NZIC Chemistry IN NEW ZEALAND

Volume 74, No.2, April 2010

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New Zealand Institute of Chemistry

supporting chemical sciences

April News

Comment from the President

In my first column, I mentioned that one of the goals of the NZIC is to raise the profile of chemistry in New Zealand. One way of doing this is through prizes and awards. This is the time of year to start thinking about nominating your NZIC colleagues, not only for the NZIC prizes but for the various medals and prizes from the RSNZ and NZ Association of Scientists, and so on. The grand prize, if you like, is the Rutherford Medal and the recipients of this award comprise some of the best scientists this country has produced. Whilst marvelling at the glittering line-up of speakers at the excellent Rutherford symposium held during the NZIC Conference in Dunedin (Dec. 2008), I made a quick mental note of the disciplines that each medallist represented, there were physicists, mathematicians, statisticians, engineers, biochemists, physiologists, soil scientists, and more. Chemistry was well represented with Bill Denny, Alan MacDiarmid, Ted Baker, and George Petersen representing biochemistry. A chemist being awarded the Rutherford Medal in 2010 would be the ideal way to kick start the International Year of Chemistry in 2011 … and another in 2011 would nicely round it off!

I had the pleasure of attending the launch of SCENZ-IChemE (Society of Chemical Engineers in New Zealand - Institute of Chemical Engineers), in Wellington on February 19. SCENZ itself began 38 years ago and currently has around 300 members and has now joined the Institute of Chemical Engineers, which has its headquarters in the UK but has branches worldwide. There are obvious synergies between the NZIC and SCENZ-IChemE and I would encourage members to visit the SCENZ-IChemE website for more information and read Max Kennedy's contribution below.

The Chemical Education group had a very successful meeting on February 4th in Wellington. The purpose of the meeting was to exchange ideas and innovations primarily related to 100-level chemistry teaching. Suzanne Boniface did an excellent job of organising the day and we had two very informative keynote talks from Danny Bedgood (Charles Sturt University) on facilitating active learning in large classrooms and Gwen Laurie (University of Queensland) on fostering learning communities in large chemistry cohorts – further details appear later in the News.

The NZIC Council met on March 12 with the major goal of framing our plans for International Year of Chemistry. Council will perform a co-ordinating role between the Branches for IYC 2011 and we are already working with the RSNZ and the MacDiarmid Institute on some high profile media events. I look forward to discussing plans for IYC with you when I visit the Branches between March and July.

Mark Waterland
President

Society of Chemical Engineers in New Zealand

Chemical Engineers / Launch IChemE in NZ

IChemE, the international professional membership organization for chemical engineers, launched its NZ Branch in February. A keynote speaker at the Wellington event was IChemE CEO, *David* ***Brown*** who addressed *the changing face of chemical and process engineering into the 21st century – global impacts and within NZ*. Brown spoke alongside other keynote speakers: Hugh Waters (Process Support Manager, Fonterra), John Chen (Auckland University) and Peter Gostomski (Head, Chemical and Process Engineering, Canterbury University).

The launch of the new group followed a November vote where members of the Society of Chemical Engineering NZ (SCENZ) voted to become the IChemE NZ Branch. Chair of the board, *Max* ***Kennedy*** says the move will benefit the country's chemical engineers: *The member vote provides the Board the mandate to develop IChemE in NZ and to enhance the networks and profile of chemical and process engineering in NZ*. Brown told delegates at the event: *IChemE is 100% committed both to the support of the New Zealand chemical and process engineering community and to contribute to the wider promotion of the engineering profession alongside leading national bodies such as the Institution of Professional Engineers (IPENZ). The new Branch will help chemical engineers in New Zealand connect with other chemical engineers and share their own knowledge and experience with a wider group*, said Brown.

IChemE in NZ members will benefit from a programme of continuing professional development, technical meetings and events, designed to enhance networks across the country, and encourage collaboration with other related organizations. More details of the NZ activities can be found at *www.icheme.org/newzealand*

NZIC NEWS

Dr *Julian* ***Eaton-Rye*** of the Otago Branch has been appointed 2nd Vice-President effective immediately.

NZIC AWARDS

Nominations for the following 2010 awards are now sought:

Fonterra Prize for Applied and Industrial Chemistry,

Maurice Wilkins Prize for Chemical Research,

ABA Books Denis Hogan Chemical Education Award.

The closing date with the NZIC Secretariat is 30 June 2009. Details and method of nomination/application can be found at *www.nzic.org.nz*

MEMBERSHIP MATTERS

FNZIC

At its March meeting, Council elected Dr *John* ***Birch*** (Department of Food Science, Otago University and Otago Branch Chairman), Dr *Adrian* ***Jull*** (Manawatu) and Dr *Michael* ***Mucalo***, (Waikato University) to the Fellowship.

MNZIC

We welcome to the Institute the following as new members:

Dr *Kirsten* ***Edgar*** (Wellington), A/Prof *Antony* ***Fairbanks*** (Canterbury), Mr *Martin* ***Gower*** (Otago), Dr *Graham* ***Saunders*** and Dr *Larry* ***Manuel*** (Waikato).

Student Members

We welcome the following new student members to the Institute:

Katherine ***Baer Jones***, *Hugh* ***Doyle***, *Peter* ***Mabbitt***, *Rajni* ***Sanyal*** and *Pourya* ***Shahpoury*** (Otago); *Nicola Jean* ***Blackmore***, *Jayne* ***Gulbransen***, *Ida* ***Nuramdhani***, *Sebastian* ***Reichau***, and *Chris* ***Saunders*** (Canterbury); *Martin* ***Heeley*** (Wellington); *Simon* ***Williams*** (Waikato); *Orla* ***Finch*** and *Katrin* ***Schuenemann*** (Auckland).

International Year of Chemistry

2011 is to be the UNESCO ***International Year of Chemistry***, *Our Life – Our Future* in partnership with IUPAC. NZIC Council was unable to award its $500 prize for best IYC idea to one individual. Instead, the prize is split ($100 each) to *Alec le* ***Gros***, *Peter* ***Hodder***, *Max* ***Kennedy***, *Rob* ***Keyzers***, and the ***Wellington*** *Branch Committee* all of Wellington, for their ideas, all of which included chemistry and art in some form or other. There is to be a photo competition in various forms, a 2011 calendar and t-shirts. Details will appear in the July issue.

Chemistry Education Specialist Group

The first of a number of activities organised by the Education Specialist Group was held in Wellington in February this year. Following a successful gathering of tertiary chemistry educators in 2009, a second teaching symposium was hosted by VUWs School of Chemical and Physical Sciences last February. Two keynote speakers were invited from Australia. Dr *Danny* ***Bedgood*** (Charles Sturt University) is the lead researcher for a project funded by the Australian Higher Education Teaching Council to promote active learning in university science. His talk highlighted the benefits of active learning including higher achievement and greater motivation on the part of the students, more frequent higher-level reasoning and deeper-level understanding and critical thinking, more positive attitudes toward subject areas and learning, and increased retention and greater ability to view situations from others' perspectives. A range of possible active learning techniques were discussed and modelled with the emphasis placed on students learning from each other in small groups. Dr *Gwen* ***Lawrie*** (University of Queensland) focused attention on the often diverse nature of a first year chemistry cohort. Her talk presented changes to first year courses at UQ, made to address this diversity while attempting to increase student engagement and enhance academic outcomes. The emphasis was the incorporation of collaborative and active learning strategies. These talks were followed by a forum where new initiatives in first year tertiary chemistry courses in NZ were shared and discussed.

The Australian project to promote active learning in university science classes provides a number of professional development opportunities for their lead teachers. One of their trainers is *Rick* ***Moog***, a project director for the *Project Orientated Guided Inquiry Learning* (POGIL) *Project* in the US. POGIL methodology is designed to promote greater student involvement and engage students more in their learning. Rick travelled to Australia in April and the NZIC Education Group organised for him to visit NZ where he ran workshops in Auckland, Wellington and Christchurch for both university and secondary school chemistry teachers**.** As a result, we hope to build resources using this methodology to match the NZ Curriculum.

The other major 2010 initiative of the Education Group is a series of workshops run throughout the country for secondary school teachers. *Peter* ***Hollamby*** (Cardiff University) was a popular speaker at ChemEd09 and he offered to return to NZ and run workshops on *Improving Teaching and Learning Chemistry using ICT* based upon those that he has run in the UK. The aim is to give teachers the tools to develop basic skills so that they can create their own high quality teaching resources. While there is a plethora of software available to help teachers with animations and visualisation to bring greater understanding to their chemistry classrooms, there is evidence that many find it difficult to assimilate all the available support material. In fact, the very presence of so much material can be counter-productive; some teachers resorting to *chalk and talk* rather than ploughing through the e-learning mountain. The workshops are designed to give teachers confidence to develop good lessons supported by IT. These are to take place as per:

Auckland	Apr. 19
North Shore	Apr. 22
Hamilton	Apr. 27
Tauranga	Apr. 29
Palmerston North	May 4
Wellington	May 6
Christchurch	May 12
Dunedin	May 14

Those interested are asked to contact *Suzanne* ***Boniface*** by email: *suzanne.boniface@vuw.ac.nz*

BRANCH NEWS

AUCKLAND

Massey University-Albany

Two NZIC Branch meetings have been hosted by the Chemists at Massey. The first of these was Prof *H.W.* ***Gaggeler***

(Bern, Switzerland) who gave the December '09 talk entitled *On the way to quantify human impact on climate: pollution records and climatic information from alpine ice cores*. This was followed by an address given in January by Prof *H.* ***Schwarz*** (Technische Universität Berlin, and President, Alexander von Humboldt Foundation) Both meetings were hosted by Prof *Peter* ***Schwerdtfeger*** (Massey-Albany). Prof Schwarz covered a range of scientific developments associated with *Gas-Phase Catalysis by Atomic and Cluster Metal Ions: The Ultimate Single-Site Catalysts*, and demonstrated how fundamental scientific investigations can lead to important practical applications, illustrated here in the area of gas phase catalysis.

University of Auckland

The 2009 year ended for with the Chemistry Department with a shift of the end of year party to the Fale Pasifika, a centre of excellence for Pacific research with a large traditional Pacific Fale meeting space. The fine feast provided was a fitting way to end the year, before a quiet close-down period.

For chemistry staff involved in summer school teaching, Jan 5 marked the first day of lectures for the stage one general education paper entitled, *Molecules that Changed the World*. When introduced a few years ago, this paper attracted a moderate number of students, but this year numbers reached 200 students, many from non-Science majors, taking valuable time away from the beach or holiday work to get further ahead with their studies. The molecules covered in 2010 were polyethylene (*Neil* ***Edmonds***), nylon (*Jadranka* ***Travas-Sejdic***), penicillin (*Viji* ***Sarojini***) and ethanol (*Paul* ***Kilmartin***), and various social and environmental issues featured in the assessment of the role of these chemicals in modern society. In the first semester Chemistry courses that will be underway when this is published, numbers appear to be up again, putting added pressure on laboratory space for teaching. The basement and 2nd floor areas have also been active building sites, with the creation of space for the XRD facilities, installation of a new 400 MHz NMR instrument, and refurbishment of A/Prof *Bob* ***Anderson***'s accelerator lab; temporary lab space has also been provided on the 2nd floor for Pharmacy research students in need of a home while their own buildings are refurbished.

Chemistry staff featured well in the inaugural Faculty General Staff Awards: *Cathy* ***Comber*** – Quality Performance in Leadership; *Mike* ***Wadsworth*** – Quality Performance in Communication; *Shane* ***Crump*** - Professional Development Award. As a way to usher in the new work year, Cathy Comber was instrumental in organizing a day of rest and recreation for the Chemistry staff and a day trip to Waiheke Island on February 17. The visit included a tour of the Fossil Bay vineyard leased by the University for the Wine Science programme, a visit to Goldwater Estate Winery, and lunch at Vino Vino.

Randy ***Weaver*** pours some of the Department's 2008 *Ingenio* Chardonnay to Chemistry staff visiting Waiheke Island's Fossil Bay vineyard on.

Seminars given in the two months prior to copy deadline have been few, but they have included Prof *Sheila* ***MacNeil*** (Sheffield) talking on *Polymers for Tissue Engineering and Regenerative Medicine,* and some remarkable approaches in the development of biomaterials to support the healing of scarred and burnt tissue; Prof *Cedric* ***Hassall*** (one time Research Director, Hoffman la Roche) on *Experiences in University and Industrial Research on Medicinal Chemistry*; Prof. *F. Ekkehardt* ***Hahn*** (Münster) on *Macrocyclic and Supramolecular Chemistry with Poly-NHC Ligands*.

CANTERBURY

The Branch congratulates Dr *Sally* ***Gaw*** on her appointment to the Ministry of Research, Science and Technology (MoRST) Scanning Network. This is part of MoRST's Futurewatch programme, reporting on new (or at the margins of current awareness) science or technology related issues and opportunities that are relevant to NZ.

University of Canterbury

Dr *Deborah* ***Crittenden*** has been appointed lecturer in Chemistry. Deborah joins the Department from ANU where she has spent the last five years working as a postdoctoral fellow with Prof *Peter* ***Gill***. Her research interests lie in the development and application of new theoretical methods and algorithms for predicting the structure and dynamics of large and/or complex biological and supramolecular systems.

A/Prof *Peter* ***Geissinger*** (University of Wisconsin-Milwaukee) is spending his sabbatical year as a visiting Erskine Fellow. His interests include biophysics, particularly the development of methods for determining quantitatively the electric fields that biological systems generate at their own active sites or other sites on interest. The long-term goal is to investigate to what degree these internal electric fields contribute to the function of a particular biosystem.

