and heteroatom donor macrocyclic ligands and their complexes with transition metals - examination of the effects of altering donor atoms on coordination geometry, oxidation state and redox potential.

The development of profluorescent nitroxide labelled therapeutic compounds to detect oxidative stress associated with specific diseases.

Oxidative stress, which includes free radicals, is implicated in the pathology of a number of important diseases. We are applying technology developed for the detection of free radicals generated during polymer degradation to detect oxidative stress associated with disease. Profluorescent nitroxides consist of a fluorophore covalently linked to a stable nitroxide radical. Nitroxide radicals have two properties which are exploited in this research, their ability to quench fluorescence and their rapid reaction with free radicals.



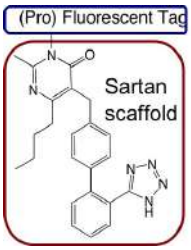


Profluorescent nitroxides used to monitor polymer degradation

A.S. Micallef; JP Blinco; GA George; DA. Reid et al. *Polym. Degrad. Stab.* **2005,** *89*, 427-435

By attaching a nitroxide to our fluorescently labelled sartans, these compounds become probes in which the fluorescence is 'switched on' in the presence of free radicals allowing us to correlate receptor distribution with oxidative stress.

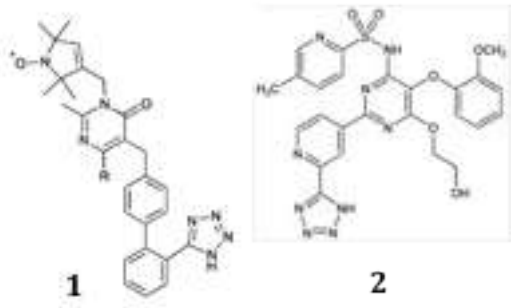
Specific projects available include:



- Synthesis of novel low molecular weight fluorophores with functionalities that will enable coupling both to a drug scaffold and to a stable nitroxide radical compound. Optimisation to control absorption and emission wavelengths, optimisation of synthetic routes. Synthesis and characterisation of drug analogues labelled with these profluorescent probes.

Development of Dual-acting drugs

The design of multi-potent drugs acting at multiple targets is an emerging area, as highlighted by the increasing number of publications and patents in this topic. A number of dual-acting drugs are now available, including Carvedilol and Celeprolol. Although a combination of selective drugs can be employed, multiple drugs can take advantage of physiological/cellular processes to alter efficacy of individual drugs for therapeutic advantage and improved patient compliance



As an Associate Investigator in the ARC Centre of Excellence for Free Radical Chemistry and Biotechnology, a recent project that I have been involved in was the development of dual-acting anti-hypertensive drugs. This project involved the incorporation of a nitroxide (anti-oxidant) into the structure of sartans (antihypertensives) eg **(1)** with promising results leading to a patent application. We now wish to pursue the incorporation of antioxidant nitroxide moieties into other drug scaffolds, specifically the Endothelin receptor (ET) antagonists.

The ETa antagonist Clazosentan **(2)** recently reached phase II clinical trials for the treatment of subarachnoid hemorrhage (SAH). However, although these compounds had a beneficial effect on vasospasm the functional outcome was not improved as much as anticipated. It has been proposed that this is due to the fact that it is not only vasospasm that effects the clinical outcome but also other factors such as oxidative stress. As such incorporating an antioxidant into the ET receptor antagonist could decrease vasospasm whilst delivering antioxidants to the sites where they are needed; combating both factors simultaneously should prove beneficial in the treatment of SAH.

This project will involve the multistep organic synthesis and characterization of nitroxide substituted selective ETa receptor antagonists, and would involve determining substitution positions that will not significantly affect the ability of the compound to bind the receptor. Through collaboration with A/Prof Ziogas (ARC Centre of Excellence for Free Radical Chemistry and Biotechnology, The University of Melbourne) compounds synthesised will be tested for receptor antagonist abilities and antioxidant capabilities.

Supramolecular Chemistry and Self-assembly.

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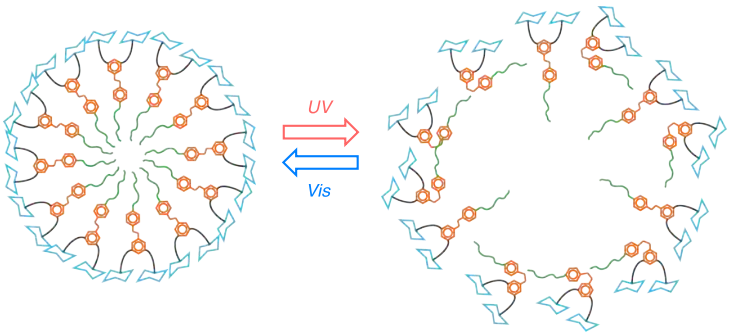
Our group works at the interface of organic synthesis, bioorganic chemistry and physical chemistry. We focus on supramolecular self-assembly processes in water to derive advanced soft materials with potential biomedical applications.

- 1D self-assembly of carbohydrate- and glycopeptide-functionalized perylene bisimide dyes.
- Dynamic covalent chemistry and molecular evolution.
- Self-assembled glycodendrimers and their biomedical applications – drug delivery, vaccines, and bacterial anti-adhesives.