PhD candidate, *Richard* ***Johari James*** (Pharmacy, Universiti Teknologi Mara, Malaysia) is working with Profs *Murray* ***Munro***, *John* ***Blunt*** and A/Prof *Tony* ***Cole***. Richard's interests centre on drug discoveries for brain-related diseases and he is working on the BACE1 pathway, which is involved in the production of β-amaloid, hallmark protein in the development of Alzheimer's disease.

French born Dr *Clément* ***Roux*** is working for a year as a postdoctoral with Prof *Alison* ***Downard***. His work will focus on the preparation of smart switchable surfaces, a project funded by the MacDiarmid Institute. Clément's French PhD concerned peptide chemistry applied to biomaterials.

CPIT

Congratulations go to the recipients of the Branch Prizes for analytical chemistry students at Christchurch Polytechnic Institute of Technology (CPIT):

Best Level 5 student - *Ron* ***Marks***

Best level 6 student - *Ron* ***Marks***

Best Level 7 student - *David* ***Mills***

ESR News

The Chemistry Laboratory at the ESR Institute has acquired an Agilent tripquad LC-MS that is to be used to

quantitate amino acids. The laboratory is particularly interested in using the new instrument in the study of proteinomics; specifically the detection of allergen and enterotoxin proteins in food matrices.

MANAWATU

On February 18, Fonterra's *David* ***Newstead*** gave a talk at the Te Manawa Museum entitled *Graphic Scale Modeling to Better Understand the Chemistry of Milk as a Charge-Stabilized Colloidal System*.

Massey University - IFS

With effect from 1 January 2010, *Simon* ***Hall*** has been promoted to Professor of Electrochemistry.

Mid-February saw a visit and seminar from Dr *Peter* ***Scott*** (Warwick University) the latter under the title *Stereogenic Metal Centres and the Mechanisms of Hydroamination*, while Dr *Mark* ***Waterland*** and *Adrian* ***Jull*** attended the Tertiary Chemistry Education Symposium at Victoria University. There they gave a presentation entitled *Trial and Error in the First Year Chemistry Laboratory: Physical Chemistry Practicals using a Guided Inquiry Format* that described new experiments involving the thermodynamics of urea dissolution and the physical chemistry of Coca-Cola®.

Dr *Carl* ***Otter*** has completed his postdoctoral research with Drs *Shane* ***Telfer*** and Mark Waterland. He developed methods for synthesizing metal nanoparticle dimmers using coordination chemistry strategies and is now an Honorary Research Fellow in IFS. *Jeremy* ***Hall***,who completed his BSc(Hons) in 2009, spent the summer in *Elmers* ***Krausz***'s laboratory at ANU as a summer student. He enjoyed the experience so much that he decided to remain at ANU for his PhD studies where he is working on the spectroscopy and photophysics of light-harvesting complexes in photosynthetic systems.

Research within the MacDiarmid group at Massey focuses in part on exploring the application of nanomaterials to sensing and photovoltaics. The team is fundamentally comprised of synthetic organic chemists, but it includes a range of disciplines from physics, biology and veterinary sciences. Projects all have a longer term commercial aim and include the development of sensors for biological materials *in vivo* and in the environment, and the development of all-plastic PV roofing tiles.

Recently, *Lara* ***Xiuqian*** submitted her thesis and she now holds a position at a University in her home town province of Hunan, China. Lara's PhD was on *Gold Nanoparticles for Biosensor Development*, during which she developed a strip sensor for the detection of low levels of steroids in the environment. *Saymore* ***Mutsamwira*** has joined the group from Zimbabwe to work on the development of novel organic materials for the roofing tile project.

OTAGO

University Chemistry Department

The Department has a new Head. Prof *Lyall* ***Hanton*** has taken over the role.

Nigel ***Lucas*** has received the Royal Australian Chemical Institute (RACI) 2009 ***Organometallic Award*** that is made to an RACI member with less than 12 years professional experience who has contributed most to the development of organometallic chemistry. Nigel's research group recently moved into renovated lab and office space on the 3rd floor of the Department.

John ***van Klink*** and *Guy* ***Jameson*** gave talks at the Biennial Australia/ New Zealand Humboldt Conference, held in Dunedin in January.

Jim ***McQuillan***'s research group saw several PhD completions in 2009: *Jing* ***Yang*** (*The Role of Siderophores in Bacterial Adhesion to Metals*), *Luigi* ***Petrone*** (*Chemistry of Green Mussel Larvae and Undaria Spore Marine Bioadhesion*), and *Brent* ***Seale*** (*Adhesion of Thermophilic Bacterial Spores to Stainless Steel*). Jim gave an invited talk on infrared and surface photovoltage studies of TiO_2 photocatalysis at a nanoelectrochemistry conference in Xiamen, China, in August 2009. *David* ***Savory*** and Jim attended the first Australian Photocatalysis Workshop at the University of New South Wales in February; Jim delivered a talk on IR spectroscopic studies of TiO_2 photocatalysis and David presented a poster.

Keith ***Gordon*** attended a number of conferences at the end of 2009. He was an invited speaker to the Forum on Challenges in Solar Cell Characterization (Wollongong; part of the International Consortium on Next Generation Solar Cells), the Asian Spectroscopy Conference (Seoul) and the Infrared and Raman Discussion Group meeting in London. Keith and his PhD student, *Samuel* ***Lind*** attended, and both spoke at the 11th Pacific Polymer Congress (Cairns). Sam is recipient of the 2010 R. H. T. Bates Postgraduate Scholarship for his project *the theoretically driven, rational design of high-performance organic photovoltaics*. Recently published work (*J. Am. Chem. Soc*. **2009**, *131*, 15,621–23) included calculations performed by PhD student *John* ***Earles*** that were pivotal in explaining the observed behaviour of some solar energy dyes. *Cushla* ***McGoverin*** (a postdoc with Gordon) has now moved to the University of Stellenbosch to study cereal crops using near-infrared spectroscopy. In collaboration with Clare Strachan and Thomas Rades (Pharmacy, Otago), Keith received a NZ Pharmacy Education and Research Foundation grant for *rapid detection of counterfeit and adulterated products using vibrational spectroscopy* that is to be conducted by new PGCert student *Sara* ***Fraser***. PhD students (with Gordon, Rades and Strachan) *Pranav* ***Karmwar*** and *Miriam* ***Haaser*** presented their research at the 12th Conference on Formulation and Delivery of Bioactives (Otago). New members to the Gordon group include *Geoffrey* ***Smith*** (MSc studying Raman imaging of foodstuffs) and *Stasi* ***Elliott***, who is also working with *Max* ***Crossley*** (Sydney) on the optical properties of extended porphyrin systems with potential NLO applications.

Brooker's Bunch welcomes back *Rajni* ***Sanyal***, who graduated BSc, 1st Class (Hons.) in December, to pursue PhD studies. *Jamie* ***Lewis*** has fitted nicely into the team and is progressing with his honours research. Postdoctorals *László* ***Mercs*** and *Victoria* ***Milway*** arrived from Hungary (via Switzerland) and Canada (via Manchester), respectively. Postdoctoral *Jonathan* ***Kitchen***, *Sally* ***Brooker*** and *Kurt* ***Krause*** (Biochemistry) secured funding for biological testing of some of their compounds last year and the recent award of a Laurenson grant will allow the most promising lead compounds to be taken to the next stage over the coming year. PhD student *Juan* ***Olguin*** gave a

seminar to Jonathan Sessler's research group at Austin, Texas and presented his results at the Southern Regional ACS meeting in El Paso; he was buzzing from the excitement of the trip. David Black (New South Wales) visited in late January (whilst attending the Humboldt Conference in Dunedin), which was particularly relevant for PhD students *Scott* ***Cameron*** and Rajni Sanyal who are following up on some of David's early work.

Grace ***Morgan*** (UC, Dublin) visited for the whole of March and gave a 4th-year lecture course on molecular magnetism and luminescence. Long standing Brooker collaborator *Annie* ***Powell*** (Karlsruhe) also visited for a week that month providing an opportunity to complete a manuscript on the first results of Otago PhD student *Humphrey* ***Feltham***.

The 2012 **International Symposium on Macrocyclic and Supramolecular Chemistry** (ISMSC-7) is to be held in Dunedin. Planning is well under way and if you have yet to register your interest, please do so via the conference website (*http://www.otago.ac.nz/ismsc2012/*) to ensure you are on the emailing list for further information.

WAIKATO

To almost round off his 2009 year as NZIC President, Prof *John* ***Spencer*** gave his presidential address to the Branch entitled *Hydrogen, the Cinderella of Chemistry?*

University of Waikato

We are pleased to welcome *Scott* ***McIndoe*** back to the Department for a period of study leave. Scott, a Waikato PhD graduate, took up a lectureship at Victoria University, British Columbia after postdoctoral research with B. F. G. Johnson at Cambridge,

Michael ***Mucalo*** attended the recent Australasian Society of Biomaterials and Tissue Engineering conference at Queensland University of Technology (Brisbane) where he gave a seminar on his *macromolecule-infiltrated sintered bovine bone as a xenograft material for bone replacement*, which had been conducted by PhD student *Dougal* ***Laird***. Dougal's thesis is submitted and he is currently in Germany. Dr Mucalo has a senior role on the Organising Committee of the 2011 NZIC conference, which is to be held in Hamilton from Nov. 30 to Dec. 3 next year.

We have had quite a number of national and international visitors to Chemistry in recent months, many of whom have given interesting seminars. These include *Faecal Sterols as Chemical Indicators of Human and Animal Pollution in Waterways* from Dr *Peter* ***Brooks*** (Sunshine Coast University, Queensland), *Wine Oxidation Chemistry – Focus on NZ Sauvignon Blanc* from A/Prof *Paul* ***Kilmartin*** (Auckland), *Darwinian Chemistry and the Origin of Life* from Dr *Andy* ***Pratt*** (Canterbury), *On the Way to Quantify Human Impact on Climate: Pollution Records and Climatic Information from Alpine Ice Cores* from Prof *Heinz* ***Gaeggeler*** (Paul Scherrer Institute, Bern University), *The Structure, Symmetry and Dynamics of the Benzene Dimer* from Prof *Phil* ***Bunker*** (NRC Canada), *Pigment Distributions in Sediments: Sensitive Markers of Environmental Change During the Holocene* from A/Prof *Brendan* ***Keely*** (York University) and *Association of Bacteria with Larvae of Marine Bryozoa in Coastal Waters of Wales* from Dr *Joanne* ***Porter*** (Heriot Watt, Edinburgh).

Lyndsay Main Retirement

A/Prof *Lyndsay* ***Main*** has retired from Waikato's Chemistry Department after 38 years of dedicated service. Lyndsay graduated with an MSc (VUW) and PhD (Auckland – working with the late Prof *Peter* ***de la Mare***) before postdoctoral studies on a Fulbright Grant at the University of California, Santa Barbara. He came as the first dedicated organic chemist to a lectureship at Waikato in 1972. Lyndsay took the main responsibility for setting up the organic teaching and research programme, and, during his time, he has supervised 15 PhD and *ca.* 40 MSc students. All of these benefited from his very supportive supervision and have gone on to successful careers, within NZ and overseas. His research has involved collaborations with Forest Research, groups at Ruakura, and with the Cancer Research Institute, as well as with colleagues within the University. Lyndsay made valuable contributions to the administration of the Department (including a successful term as CoD), the School of Science, and of the University with a particularly notable contribution to international student issues. Lyndsay has always been active in the NZIC, and it was while he was Branch Chairman that he introduced the NZIC analytical chemistry competition, which continues to run annually.

His love of art is well known and at a most enjoyable, but somewhat emotional, farewell held by the Faculty for him recently, he enjoyed browsing the *artworks* created for him by colleagues. These included an ostrich made from lab bottle brushes, an abstract work from a used piece of benchcoat) and an installation in the style of Damien Hurst where a *My Little Pony* had been immortalized.

Lyndsay has been a successful scientist, a thoughtful and considerate lecturer, and a very congenial colleague. We, and his many friends and colleagues around the country, wish him and Mal a very enjoyable retirement.

NIWA

The New Year has seen a mini-exodus of sorts from the Chemistry and Ecotoxicology group at NIWA. After three years, first as a postdoc and then as a permanent staff member, *Hilke* ***Giles*** has taken up a position at Environment Waikato; *Craig* ***Depree*** has taken over Hilke's sediment profiling research. After a two-year postdoctoral focussing on different aspects of aquatic trace metal chemistry, *Micha* ***Rijkenberg*** left in mid-April for a second postdoctoral at the Royal Netherlands Institute for Sea Research. There she is working in the GEOTRACERS programme to investigate what determines metal distributions in the global oceans.

WELLINGTON

The inaugural meeting for 2010 was a lecture by Dr *Justin* ***Hodgkiss***, VUWs recently appointed (2009) lecturer in Physical Chemistry (see: *This Journal,* **2009***,73*, 136) who spoke on *Next generation conjugated polymers for electronic applications*. His talk encompassed the period since the discovery of electroluminescence from conjugated polymers 20 years ago, and focussed on the emerging classes of conjugated polymers whose chemical structures engender new electronic properties, namely conjugated block and conjugated polyelectrolytes containing ions that can interact with electronic charge carriers in the polymer backbone.

Victoria University

In mid-January, Dr *Robyn* ***Schofield*** (Alfred Wegener Institute for Polar and Marine Research Potsdam) spoke on some of the climate change work that has been done in that institution and which gained prominence following the climate change conference in Copenhagen under the title: *Atmospheric composition and kinetic parameters derived from spectroscopic and* in-situ *measurements*. Despite the vacation period there was a good-sized audience. Other more recent visitors to the School have included Dr *Michael* ***Edmonds*** from the Christchurch PTI. He attended the tertiary teachers' day (see NZIC Education Group) and stayed on to visit within the School and speak to us on his experiences under the title *The road less travelled: a decade as a chemistry researcher and educator in the polytechnic sector*, a fascinating insight to his successful marriage of research and teaching in UC and CPIT. In mid-February Prof *Peter* ***Scott*** (University of Warwick) visited and gave a seminar on *Stereogenic metal centres and the mechanisms of hydroamination* that outlined his synthetically accessible methods for the creation of optically pure complexes with various architectures involving stereogenic metal atoms that have led to some the complexes are now being applied to a new and unexpectedly active class of catalyst for enantioselective cyclohydroamination. The following day Dr *Matthais* ***Lein*** (Massey-Auckland) visited and gave a fascinating lecture on the *scope and relevance of computational chemistry; from catalysis to weak electronic interactions* that detailed some of his computational studies on both gold catalysis and agnostic interactions. On Friday Feb. 19 Dr *Cather* ***Simpson*** (Auckland) gave an address entitled *A new twist in the tale: ultra fast dynamics of diphosphenes*. However, the seminar time was divided between this research and the structure and operation of the Auckland *Photon Factory*. The detailed spectroscopic examination of *E/Z* isomerizations and photochemical activations proved a fascinating piece of fundamental chemistry. Towards the end of February A/Prof *Merilyn* ***Manley-Harris*** (Waikato) visited and gave her seminar *The origin of antibacterial activity of NZ manuka honey*. The non-peroxide antibacterial activity of the honey is ascribed to the presence of methylglyoxal (MeCOCHO) (formed by formal dehydration of 1,3-dihydroxyacetone) that is present in the nectar of the manuka flower.

A/Prof *Kate* ***McGrath*** is on research and study leave that she is spending on campus attending to research writing and the like. As noted elsewhere in this issue, Prof *Martin* ***Banwell*** (ANU) who gained his degrees at VUW in the 1970s (PhD under *Brian* ***Halton***'s supervision) is to be awarded an Honorary DSc by the university. The event is being coupled with a special SCPS symposium to mark the occasion.

Promoting Scientific Exchange in the Pacific Basin for a Healthy and Sustainable Future

15 - 20 December 2010

Pacifichem 2010 is the 6th in the series of Pacific Basin Chemistry Congresses - initiated in 1984. These conferences have been held in Honolulu, Hawaii, approximately every five years and feature programs highlighting recent research contributions over the full range of chemistry.

NZIC is one of the seven sponsoring chemical societies for this conference.

237 symposia have been accepted into the technical program of Pacifichem 2010.

Abstract submission is open until April 5, 2010 and must be submitted online through the Pacifichem Abstract System. The Technical Symposia listing is in *Chemical & Engineering News*, Jan. 11, 2010; Vol. 88, No. 2; pp. 46-49.

A student poster competition will form part of the meeting.

REGISTRATION FOR PACIFICHEM 2010 WILL OPEN IN JUNE 2010

For more details see *www.pacifichem.org*

For informal information and general background please contact the NZIC representative on the organizing committee:
Prof Rob Smith, Chemistry Department, University of Otago, Dunedin
(Ph: 03 4797924; e-mail: rajsmith@chemistry.otago.ac.nz)

Feature

The 2009 NZIC Presidential Address

Magic Metals: The Special Affinity of Transition Metals for Hydrogen

John L. Spencer

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Thomas Graham, the first president of the Chemical Society (London) was a remarkable chemist who contributed in many ways to the development of the subject. However, perhaps his most remarkable discovery (though not the one for which he is best known) was that palladium, an unreactive precious metal, would absorb and release hydrogen gas under mild conditions. This observation was a prelude to the nickel-metal hydride (NiMH) battery technology that is widely used today and to the current interest in hydrogen storage in metal systems. Several years prior to Graham's discovery, William Grove had developed a fuel cell that relied on the interaction of hydrogen gas with platinum electrodes to generate an electric current. Both systems are evidence of the affinity of hydrogen for transition metals, and that affinity has been the basis of many scientific discoveries and valuable technologies since the mid-19th century. Today, there is interest and speculation around the prospects for a *Hydrogen Economy*, namely, an economy based on the use of hydrogen and hydrogen-rich materials as secondary fuels replacing hydrocarbons in key applications, notably transport.

The early experiments of Grove and Graham illustrate two of the key features of the interaction of transition metals and hydrogen: the ease with which the strong H–H bond is cleaved by many transition metals and, once present as discrete hydrogen atoms bound to the metal, the ease with which hydrogen moves over a metal surface or through a metal lattice. This behaviour results, in part, from the availability of *d*-orbitals on the transition metal and the spherical symmetry of the 1*s* bonding orbital of hydrogen. In this article some of the interesting chemical and technological consequences of this unique relationship are explored.

Hydrogen is the most abundant element in the universe and is 9th most abundant by weight in the earth's crust (including the oceans), or 5th by number of atoms, and it forms compounds with virtually all the elements of the Periodic Table except for the Noble Gases. The diatomic molecule, H_2, is notable for the very strong single bond (435 kJ/mol), which makes molecular hydrogen rather unreactive unless there is a significant energy input to overcome the activation barrier. This is where the magic of transition metals comes in as they are able to reduce the activation barrier to negligible levels. A hydrogen molecule approaching a metal atom on the surface of a particle or in a metal complex is readily cleaved into two hydrogen atoms that may then go on to react further with other molecules in the environment. In the case of Graham's palladium experiment, the hydrogen atoms released on the surface of the metal are free to diffuse into the holes, or interstices, in the metallic lattice. In Grove's fuel cell, the platinum atoms on the surface of the electrode cleave the hydrogen molecule and thereby assist in the formation of hydrogen cations, releasing an electron into the electrical circuit.

Significant though fuel cells and hydrogen storage are to modern society, they do not compare with the importance of catalysis involving hydrogen. The French chemist, Paul Sabatier first reported the catalytic hydrogenation of alkenes in 1897 and deservedly won the 1912 Nobel Prize in chemistry for his discovery. However, it was William Norman who developed the first commercial process, the nickel-catalysed hydrogenation of vegetable oils to make fats, which were of more value than oils at that time. Norman's was the first of many chemical processes to employ a metal to lower the activation energy of reactions involving molecular hydrogen and hydrogen-containing molecules to the extent that metal-hydrogen catalysis provides the technological basis of much of the chemical industry.

The hydrogenation of vegetable oils is a relatively non-demanding application of transition metal catalysis as it employs small metal particles that are easily manufactured. However, much more sophisticated reactions are now possible, including the stereospecific hydrogenation of prochiral alkenes to generate molecules of a single chirality. This reaction has enormous potential significance, for example, in the pharmaceutical industry as recognized in 2001 by the award of the Chemistry Nobel Prize to William Knowles and Ryoji Noyori (jointly with Barry Sharpless) for the discovery of catalyst complexes that would induce chirality in the products of their reactions.[1] The Knowles and Noyori successes depend upon using other ligands bound to the transition metal to create a hydrogenation reaction site of the correct shape to produce the desired enantiomer. Knowles' work led to the industrial synthesis of the chiral drug L-DOPA used in the treatment of Parkinson's disease. Molecular (or homogeneous) catalysts can be designed in this way, but the approach would be impossible with the basic metal particle (heterogeneous) catalysts used by Norman and still widely used in routine hydrogenation reactions.

Amongst the many significant catalytic reactions involving hydrogen and transition metals (or their compounds) as catalysts is the synthesis of ammonia, developed by Haber and Bosch in 1909, that provides the feedstock for the fertilizer, explosives and parts of the synthetic fibre industries. This process is reckoned to provide food for one third of the world's population through the use of nitrogen fertilizers. There is also the 1926 Fischer-Tropsch process that converts a mixture of CO and H_2 (synthesis

gas) into liquid fuels and other chemical feedstocks. The South African SASOL Company developed this process to a level of sophistication during the period of economic isolation associated with the apartheid era in that country. A further application of synthesis gas is in the hydroformylation reaction discovered by Otto Roelen in the 1930s. This process can be employed to convert terminal alkenes into either aldehydes or alcohols from the addition of a formyl group (CHO) and a hydrogen atom to a carbon-carbon double bond. It differs from the Haber-Bosch and Fischer-Tropsch processes in that the catalyst is a discrete metal complex in the same phase as the reactants, *viz*. a homogeneous catalyst, rather than a metal-containing, heterogeneous solid catalyst. In this respect the hydroformylation catalyst resembles the hydrogenation catalysts developed by Knowles and Noyori.

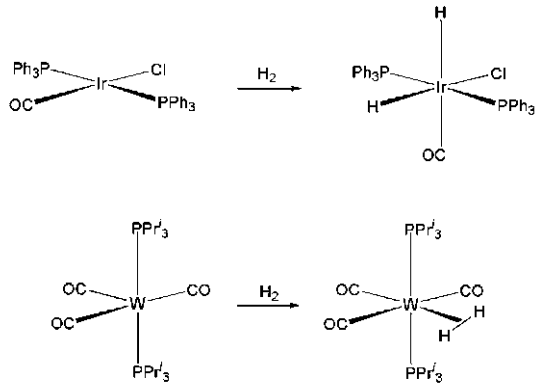
Hydrogen gas is produced in NZ on a significant scale as a key material in several industrially important processes. Methanex NZ operates two plants in Taranaki that convert methane into methanol in a process that first combines CH_4 and H_2O to give synthesis gas, and then recombines the CO and H_2 affording methanol. Over 90% of the methanol is exported and the plants are operated flexibly to meet international demand. Typical recent production is in the region of 2500 tonnes per day, but it varies according to international demand and the availability of methane; a nickel catalyst is used in the production of methanol.

New Zealand's agricultural economy is heavily dependent on the judicious use of nitrogen fertilizers to promote grass growth. Some of that nitrogenous fertilizer is supplied by the Balance Agri-Nutrients ammonia-urea plant at Kapuni, also in Taranaki. The ammonia is produced from synthesis gas by the Haber-Bosch catalytic process. Much of the ammonia is then converted to urea for agricultural applications. A third major producer of hydrogen in NZ is the oil refinery at Marsden Point. Once again some of the key processes in petroleum refining depend for their operation on the interaction of hydrogen with transition metals.

Having established the economic importance of the interaction of hydrogen and transition metals, one should ask what is known about the fundamental nature of the interaction of hydrogen and transition metals. There has been detailed study of that interaction both with the surface of bulk metals and with metal centres in discrete metal complexes. However, there appears to be no fundamental difference in the nature of the interactions, although the environments are clearly different. As it is generally true that a wider range of experimental techniques can be brought to bear on metal complexes, the remainder of this article is focused in that direction.

All transition metals form complexes with hydrogen in which individual hydrogen atoms are covalently bound to one or more transition metals. As the electronegativity of hydrogen is similar to that of many transition metals, the bonds are not very polar and they rarely display ionic character. Although there are examples of both classical acidic or hydridic (the tendency of transition metal hydride complexes to behave as true hydrides) behaviour by individual complexes, these are not the predominant reactivity patterns of hydride complexes.

The first hydride complexes were reported by Walter Hieber in the 1930s, but interest in them expanded only in the 1950s. This was in parallel with the rapid growth of transition metal organometallic chemistry and the development of instrumental techniques particularly suited to the identification of hydride ligands, *e.g.* IR and NMR spectroscopies. Whereas there are only a few examples of complexes such as the remarkable $[ReH_9]^{2-}$, in which the metal is stabilized only by hydride ligands, there are many hydride complexes that contain other ligands that are often influential in dictating the chemical behaviour of the hydride ligands themselves. There are many ways of synthesising transition metal hydride complexes, including direct reaction with hydrogen gas. A landmark paper in the area, published in 1962 by Vaska and DiLuzio,[2] described the reaction of molecular hydrogen with an iridium complex $[IrCl(CO)(PPh_3)_2]$. Under mild conditions, the very strong H–H single bond (435 kJ/mol) is broken and two discrete hydride ligands are formed (Scheme 1). This reaction provides a model for the key step in the catalytic hydrogenation reaction discovered many years earlier by Sabatier.



Scheme 1. Contrasting interactions of H_2 with transition metal complexes.

Twenty years later Kubas *et al*.[3] provided a further insight into this critical reaction when they reacted hydrogen gas with the tungsten complex $[W(CO)_3\{P(C_6H_{11})_3\}_2]$ and isolated a complex of *molecular* hydrogen, *i.e.* a complex in which the single bond of the H_2 molecule was not fully broken by interaction with the metal (Scheme 1). Not only did this provide evidence for the mechanism of H–H bond cleavage by transition metals but it also forced transition metal chemists to rethink their ideas of the metal – ligand bond that had been ingrained over many years. In the classical view, the metal is a Lewis acid with a vacant orbital and the ligand is a Lewis base with a pair of non-bonding electrons that can be *donated* to the metal orbital. Thus, molecules like NH_3 or PPh_3 that have lone pairs on N and P, respectively, are excellent ligands for transition metal complexes. With the development of transition metal organometallic chemistry, chemists had to broaden the definition of *donor electrons* to include the high-energy π electrons in unsaturated molecules such as ethene. However, in Kubas' molecular hydrogen compound, it is the very stable electrons in the H–H σ bond that are act-

ing as the donor electrons. An understanding of the way transition metals interact with the H–H σ bond, and other σ bonds in molecules such as methane, is likely to have a profound effect on the development of catalysis in the future.