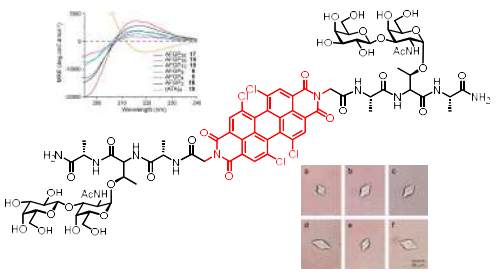
Photocontrollable Janus glycodendrimers



Multivalent carbohydrates are ubiquitous in nature and are essential mediators of biological processes including microbial infection, inflammation, fertilization, immune regulation and cancer. In this project you will synthesize and characterize a family of self-assembled, light-responsive nanomaterials that mimic natural carbohydrate-protein binding events, with a view of designing new probes and therapies for bacterial infection and cancer. Using a modular approach, a library of amphiphilic glycodendrons incorporating a variable carbohydrate head group(s) appended to a hydrophobic, light-responsive azobenzene core will be synthesised. This will generate structurally diverse self-assembled structures with tuneable physical properties and bioactivities (micelles, vesicles and liquid crystals). These will be assessed as inhibitors of carbohydrate binding proteins implicated in disease processes, including cancer (Gal-1 and -3) and microbial infection (LecA and LecB from *P. aeruginosa*). This project is in collaboration with Dr Rico Tabor (Monash), Chris Garvey (ANSTO) and Alexander Titz (Heilmholz, Germany).

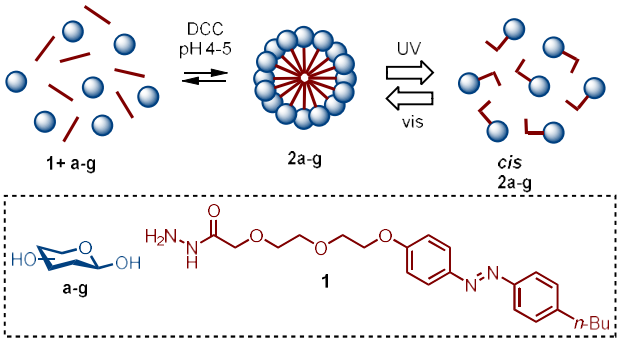
1D Self-assembled glycopeptide antifreeze agents

Cryopreservation is an important biomedical technique that employs sub-zero temperatures for the long term storage of tissues and cells, thus protecting them from damage from biochemical insult and ageing. Despite decades of research, cryopreservation is currently limited to a small number of cells and tissues, largely due to the toxicity and lack of effectiveness of the



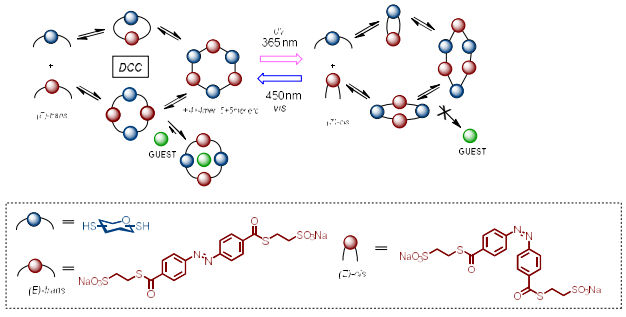
cryoprotectants used. In this project, you will design and synthesize a new class of carbohydrate-based cryoprotectant, including per-fluorinated alkyl glycosides and self-assembled perylene bisimide dyes (pictured). The ice recrystallization inhibition (IRI) activity and cytotoxicity of these novel compounds will be evaluated, along with cell permeation and phase simulation of the synthesized molecules, in collaboration with Profs. Rob Ben (Ottawa), Gary Bryant (RMIT) and Peter Daivis (RMIT). Promising compounds will be further screened for their ability to protect RBCs and stem cells during freezing and thawing cycles of cryopreservation. It is anticipated that this project will help shape future rational design efforts for the development of new cryoprotectants for medicine, veterinary and medical research, and the long term preservation of endangered plants and animals.

Dynamic carbohydrate surfactants



Carbohydrate-based surfactants (CBS) have found widespread industrial use and are readily obtained from renewable resources. They are attractive alternatives to surfactants from petrochemical origin owing to the clinical mildness and biocompatibility, as well as favourable physicochemical properties. In this project, you will develop a high-throughput synthetic strategy for deriving a new class of dual pH- and light-responsive carbohydrate based surfactant in water. You will employ reversible covalent bond forming reactions (S-S, C=N) in water under mild pH coupled with azobenzene *trans-cis* photoisomerization to independently modulate interfacial activity and self-assembly. This project will establish important structure-function relationships for the discovery of responsive, biocompatible soft materials including surfactants, hydrogels and liquid crystals with potential biomedical and nanotechnology applications (e.g. drug delivery, tissue engineering and wound repair, and bacterial antiadhesives). This project is in collaboration with Rico Tabor (Monash) and Chris Garvey (ANSTO).

Templated synthesis of Dynamic carbohydrate macrocycles



Carbohydrate macrocycles have been used extensively in industry and in bio- and nanotechnology research as drug carriers, excipients and building blocks for advanced biocompatible materials. The demand for new water-soluble macrocycles has risen dramatically in recent years, yet access to new macrocycles with tailored properties is hampered by difficulties associated with the synthetic modification of naturally occurring CD hosts, as well as the isolation of pure materials from natural sources. In this project you will develop a new high-throughput synthetic strategy for rapidly accessing new and unusual carbohydrate macrocycles with pH- and light-addressable properties in water. You will synthesize modified carbohydrate building blocks that will undergo reversible cyclooligomerization in water at near neutral pH in the presence of a 'guest' template. These responsive chemical systems are anticipated to find broad application in diverse research fields, including drug delivery, biomimetic chemistry, catalysis, and as tools for controlling the self-assembly of hydrogels.