We have been interested in the structure and reactivity of *polyhydrides*, complexes with large numbers of hydride ligands and close relatives of $[ReH_9]^{2-}$. Some years ago, in collaboration with Professor Judith Howard,[4] we established that the structure of the osmium polyhydride $[OsH_6(PPr^i_2Ph)_2]$ was a distorted triangular dodecahedron with six discrete hydride ligands. More recently,[5] we investigated the reactions of these molecules with acids and were able to identify an unstable cationic intermediate $[OsH_7(PPr^i_2Ph)_2]^+$. What structure did this complex have? We suspected that some of the hydrogen atoms might be bonded together as coordinated H_2 molecules in a way similar to that in Kubas' compound, but how could that be established? The proton NMR spectrum showed only one signal for all seven hydride ligands. As these cannot be equivalent, the signal merely indicates that there are very low energy barriers to internal molecular rearrangement and that all seven hydrogens exchange positions rapidly on the NMR timescale. Single crystal neutron diffraction is the definitive technique for establishing the structure of hydride complexes involving heavy atoms such as osmium. However, neutron diffraction requires relatively large stable crystals and these were not available in this case. We chose, therefore, to use a technique that had been developed by Crabtree[6] and others to identify the presence of close H–H contacts – the NMR relaxation parameter, T_1. This parameter is highly dependent on the closeness of the hydrogens, so that a typical value for T_1 in a classical transition metal hydride (where hydride ligands may be >170 pm apart) is 300 ms. Fig. 1 shows the measured value of T_1 for $[OsH_7(PPr^i_2Ph)_2]^+$ at various temperatures and the extrapolated minimum value of approximately 18 ms is good evidence that the complex should be correctly formulated as $[OsH_5(H_2)(PPr^i_2Ph)_2]^+$ or even $[OsH_3(H_2)_2(PPr^i_2Ph)_2]^+$ with one or two molecular hydrogen ligands respectively.[5]

Of course molecular hydrogen is an excellent leaving group as the interaction between the metal and the H–H σ bond is relatively weak. It is no surprise, therefore, that $[OsH_7(PPr^i_2Ph)_2]^+$ decomposes readily at room temperature to form the diosmium complex $[Os_2H_7(PPr^i_2Ph)_4]^+$ with loss of H_2. Complexes or clusters with several metal atoms and multiple hydride ligands are fascinating molecules and are not uncommon. As our example illustrates, the hydrogen atom, with only a single σ-orbital for bonding, will, nevertheless, interact strongly with two or more transition metals. Another interesting feature of molecules of this type is that the hydrogen atoms are often very mobile and, unlike the hydrogen atoms in organic molecules, they will readily exchange positions in the structure. The hydrogen atoms in transition metal clusters are frequently chemically reactive, and because the metal-metal bonds ensure the integrity of the cluster, hydrogen can often be added and removed reversibly.[7] An example[8] is the platinum cluster $[Pt_4(PBu^t_3)_4H_7]^+$ that is readily oxidized,

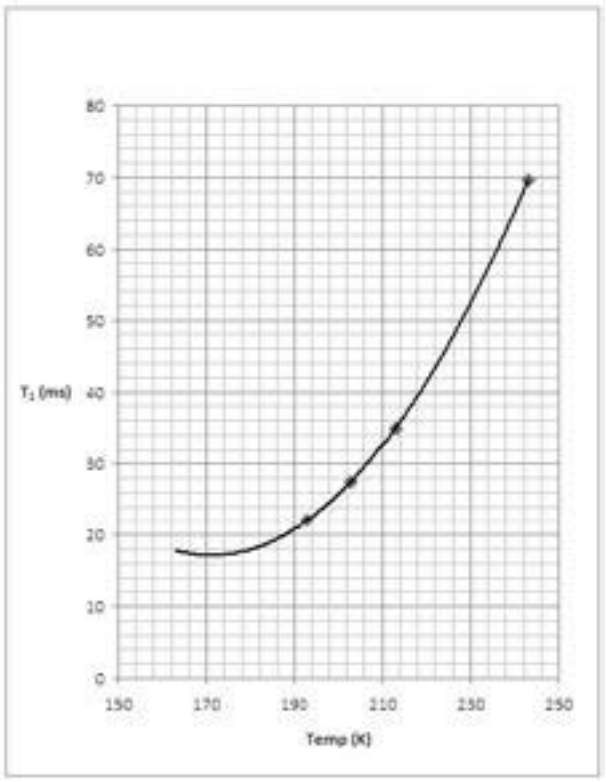
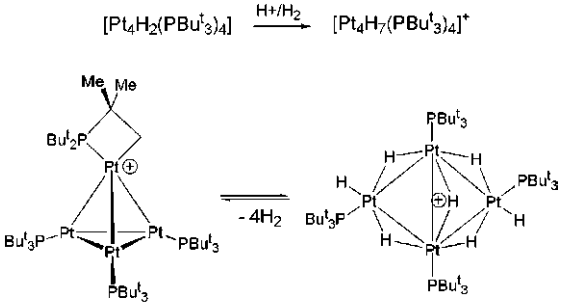


Fig. 1. Spin-lattice relaxation time, T_1 for $[OsH_7(PPr^i_2Ph)_2]^+$ measured at low temperature (300 MHz, CD_2Cl_2).

losing four molecules of H_2, to afford $[Pt_4(PBu^t_2CMe_2CH_2)(PBu^t_3)_3]^+$ (Scheme 2). The original cluster is readily regenerated under mild conditions by exposing the sample to hydrogen and it is the molecular analogue of Graham's reversible reaction of hydrogen with palladium metal.



Scheme 2. Reversible uptake of H_2 by a transition metal cluster.

Although this may seem to be a rather specialized piece of research, the important point it illustrates is that transition metals allow the very fast formation and cleavage of strong σ bonds. A logical extension of the concept is to the catalytic cleavage or activation of the inert C–H bonds in alkanes, such as methane. Methane resources are enormous but its conversion into more useful feedstocks for the chemical industry is not a very efficient process, as the methane to methanol example mentioned above illustrates. With current technology, it is necessary to first convert CH_4 and H_2O into CO and H_2 before reassembling the synthesis gas into methanol. Although this is a mature technology and can be implemented on a very large scale, the process requires high temperatures and, for that reason, it is not energy efficient. A more elegant synthesis would cleave a single C–H bond leaving a CH_3 group intact. A major goal of organometallic chemistry is the

catalytic activation of C–H bonds under mild conditions. If that is ever achieved then the energetics of the process will be driven by the strong bonds that form between transition metals and hydrogen and by the facility with which transition metals interact with σ bonds.

The race to develop new energy technologies to replace oil has led to a renewed interest in the ability of transition metals to interact with hydrogen and hydrogen-containing compounds. A particular issue is the storage and release of hydrogen. Unfortunately, the platinum clusters given as examples above cannot form the basis of a workable commercial hydrogen storage system simply because of the cost and rarity of platinum, and the modest storage capacity involved. However, the original work of Graham that demonstrated the ability of palladium to absorb large quantities of hydrogen gas under mild conditions was a precursor of modern NiMH battery technology that now is widely used in hybrid cars and was previously common in laptop computers until it was displaced by lithium ion batteries that have a better energy-to-weight ratio. In NiMH batteries, hydrogen is electrochemically generated during recharging and stored in the interstices of an AB_5 alloy of a lanthanide metal (A) and a transition metal (B). To meet the power demands of rapid acceleration in a hybrid car, hydrogen must be able to diffuse rapidly through the metallic lattice and be released easily for oxidation at the anode. Unfortunately, as with most battery technologies, the low energy-to-weight ratio of NiMH batteries means that they will never be a direct replacement for the internal combustion engine.

Fuel cells that rely on hydrogen or a hydrogen-rich fuel are a potential replacement for the petrol engine in transport. Many fuel cell designs depend on a platinum activated electrode, just as the original Grove cell of 1842 did. However, platinum is a rare and expensive element and it is questionable whether there is enough in the earth's crust for all the fuel cells that might be required for the *hydrogen economy*. The search is on for cheaper replacements for platinum as the electrode material. However, a much greater problem preventing the adoption of the hydrogen fuel cell is the lack of a convenient reversible method of storing hydrogen. As pointed out above, the AB_5 alloys are too heavy to be practical. Light metals such as magnesium will store large quantities of hydrogen but the lack of *d*-orbitals means that the activation barriers for absorption and release of hydrogen are high. The non-metallic hydrides such as those of boron and nitrogen, and even carbon itself, are very attractive on grounds of high energy density. But once again the activation barriers and thermodynamic parameters are unfavourable. Transition metal catalysts, and in particular those made from the cheaper and more abundant metals, are strong candidates to lower the activation barriers to acceptable levels. With careful design, this could lead to a light atom hydrogen storage system where the energy differences and activation barriers between the hydrogenated and dehydrogenated forms are relatively low; it could thus form the basis of a practical hydrogen economy. Transition metals are also likely to have a significant role in the development of technologies for the renewable production of hydrogen from sunlight.[9]

Despite the long scientific and technological history of the interaction of transition metals with hydrogen, it is likely that many important discoveries are still to be made, and new technologies will be developed. Transition metals lower activation barriers for reactions that involve hydrogen and hydrogen-containing compounds. Because of this, it is probable that they will play a critical role in the development of technologies to reduce the energy requirements of the chemical industry, and provide working solutions to the problem of finding an alternative to fossil fuels.

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Article

The Development of Zwitterionic Second Order Nonlinear Optical Organic Materials

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Introduction

The development of second order nonlinear optical (NLO) organic materials has been an area of intense research over the last 25 years.[1] This has been largely driven by the expectation that next-generation devices in, for example, telecommunications, sensing and computing will contain NLO materials as the active components. These devices will, in turn, underpin the rapidly increasing global photonics industry, which is already worth over $NZ 800 billion p.a.[2] Nonetheless, the uptake and commercialization of organic NLO materials has been slow, mainly due to competition from existing inorganic materials as well as issues with the long-term stability of organic compounds when exposed to high intensity light.[3] Consequently, there is still a significant quantity of research needed before the widespread deployment of device-quality organic NLO materials is realised,[4,5] and in particular those that will allow operation at relatively low power levels.[6] This article describes some of the research that has been undertaken by the Photonics team at IRL on the development of organic NLO chromophores. It includes some theoretical aspects around the design of NLO materials, options for optimizing their response and stability, and outlines the specific approach taken by IRL towards developing our materials.

Fundamental Concepts of Organic NLO Materials

Optical nonlinearity occurs when an external field (either high intensity light or an electric field) is applied to a dielectric medium to produce light that is altered in phase, amplitude or frequency.[7] In order for a medium to exhibit nonlinearity, the field must be of sufficient strength to overcome any internal electrostatic interactions. As a result, NLO materials need to contain weakly bound or highly polarizable electrons. A straightforward way of viewing NLO materials is to regard them as compounds in which a large change in refractive index can be obtained by applying a field. This, in turn, allows for the development of materials in which it is possible to *control* light as it passes through them, and this is of considerable interest to optics and physics researchers. The magnitude of the NLO effect is defined by the second term of the equations that describe polarisation as a function of the applied electric field; hence the materials are termed *second order*. These equations, or power series, can describe both the molecular (Eq. 1) and macroscopic (Eq. 2) polarization:[1]

$$p = \alpha E + \beta EE + \gamma EEE + \ldots \quad \ldots. \text{ Eq. 1}$$

$$P = \chi^{(1)}E + \chi^{(2)}EE + \chi^{(3)}EEE + \ldots \quad \ldots. \text{ Eq. 2}$$

Equation 1 provides the first hyperpolarizability, β; it is of particular interest as it is the component we aim to maximize. Equation 2 contains the second-order susceptibility, $\chi^{(2)}$, a further value that must be maximised. The $\chi^{(2)}$ value is calculated from what is termed *the* r_{33} *value*, which is the experimentally measured electro-optic coefficient. Not surprisingly, the incorporation of molecules that have high β values into bulk materials (or polymers) results in materials with the highest macroscopic responses [$\chi^{(2)}$]. Furthermore, in order to observe a macroscopic response, it is essential that the bulk material is non-centrosymmetric; for organic compounds this typically means that the dipole moments of the embedded chromophores must be at least partially aligned. This can be achieved by heating a thin film of an NLO material to its glass transition temperature and then applying an electric field of sufficient strength to force the dipole moments into alignment. The larger the dipole moment (μ) of the embedded chromophore, the more efficiently this can be achieved. Consequently, when selecting a molecule as a potential candidate for use in an NLO material, a key requirement is for it to have what is termed *a large figure of merit*; it is the product of the first hyperpolarizability and dipole moment, *i.e.* μ × β esu, and given as the value × 10^{-48} esu.

Organic compounds with the highest NLO responses typically contain donor and acceptor groups that are separated by a conjugated polyene spacer, *i.e.* Donor-π-Acceptor. In a push-pull system such as this, the π electrons will almost always be polarized asymmetrically. Furthermore, the degree of polarization of such an NLO molecule in its ground state allows for its classification as either neutral or ionic. This led Marder *et al*. to use the concept of bond length alternation (BLA) in a compound for the classification of NLO chromophores as either left hand side (LHS), right hand side (RHS) or neutral (Fig. 1).[8] From Fig. 1 it can be seen that there are two opportunities to maximize the first hyperpolarizability, β. By tuning the strength of the donor and acceptor moieties, as well as the length of the conjugated interconnect, it is theoretically possible - although not necessarily easy - to tune the magnitude of BLA within a compound in order to maximize the NLO response. Over the last two decades LHS molecules, those with a positive BLA, have been extensively studied by a number of researchers,[1,6] whereas negative BLA molecules of the RHS type remain largely unexplored. As a consequence, we decided that focusing on RHS molecules would provide the greatest scope to develop a novel suite of compounds. In taking this approach some of the key considerations were:

- ease of synthesis,
- a unique, and therefore patentable, series of compounds,
- a *building block* synthesis that would allow for easy introduction and modification of the donor, acceptor, and π interconnect components,

- figures of merit greater than 5,000 x 10^{-48} esu and thermal stabilities not less than 230 °C, and
- easy incorporation of functionality to allow for tethering to a polymer backbone (improving solubility) or reducing aggregation.

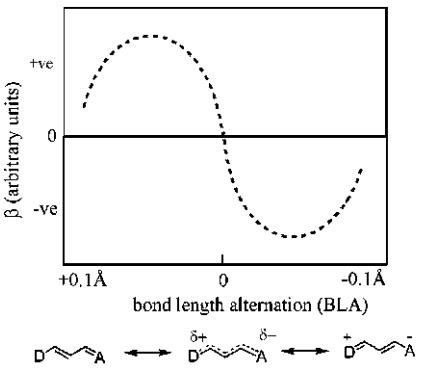


Fig. 1. NLO response (or first order hyperpolarizability) dependence on chromophore bond length alternation; LHS = +ve BLA, RHS = -ve BLA

First Generation NLO Materials

A straightforward method for creating chromophores with zwitterionic ground states is to synthesise molecules that gain in aromatic stabilization energy upon transfer of charge from the donor to the acceptor. Consequently, our initial strategies focussed primarily on the synthesis of planar conjugated molecules with a donor (4-pyridinylidene, 4-quinolinylidene or benzothiazolidinylidene) capable of aromatization and a range of acceptors (Fig. 2).[9,10] While almost all of the compounds synthesised had respectable figures of merit, it was found that the combination of either a pyridinylidene or quinolinylidene donor with a cyano(dicyanomethylidene)dihydrofuranyl (*CDF* – see Scheme 1) acceptor led to molecules with the highest NLO responses.[11] This class of compounds has become the focus of our research.

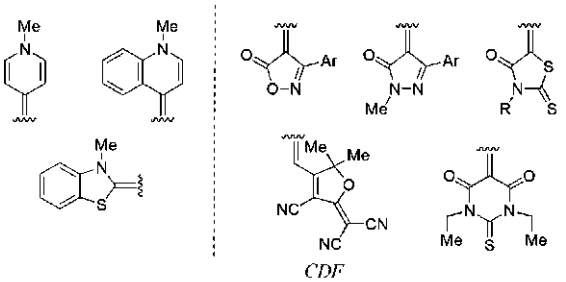
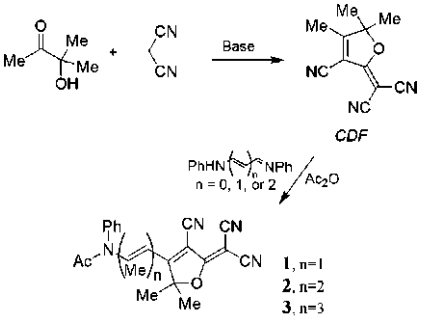
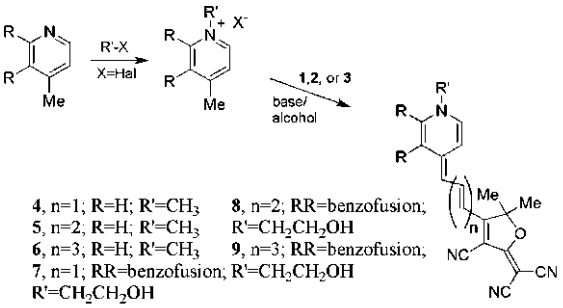


Fig. 2 Some of the donor (left) and acceptor (right) systems studied during our early work.

The original synthesis of these new chromophores is shown in Scheme 1.[11] The CDF acceptor is readily available from condensation of excess malononitrile with an α-hydroxy-α,α-disubstituted methyl ketone (in this case 3-hydroxy-3-methylbutanone).[12] The acceptor is then reacted with the appropriate dialdehyde bisanil in acetic anhydride to give the corresponding (*oligo*en)amido dihydrofurans **1-3**. These can then be condensed with either an *N*-substituted 4-methylpyridinium or a 4-methylquinolinium salt to give the final chromophores **4-9** (Scheme 2). A significant advantage of this approach is that compounds such as **1-9** almost always precipitate from the crude reaction mixture. Simple filtration and washing typically gives a product suitable for immediate use. If necessary the compounds can be further purified by recrystallization. A further advantage of this approach is that it achieves our aim of developing a *building block* approach. For example, it is easy to change the donor group (or indeed the substituent on the donor N atom), the length of the interconnect or the nature of the alkyl substituents on the acceptor.



Scheme 1. Synthesis of the basic acceptor unit.



Scheme 2. Synthesis of first generation NLO materials with aromatisable donors and CDF acceptor

The linear and nonlinear optical properties of compounds **4-9** are summarised in Table 1. It can be seen that these compounds are very solvatochromic, with changes in the measured absorption maxima of up to 155 nm in the spectra from polar (methanol) to non-polar solvents (pyridine). This reflects the fact that the molecules are much more zwitterionic in character in polar solvents compared with a non-polar solvent where the neutral form will dominate (Fig. 3). It is also notable that increasing the number of carbon atoms in the conjugated interconnect from three to five to seven carbon leads to a steady increase in the observed NLO response. Increasing the conjugation length reduces the HOMO-LUMO gap, which accounts for the large β values seen for compounds such as **6** and **9**.

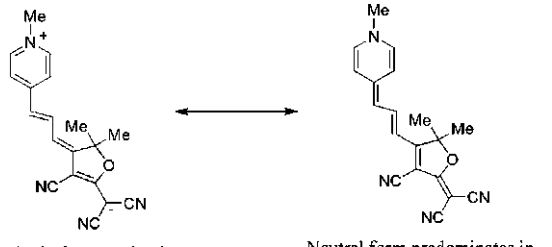


Fig. 3. Canonical forms of compound **4**.

While it would appear that compounds **7-9** with quinoline donors have greater NLO responses compared to their pyridine analogues, the situation is, in fact, far more

Table 1. Calculated and experimental linear and nonlinear optical properties of first generation chromophores **4-9**.

Compound	λ_{max} (nm) DMF ($\log_{10}\varepsilon$)	λ_{max} (nm) MeOH	λ_{max} (nm) pyridine	μ^a (calc.)/ 10^{-18} esu	β (exp.)/ 10^{-30} esu DMSO	$\mu_{(calc.)}.\beta_{(exp.)}$/ 10^{-48} esu	T_d (° C)
4	570 (4.86)	564	600	17.7	250	4,425	294
5	600 (4.78)	592	670	17.9	660	11,815	283
6	615 (4.76)	595	685	17.8	920	16,375	254
7	660 (5.00)	654	682	15.5	790	12,245	308
8	735 (4.88)	724	782	12.7	1,270	16,130	271
9	735 (4.70)	705	860	13.8	1,660	22,910	262

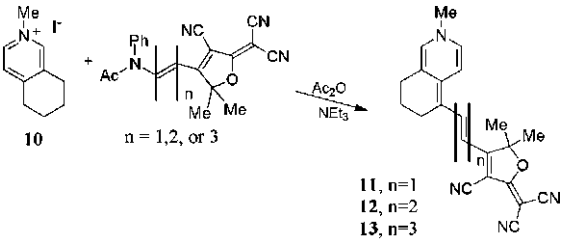
[a]MOPAC (CS Chem3D pro, Cambridge soft) AM1 level using the precise keyword. Poor solubility prevented measurement of the dipole moment of any of the compounds.

complex. This is because the relationship between various donors (and acceptors) and the measured first hyperpolarizability is solvent dependant.[13] Consequently, strictly speaking, the trend observed here is only valid for values obtained in media of similar polarity to DMSO. Given that all of the first generation chromophores were thermally stable (T_d > 250 °C) and that a number of them have figures of merit above 10,000 × 10^{-48} esu, it was decided to modify them further in order to optimise their performance.

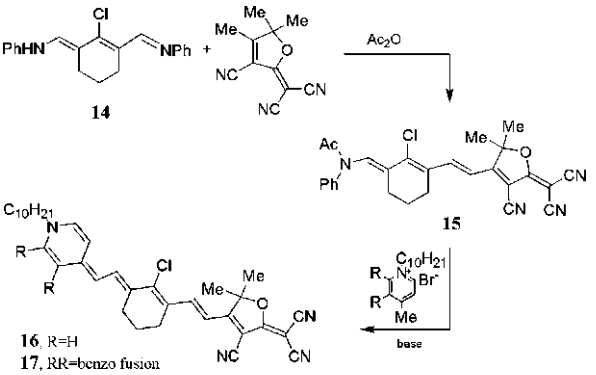
Second Generation NLO Materials

A number of methods have been used previously to enhance the NLO response of organic compounds. These include ring-locking of the chromophore backbone,[14] incorporation of donor/acceptor groups onto the conjugated inteconnect,[15] development of multi-chromophore macromolecular systems,[16] and induction of a very large twist angle (*ca*. 89 °) between the donor and acceptor units in zwitterionic chromophores.[17] Using our initial methodology, we saw an opportunity to introduce ring-locking into our molecules to enhance rigidity and planarity via modification of either the donor unit or the conjugated interconnect. This should also improve the thermal and photochemical stabilities due to buttressing of the structure. Therefore, following the method of Scheme 2 but replacing 4-methylpyridine methiodide by its tetrahydroisoquinoline analogue **10**, we were able to prepare the ring-locked chromophores **11-13** (Scheme 3).[18] As was the case for the earlier compounds, the final products readily precipitated from solution and were isolated essentially pure by filtering and washing. A second iteration using the cyclic bisanil **14** gave precursor **15**, which in turn afforded ring-locked compounds **16** and **17** (Scheme 4).

Whilst it would have been interesting to couple the tetrahydroisoquinoline donor **10** to **15** to give a double ring-locked system, all attempts to carry this out were unsuccessful. The properties of the second generation chromophores are summarised in Table 2. Not only are the decomposition temperatures of the new compounds about 15 °C higher, but also the β values of **11-13** are *ca*. 50% higher than that of parents **4-6**, respectively. While it is logical to assume this stems from the improved pla-



Scheme 3. Synthesis of chromophores containing a tetrahydroisoquinolinyl donor.



Scheme 4. Synthesis of chromophores with ring locking in the conjugated interconnect.

narity of the molecular skeleton,[14] it has been shown that ring-locked compounds may be less planner due to steric interactions between the ring methylene groups and the protons of the polyenic conjugated system.[19] This twisting (*ca*. 30°) leads to a reduction in the dipole moment by around 50%. However, given that the extinction coefficients and calculated dipole moments (and planarities) of **11-13** are essentially identical to **4-6** it is unlikely that is occurring.

In the case of compounds **16** and **17**, it was not possible to obtain data for the first hyperpolarizability using DMSO or DMF as solvent; only in THF could data be obtained. Compound **16** (pyridinylidene donor) has a respectable response of 1,000 × 10^{-30} esu but **17**, with the quinolinylidene donor, has a β value of only 350 × 10^{-30} esu. This serves to emphasise that the response obtained with a given donor is heavily dependent on the polarity of the solvent. This is due to how the various donors determine

Table 2. Calculated and experimental linear and nonlinear optical properties of ring-locked chromophores **11**-**13**, **16**, and **17**.

Compound	λ_{max} (nm) DMF ($\log_{10}\varepsilon$)	λ_{max} (nm) MeOH	λ_{max} (nm) Pyridine	μ^a (calc.)/ 10^{-18} esu	β (exp.)/ 10^{-30} esu DMSO	$\mu_{(calc.)}\cdot\beta_{(exp.)}$/ 10^{-48} esu	T_d (° C)
11	573 (4.79)	564	602	17.1	400	4,425	310
12	598 (4.71)	586	657	17.2	1070	11,815	301
13	611 (4.77)	590	670	17.2	1110	16,375	265
16	637 (4.55)	622	700	17.1	1000[b]	17,100	308
17	739 (4.71)	715	878	16.8	350[b]	5,880	277

[a]MOPAC (CS Chem3D pro, Cambridge soft) AM1 level using the precise keyword. [b]Measured in THF.

where the chromophores sit on the hyperpolarizability vs BLA curve shown in Fig. 1, combined with the effect of solvent polarity on BLA in the ground state structure.[13,18]

Aggregation: a Significant Challenge

The NLO compounds we have developed ultimately are to be used in polymer systems, which have dielectric constants (ε) of 1-7. Thus, it is necessary to study their behaviour in environments similar to these. This is particularly important because the asymmetric distribution of electrons in a compound typically leads to intermolecular interactions between neighboring molecules in both solution and/or the solid state. This phenomenon is very common in the cyanine and merocyanine dyes and is termed *aggregation* or *self-association*. Aggregation of chromophores causes the shape of their UV spectra to deviate from normal and results in the appearance of extra bands (or shoulders). The position of these shoulders depends on the type of the aggregation present, *e.g*. H (hypsochromic) or J (named after Jelly)[20] aggregation. H-aggregation has shoulders that appear on the high energy side of the main absorption band whereas J-aggregation has them on the low energy side. Organic chromophores with highly polar, *i.e*. zwitterionic, ground states often exhibit poor solubilities and tend to readily form aggregates.[21] This can be seen from the various absorption spectra of 18, which is a basic chromophore with a $C_{10}H_{21}$ substituent attached to improve solubility (see Fig. 4).[18] The spectrum of **18** in DMF, THF and $CHCl_3$ (ε,: 38, 7.5 and 4.8, respectively) each displays a single symmetrical absorption band that

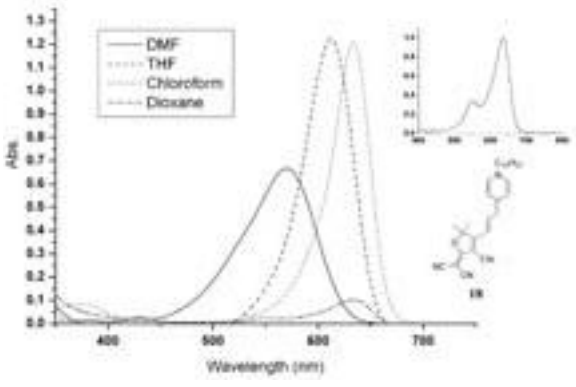


Fig. 4. UV-Vis absorption spectra of C10-containing chromophore **18**, in a range of solvents and (inset) in a host-guest thin film – 10% loading in amorphous polycarbonate.

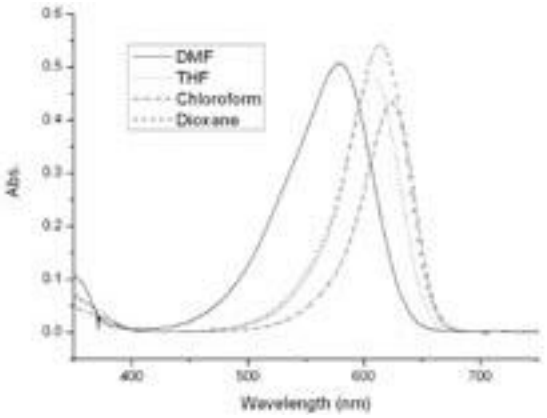
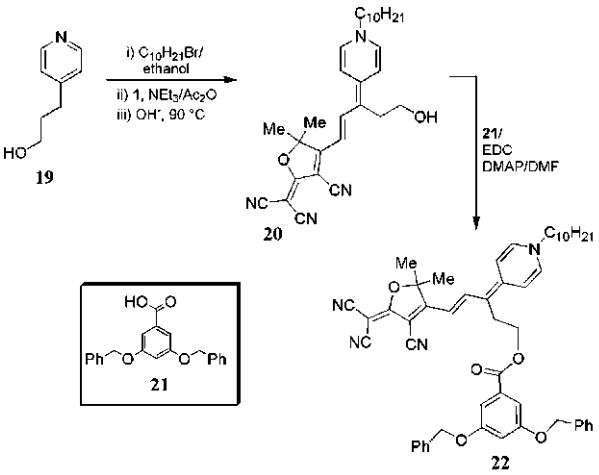


Fig.5. UV-Vis absorption spectra of **22** in different solvents.



Scheme 5. Synthetic route to chromophores with bulky groups attached to the interconnect.

indicates no aggregation to be present. However, when the spectrum is obtained in dioxane (ε = 2.2) the extinction coefficient drops and a high energy shoulder becomes evident especially in the thin film (see Fig. 4 inset) – this is indicative of significant aggregation. This is a potential pitfall when considering usage in NLO materials as it indicates that they may not be capable of incorporation into a host polymer at high loadings. Furthermore, the presence of significant aggregation will also lower the overall poling efficiency of the final NLO material as well as increase the propensity for relaxation of the aligned dipoles post-poling. This will result in a gradual decline over time of the observed macroscopic response.

As a result of these observations, further structural modifications to the active chromophores were needed to minimise aggregation. The inclusion of bulky, *arene-rich* substituents has been shown to be very effective in reducing aggregation and increasing the observed NLO response.[22] In particular, the inclusion of substituents that give the chromophore a more oblate (or disc shaped) structure are known to be the most effective. Consequently, we decided to synthesise some new compounds with bulky groups attached to the conjugated interconnect (Scheme 5). Once again the building block approach allows for easy introduction of a new component, in this case 4-pyridinylpropanol (**19**) in place of 4-methylpyridine. This provides ready access to **20**, which has a free alcohol group to which a range of substituents can be tethered. By way of example, coupling **20** with 3,5-dibenzyloxybenzoic acid (**21**) affords the bulky group-containing ester **22**.[23] A comparison of the UV-Vis absorption spectra of **18** (Fig. 4) and **22** (Fig. 5) shows the effectiveness of incorporating the bulky substituent. The spectra of **22** in all the solvents we have used give similar extinction coefficients and are free of shoulders. This, therefore, confirms that incorporating bulky groups onto the conjugated interconnects of our compounds provides a valid strategy for mitigating aggregation.

Future Directions

A number of the compounds described herein have been subjected to further study, especially to examine their photochemical stability and to determine their macroscopic NLO response (r_{33} value). Our molecules are quite robust on exposure to high intensity visible laser light. *e.g.* 633 nm, and their lifetimes are significantly increased when oxygen is absent.[24] Further studies to examine the usefulness of including additives such as anti-oxidants, *e.g.* β-carotene, are underway. More significantly, host-guest thin films containing these compounds have measured r_{33} values of over 300 pm/V.[25] This is approximately 10 times higher than the value found for the benchmark inorganic material lithium niobate (32 pm/V). Although the response slowly decays to around 50 pm/V over several weeks, this is not unexpected as we have yet to freeze the chromophores in place following poling using methods such as polymer cross-linking. We have also explored the covalent attachment of chromophores to the thermally robust polyimide backbones.[26] Another important step will be to modify the chromophores to improve solubility further. This will allow us to increase the number density of the chromophores in polymer matrices, which should, in theory, allow us access to materials with even higher macroscopic nonlinearities.

Acknowledgments

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The Ramberg-Bäcklund Reaction 70 Years On

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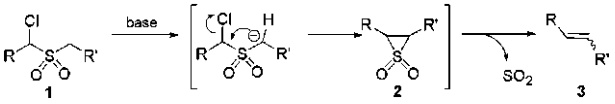
Introduction

Ten years ago, on a train between Warsaw and Krakow, I (JEH) learned about the Ramberg-Bäcklund reaction (RBR). At the time, I was a PhD student at the Australian National University, and my informant was Margaret Brimble, then at the University of Sydney. We had both attended the ICOS-13 conference in Warsaw. Subsequently, I spent three years as a post-doctoral fellow with Richard Taylor in York whose studies have pioneered many of the recent synthetic applications of the RBR. Now, 70 years after the initial disclosure of this reaction and with the Victoria University Organic Synthesis group beginning to apply the RBR in some of its synthetic endeavours, it seemed appropriate to provide some context for this fascinating and useful reaction in the modern setting. There have been many excellent reviews previously published on the Ramberg-Bäcklund reaction.[1] Our article focuses on recent applications (2005-2010) of the RBR in synthetic approaches to natural products and other bioactive molecules.

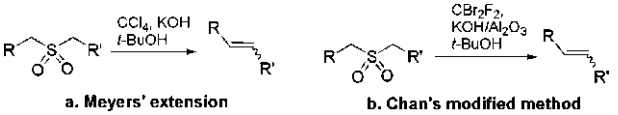
Background

In 1940, Swedish chemist Ludwig Ramberg and his student Birger Bäcklund published a method for transforming α-halosulfones into alkenes (Scheme 1).[2] Subsequent mechanistic investigations indicated that abstraction of a proton from the non-halogenated α-centre of **1** leads to formation of an episulfone **2**, which extrudes sulfur dioxide to provide the product alkene **3**.[3] The intermediacy of an episulfone was confirmed by Sutherland and Taylor through the isolation of an episulfone from a low-temperature RBR and its subsequent transformation to an alkene.[4]



Scheme 1

The utility of this reaction was greatly augmented by Meyers' development of a one-pot chlorination/RBR sequence, which overall converts a sulfone into an alkene using carbon tetrachloride, potassium hydroxide, water and *t*-butanol (Scheme 2a)[5] however, the formation of dichlorocarbene as a by-product of the reaction can lead to undesired reactivity in some instances.[1] There have been several variations of the one-pot halogenation/RBR, notably that by Chan in which the halogen source is dibromodifluoromethane and the KOH is adsorbed on an alumina support (Scheme 2b).[6] The starting sulfones can be prepared in a multitude of different ways.[1,7] One popular method involves oxidation of a thioether, which in turn may be generated by nucleophilic substitution of a halide (or similar leaving group) on one substrate by a thiol. This overall sequence has the potential to represent a major disconnection in a convergent synthetic strategy.



Scheme 2

The RBR has become a versatile method for preparation of alkene π bonds within a variety of structural motifs, including strained cyclic systems.[1] The position of an alkene prepared by the RBR is unambiguous, as required in modern target-oriented synthetic chemistry. Furthermore, SO_2 extrusion as a method for forming complex alkenes is more atom-economic[8] than several of the common alternative strategies, such as the popular Wittig and Horner-Wadsworth-Emmons reactions, and the Julia-Kocienski reaction.[9] Despite the fact that the alkene geometry cannot be predicted with certainty in all cases,[1] the utility of the RBR is amply demonstrated by its application in the synthesis of targets as diverse as dendrimers[10] and cyclophanes.[1] It has been used to provide key connections in synthetic routes to constituents of most natural product classes,[1] from alkaloids[11] and terpene derivatives[12] to enediynes[1] and complex polycycles.

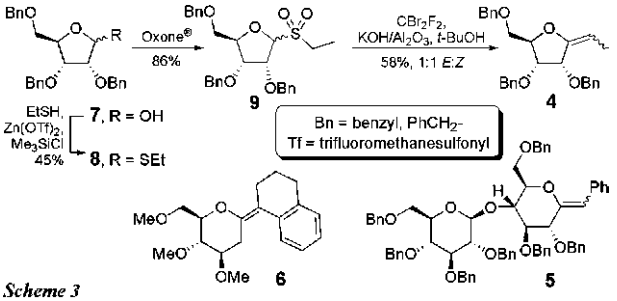
Synthesis of Targets Containing Modified Carbohydrates

A vast number of carbohydrates and their analogues have been synthesized using the RBR, with the Taylor and Franck groups making tremendous contributions to the field. Numerous other players have made valuable advances and diversified the applications of this chemistry.[13]

exo-*Glycals*

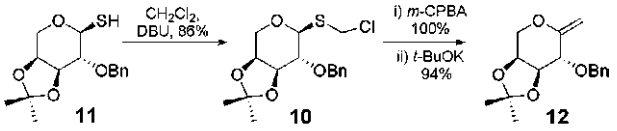
exo-Glycals are unsaturated carbohydrates with an exocyclic π bond at the anomeric site.[14] They have attracted attention as synthetic targets, in part because they can be transformed into a wide range of *C*-glycosides (*vide infra*) but also because of their potential use as glycosidase inhibitors.[15] The RBR is particularly versatile and allows for the synthesis of more highly substituted variants than other methods.[13] For instance, the Taylor group has prepared a number of diverse *exo*-glycals such as furanose **4** and disaccharide **5** (Scheme 3),[16] while Franck *et al*. have synthesized a variety that includes tricycle **6**.[17] The synthesis (shown for **4**) involves the ready conversion of a suitably protected sugar **7** into a thioglycoside **8** that is oxidized by one of a range of oxidants[16–18] to sulfone **9**. This undergoes halogenation/RBR to *exo*-glycal **4**.

A related method for the synthesis of methylidene *exo*-glycals has recently been reported;[19] (chloromethyl)thiogl ycosides, such as **10** (Scheme 4), are oxidized and using a



Scheme 3

classic (one-step) RBR. The thioglycosides are prepared from the appropriate glycosyl thiols, *e.g.* **11**, by reaction with CH_2Cl_2 in the presence of base. Oxidation with *m*-chloroperoxybenzoic acid provides access to sulfones that give the *exo*-glycals **12** when treated with base.

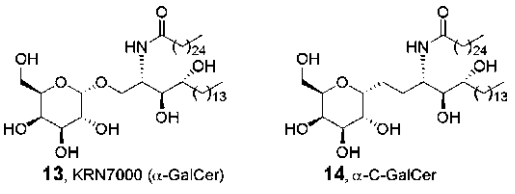


Scheme 4

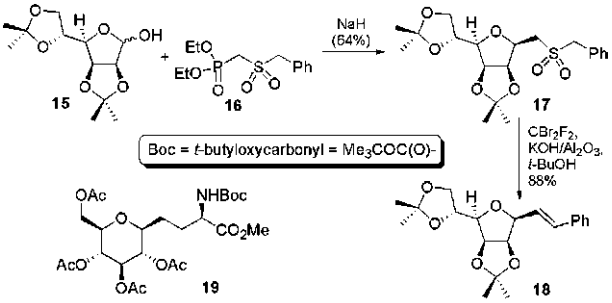
C-*Glycosides*

C-Glycosides are carbohydrate analogues in which the exocyclic oxygen of the anomeric acetal is replaced by carbon. The *C*-analogues tend to be more resistant to hydrolysis, which can enhance their efficacy as enzyme inhibitors and in binding to other biological molecules.

The Taylor and Franck groups have prepared a number of *C*-glycosides from *exo*-glycals using the RBR,[13,17,20] including an analogue of the potent immunostimulant KRN7000 (α-GalCer; **13**).[21] In fact, the *C*-linked analogue **14** stimulates increased production of certain cytokines involved in the immune response, and shows more pronounced anti-tumour effects in mice. The synthesis of **14** and discovery of its bioactivity has encouraged the design of ever more potent *C*-glycoside agents for adjuvant immunotherapy in humans. This discovery validated the ideas of using *C*-linked analogues of natural glycosides to achieve increased binding affinity for biological targets and thus obtain greater efficacy against many diseases.[22]



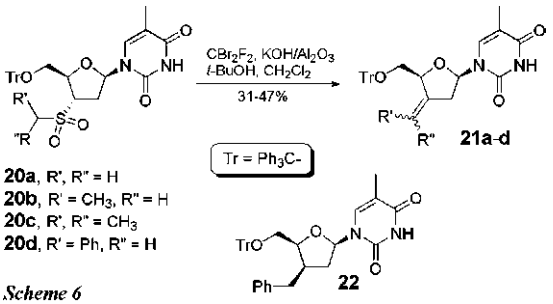
A direct route to unsaturated *C*-glycosides using the RBR has been developed by Taylor's group.[13] This is illustrated by the example of Scheme 5 that involves the Horner-Wadsworth-Emmons reaction of reducing sugar **15** with sulfonyl phosphonate **16**. Spontaneous conjugate addition of the resulting hydroxyl group to the resulting *α,β*-unsaturated sulfone gives ring-closed **17** that undergoes halogenation/RBR to *C*-glycoside **18**. This sequence can be achieved in a single pot,[13] on unprotected carbohydrates,[23] and with more complex phosphonates, making it a highly efficient route to *C*-glycosides, *C*-disaccharides, and *C*-linked glycosyl amino acids, such as **19**.[13] While the example of Scheme 5 displays excellent stereoselectivity in the conjugate addition step by providing only β-pseudo-anomer **18**, mixtures of isomers can arise. Recent research shows that, in some cases, stereoselectivity can be controlled by altering the temperature for the conjugate addition.[24]



Scheme 5

Thymidine analogues

A series of thymidine analogues with potential drug applications have recently been prepared in moderate yields using the RBR (Scheme 6).[25] Under Chan's conditions, 3′-deoxy-3′-sulfonylated thymidines **20a–d** provided the exocyclic methylidene products **21a–d** in 31–47% yield. For **21b**, an isomeric mixture of alkenes was formed, whereas **21d** was the sole isomer that gave the 3′-deoxy-3′-benzylthymidine **22**, a putative analogue of the anti-HIV drug AZT, on hydrogenation.[25]



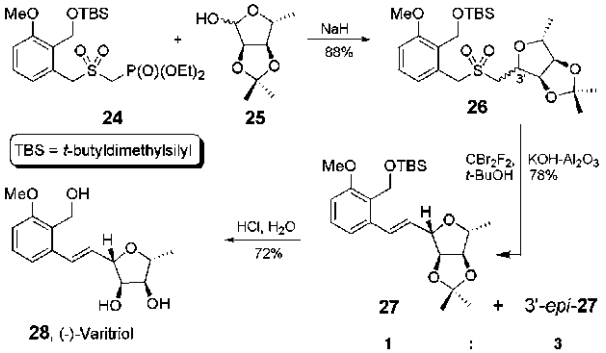
Scheme 6

Varitriol

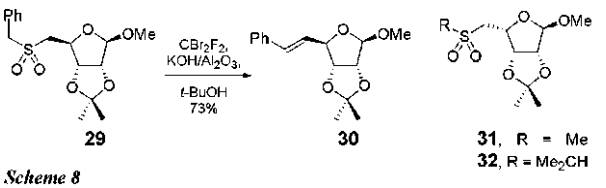
(+)-Varitriol was isolated from the fungus *Emericella variecolor* and is cytotoxic towards several cancer cell lines. A RBR-based synthesis of the unnatural enantiomer from D-ribose has been achieved by the Taylor group (Scheme 7).[26] The sulfonyl phosphonate **24** was prepared from methyl 2-methoxy-6-methylbenzoate in five steps. Coupling of this Horner-Wadsworth-Emmons reagent with D-ribose-derived **25** provided sulfone **26** as a mixture of 3′-isomers. RBR under Chan's conditions then provided the desired isomer of product **27** and its 3′-epimer, which were separately converted to the enantiomer of the natural product (**28**) and its 3′-epimer in a 1:3 ratio; the proportion of the desired isomer was improved to 1:1.3 by performing the HWE/RBR sequence as a single-pot process in THF with no added t-butanol. This indicates that tinkering with the reaction conditions may augment stereoselectivity. This synthesis provides a means to access both the natural product and a stereoisomeric analogue.

The related RBR of unsubstituted benzyl sulfone **29** gave alkene **30** in good yield as expected (Scheme 8).[27] How-

ever, the corresponding methyl and isopropyl sulfones did not undergo reaction but epimerized to **31** and **32** instead.



Scheme 7

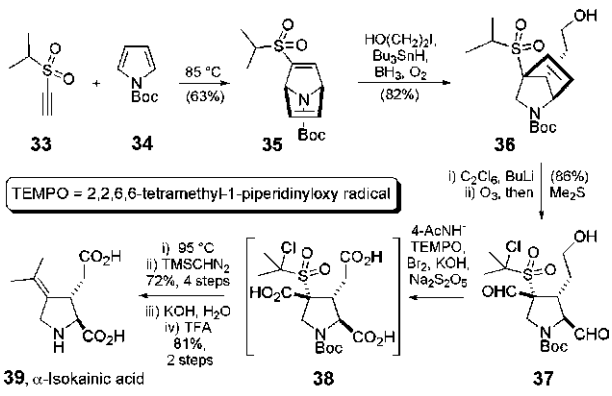


Scheme 8

Synthesis of Amino Acids

(+)-α-Isokainic acid

Kainoids are non-proteinogenic amino acids that have important roles as neurotransmitters in the mammalian nervous system. In a recent synthesis of (±)-α-isokainic acid (**39**),[28] a decarboxylative RBR is part of the sequence that forms the exocyclic alkene (Scheme 9). The key steps involve [4+2] cycloaddition of **33** and **34**, followed by radical-based conjugate addition of 2-iodoethanol to the unsaturated sulfone of **35** and consequent rearrangement of the bicyclic framework to the 2-azabicycle **36**. α-Chlorination and ozonolysis provided **37** that was isolated as a mixture of cyclic hemiacetals. Without purification, **37** was oxidized to triacid intermediate **38** that underwent decarboxylation and RBR. Subsequent methylation of the carboxylic acid moieties, purification, saponification and cleavage of the *N*-protecting group gave natural product **39**.



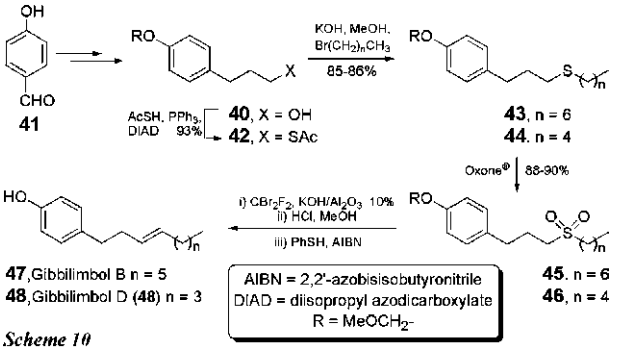
Scheme 9

Synthesis of Aromatic Natural Products

The RBR lends itself particularly well to the synthesis of natural products containing aromatic rings because of the ease with which benzylic sites undergo halogenation and proton abstraction. Nonetheless, this section includes examples where reaction occurs at non-benzylic positions.

Gibbilimbols B and D

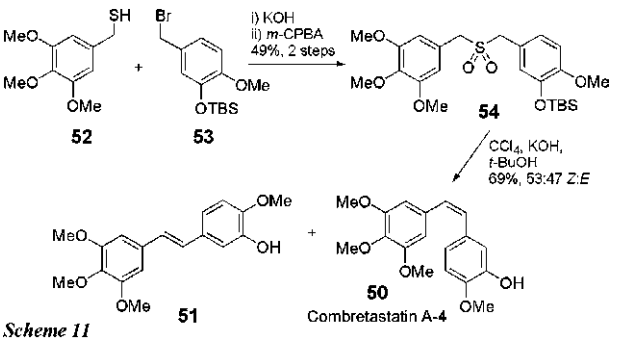
The leaves and juices from the bark of the Papua New Guinean shrub *Piper gibbilimbum* have been used as antiseptics to treat skin and internal ailments, and also some forms of cancer. Extraction of the leaves yields a family of natural products, the gibbilimbols, which display moderate anti-cancer and antibacterial activity.[29] A recent synthesis of gibbilimbols B and D (Scheme 10) was based upon the RBR.[30] The sulfone starting material was generated by Mitsunobu reaction of alcohol **40** [prepared from *p*-hydroxybenzaldehyde (**41**)] with thioacetic acid, followed by acetate deprotection of **42** and substitution of the appropriate alkyl bromide (1-bromoheptane or 1-bromopentane) by the resulting thiolate. Oxidation of thioethers **43** and **44** using Oxone® led to sulfones **45** and **46**. The RBR was sluggish, giving only 10% conversion and requiring recycling of the sulfone for further iterations. Adding to the poor reactivity was the fact that the products were generated as *ca*. 1:1 mixtures of *E*/*Z*-alkenes. However, after MOM deprotection, the (*Z*)-isomers underwent radical-induced isomerization to the thermodynamically favoured (*E*)-isomers **47** and **48**.



Scheme 10

Combretastatin A-4

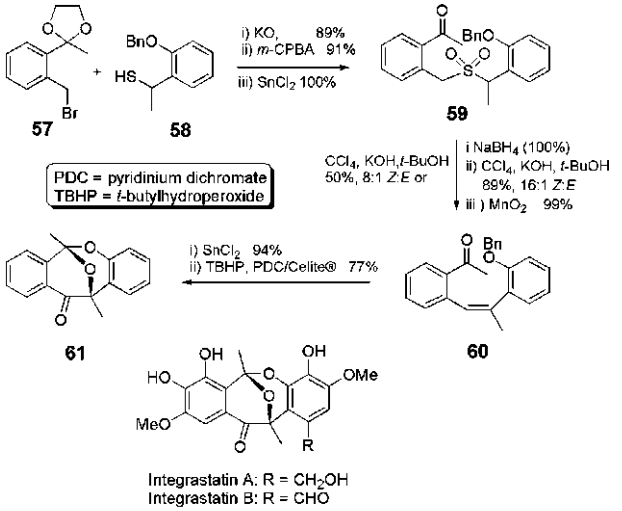
A series of stilbenes was generated using the RBR with interesting *E*/*Z* stereoselectivity gained by varying the reaction conditions.[31] These results include the synthesis of the anti-cancer agent combretastatin A-4 (**50**) and its (*E*)-isomer **51** (Scheme 11). Combretastatin A-4, from the bark of the African bush willow tree *Combretum caffrum*, binds tubulin and causes tumour cell necrosis.[32] Coupling of thiol **52** with benzylic bromide **53** and oxidation of the resultant thioether provided sulfone **54**. Subjection to a variety of RBR conditions gave mixtures of (*E*)- and (*Z*)-alkenes. Interestingly, Meyers' conditions gave significantly higher proportions of the desired (*Z*)-alkene **50** than those of either Chan or Franck (which uses $C_2Br_2F_4$ as the halogen source).



Scheme 11

Integrastatin nucleus

Integrastatins A and B, isolated in 2002, are potential HIV inhibitors.[33] Their bridged tetracyclic framework encompasses a high degree of oxygenation and was generated using a RBR as a key part of the strategy.[34] Coupling of the benzylic bromide **57** and thiol **58** (Scheme 12), followed by thioether oxidation and acetal hydrolysis gave sulfone **59**, which underwent RBR using Meyers' conditions to provide the (*Z*)-stilbene **60**. However, a higher yield and better (*Z*)-selectivity came from a reduction, RBR, and oxidation sequence. Improved (*Z*)-selectivity in the RBR of sulfones containing appropriately positioned benzylic hydroxyl groups, *viz*. the reduced form of **59**, likely comes from intramolecular promotion of SO_2 extrusion by the adjacent alkoxide.[35] Lewis acid-promoted benzyl ether deprotection and acetal formation was followed by benzylic oxidation to provide the tetracyclic core of the integrastatins in the form of structure **61** (Scheme 12).



Scheme 12

Synthesis of Polyenes

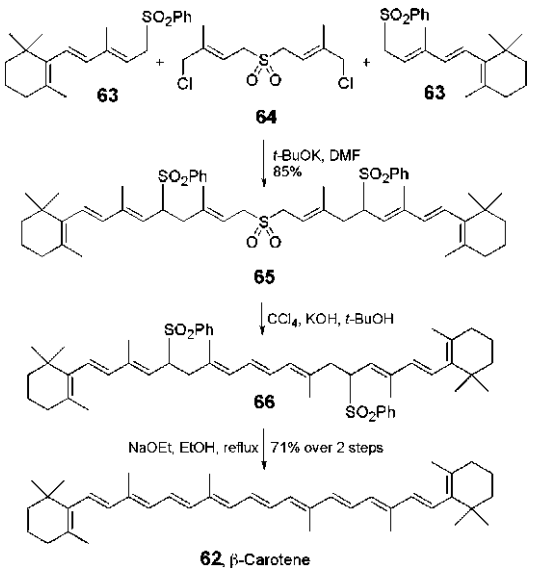
The RBR provides a useful method for preparing polyenes.[1,36] The precursor sulfones (or thioethers) are effectively *protected* alkenes, as they can be converted into the target alkenes but in the meantime lack many of the undesirable reactivity properties of a polyene, making them useful intermediates for chemical manipulations.

Carotenoids

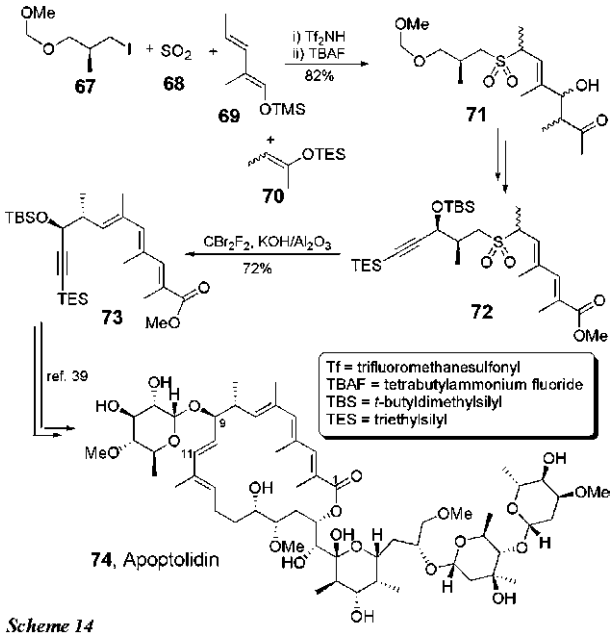
A number of carotenoids have been generated through use of dual sulfone chemistry, in which the RBR is a key player.[37] Amongst the products obtained have been β-carotene (**62**) and its oxidized counterparts canthaxanthin, astaxanthin, and astacene. The synthetic strategy, shown in Scheme 13 for β-carotene, involves coupling of sulfone α-anions (derived from **63**) with sulfone-containing dichloride **64** to produce trisulfone **65**. The chain-embedded sulfone then partakes in a RBR to form conjugated triene **66**; subsequent base-promoted dehydrosulfonation provides the fully conjugated carotenoid **62**.

Apoptolidin (formal synthesis)

A formal total synthesis of the cytotoxic agent, apoptolidin, was realized[38] through use of Ramberg-Bäcklund technology to generate a key intermediate from a previous route.[39] The four components, **67**–**70**, were coupled in a one-pot reaction by electrophilic conjugate addition of sulfur dioxide (**68**) to enol ether **69**, attack of enol ether **70** on the resulting intermediate, and, upon addition of iodide **67** and a desilylating agent, formation of sulfone **71** (Scheme 14). A series of transformations yielded alkyne **72** that underwent a RBR using Chan's conditions to produce Nicolaou's apoptolidin fragment **73**, constituting the C1-C11 portion of the natural product **74**.



Scheme 13



Scheme 14

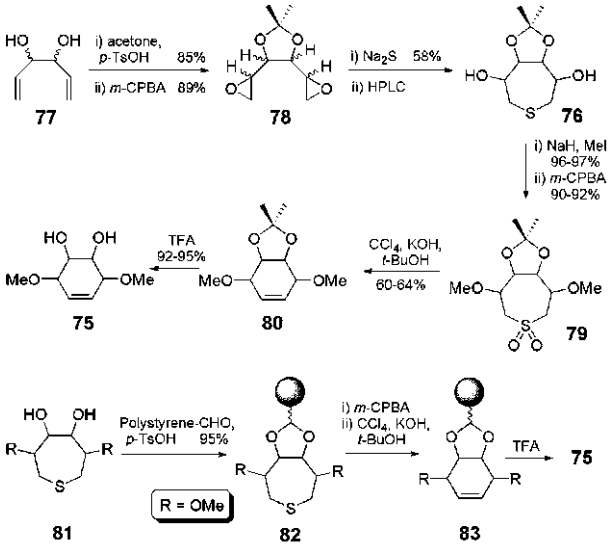
Ring Formations by the RBR in the Synthesis of Cyclic Natural Products

The Ramberg-Bäcklund reaction is finding an important role in the synthesis of medium-to-large ring compounds.[40] Its efficacy in forming cyclic compounds can be attributed to the fact that it operates as part of a two-step process: ring closure (often by nucleophilic attack of a thiol on a halide) forms an (*n*+1) cycle and is followed (not necessarily immediately) by the RBR which causes ring contraction to the target cyclic compound with ring size *n*. This sequence can provide benefits over other methods that involve direct ring closure because, in com-

parison to the desired *n* ring system, the formation of a larger (*n*+1) ring system typically reduces the amount of ring strain that must be overcome in the cyclization step. Furthermore, thiols are very reactive nucleophiles as a result of their polarizability, electron density and basicity,[41] meaning that they are well suited to cyclization reactions with large activation barriers. The recent examples presented here are in order of increasing ring size produced in the RBR.

Conduritols

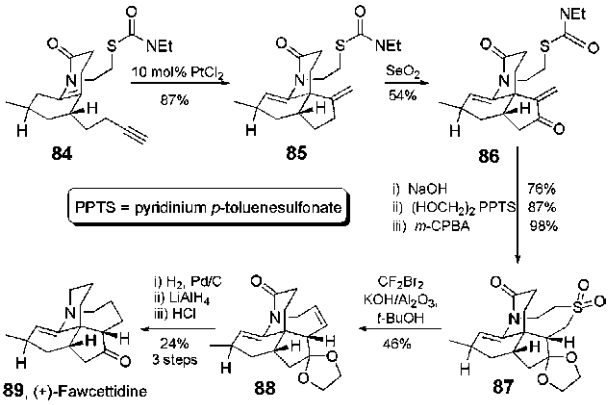
The conduritols are a family of stereoisomeric unsaturated cyclitols, which have shown biological activity as glycosidase inhibitors.[42] Conduritol was isolated from the bark of the vine *Marsdenia condurango* in 1908, but its structure and stereochemistry was not determined until 30 years later. The biogenesis of the natural conduritols has been traced back to D-glucose and D-galactose. Syntheses of ***all ten*** stereoisomeric conduritols (as the dimethyl analogues **75**) have been achieved through oxidation and RBR of thiepane isomers **76** (Scheme 15).[43] Thus, a mixture of stereoisomeric allylic diols **77** were protected and epoxidized to give **78**, which reacted with sodium sulfide in a double substitution reaction to afford the stereoisomeric thiepanes **76**. The ten separated (HPLC) thiepanes **76** were then methylated and oxidized to the corresponding sulfones **79**. RBR under Meyers' conditions then afforded cyclohexenes **80**, and deprotection gave products **75**. Notably, the chemistry was demonstrated to work equally well on solid supports. Thus, a polystyrene-CHO resin was appended to the thiepanes **81** to give acetals **82**. After oxidation, the RBR was carried out to provide alkenes **83**, which, after removal from the resin, led to two conduritol isomers **75**.



Scheme 15

Fawcettidine

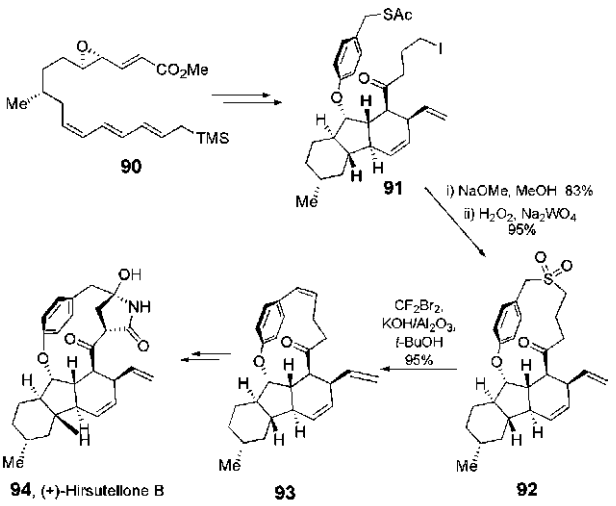
Fawcettidine contains a complex tetracyclic ring system and is a member of the *Lycopodium* family of alkaloids, some of which inhibit acetylcholine esterase, a promising target for the treatment of Alzheimer's disease. The seminal total synthesis of (+)-fawcettidine by Kozak and Dake employed the RBR in an elegant late-stage construction of the seven-membered ring.[44] Bicyclic alkyne **84** (Scheme 16), prepared from the monoterpenoid chiral pool reagent (*R*)-(+)-pulegone, underwent a Pt(II)-catalyzed annulation to form tricycle **85**. This was followed by allylic oxidation to **86** using selenium dioxide. The thiocarbamate protecting group was cleaved under basic conditions, and conjugate addition of the resulting thiolate occurred spontaneously. Ketone protection as a cyclic ketal and thioether oxidation gave sulfone **87**. RBR of this using Chan's procedure successfully produced the desired tetracyclic product **88**, which was hydrogenated, the amide group reduced to an amine, and the ketone revealed to afford the natural product **89**.



Scheme 16

Hirsutellone

Hirsutellone B is a fungal secondary metabolite that displays exciting antimicrobial activity against *Mycobacterium tuberculosis*, the causative pathogen of tuberculosis. In the seminal total synthesis of (+)-hirsutellone B, Nicolaou and co-workers used a RBR to form a highly strained, 13-membered *p*-cyclophane ether.[45] The fused tricyclic system was generated by an elegant intramolecular epoxide opening/Diels-Alder cascade reaction of epoxide **90** (Scheme 17), itself prepared by chain extension of (+)-citronellal. While the cascade reaction proceeded in a modest 50% yield, the desired [6.5.6] tricycle was obtained as a single stereoisomer! A series of transformations led to the iodothioacetate **91**, which underwent deacetylation and immediate cyclization with base. The resulting 14-membered thioether was oxidized to the corresponding sulfone **92** using hydrogen peroxide and so-

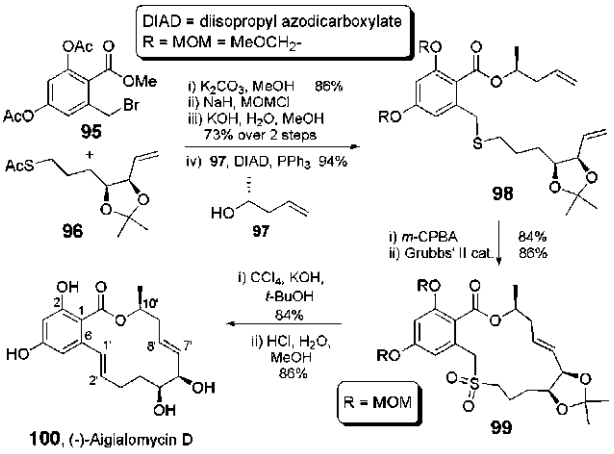


Scheme 17

dium tungstate. The RBR was performed using the Chan protocol and produced the desired 13-membered ring **93** in 95% yield, suitably functionalized for conversion to the natural product **94**.

Aigialomycin D

The family of resorcylic acid lactone natural products is synthetically sought after for the myriad of biological activities engendered by its components.[46] (-)-Aigialomycin D, isolated[47] in 2002, displays moderate anti-malarial and anti-cancer properties, inhibiting kinases CDK1, CDK5 and GSK3. Last year, our team published a synthetic route to this macrocyclic natural product, **100**, that relies upon a ring-closing metathesis/RBR sequence to form the 1,7-diene (Scheme 18).[48] The methyl orsellinate-derived benzyl bromide **95** underwent nucleophilic substitution by a D-ribose-derived thiol formed by deacetylation of **96**. After protection of the thus-formed phenolic groups and ester hydrolysis, a Mitsunobu reaction of the resulting acid with homoallylic alcohol **97** allowed installation of the branched ester within **98**. Oxidation of the thioether preceded the RCM step in order to avoid unwanted complexation of Grubbs' second generation catalyst by the thioether. The sulfone **99** represents a masked alkene, necessary to avoid a competing RCM process to a cyclohexene by-product, as seen in other routes.[49] A high-yielding and completely *E*-stereoselective RBR using Meyers' conditions afforded protected aigialomycin D, which was transformed efficiently to the natural product **100**.



Scheme 18

Concluding Remarks

The past 70 years have seen the RBR progress from a mechanistically interesting observation to part of the synthetic chemist's toolbox of versatile and widely applied transformations. We have endeavoured here to demonstrate the diversity of uses for the RBR in recent times and to showcase the considerable potential that this reaction holds for future synthetic efforts.

Acknowledgements

We thank Victoria University for a PhD Scholarship (MB) and the Tertiary Education Commission (Bright Futures) for support of our work. We are very grateful to Prof. Richard Taylor for assistance with this article.

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Obituary: Raymund Marshall Golding AO (1935-2009)

Prof R. M. Golding MSc (NZ), PhD (Canterbury), DSc (NSW) died at his Mooloolah home in Queensland on 21 November 2009 after an illness of some months. He was a Fellow of NZIC (1966) and its 1967 Easterfield Medal recipient. He had distinguished scientific and academic careers on both sides of the Tasman.

Ray was born at Westport on 17 June 1935 to parents who were teachers in the Buller area. He received his secondary schooling at Auckland Grammar (1949-53), and attended Auckland University (1954-57) gaining MSc (Chemistry, 1st Class). He became a Scientific Officer in the Dominion Laboratory (later Chemistry Division, DSIR) in 1958 and then, in 1960 he took up a NZ National Research Fellowship at Cambridge University gaining his PhD in 1963. On return to DSIR he was appointed head of a new Theoretical Chemistry Section and he set about putting each of three relatively new spin resonance techniques, NMR, ESR and Mössbauer spectroscopy on a sound theoretical footing. The latter technique, introduced to NZ by the late Prof James Duncan, was the catalyst for a fruitful Golding-Duncan collaboration during the 60s. During this period Ray also completed his first book *Applied Wave Mechanics* (van Nostrand, 1969) which resulted, largely, from a two-year post-graduate lecture series given during 1964 and 1965 at VUW.

In 1968 he applied successfully for the vacant chair in Physical and Theoretical Chemistry at the University of New South Wales, a position that he held until 1978 whilst maintaining his contacts with NZ science and academia. David Rae (AU and DSIR) joined his staff as lecturer and the writer was a Teaching Fellow in his department (1969-71). Other postdoctorals/Visiting Fellows included Margaret Halton and Gary Burns (VUW), Barrie Peake (UC, later Otago) and Helen Bergen (Massey). In 1978, Ray became Pro-Vice-Chancellor at UNSW, a position that he held until 1986. In this capacity he was largely responsible for setting up the Australian Defence Force Academy in Canberra. In 1986, he became Vice-Chancellor at James Cook University in Townsville, a position that he held until his retirement in 1996. During his tenure at James Cook, the university doubled its student numbers, expanded its course offerings by a factor of three, became a multi-campus university with associated commercial companies, and doubled its assets. For services to education, science and the arts he was awarded Officer of the Order of Australia, General Division, in 1994.

As a scientist, Ray had an extraordinarily wide range of interests that did not cease when he moved into university administration. Together with one or two enthusiastic Research Fellows, he continued to work and publish in subjects that ranged from abstract group theory and quantum mechanics to medically-oriented publications and, until ill health intervened in mid-2009, effects of climate change. During his 10 years at James Cook he drafted 9 of 11 chapters of a new advanced text on quantum mechanics, a book eventually published in 2008. Ray's versatility is evident from his authoring of more than 120 research papers, a book chapter, and the following four books:

> *Applied Wave Mechanics*, van Nostrand: London, 1969; *Chemistry, Multistrand Senior Science for High School Students*, 1975; *The Goldings of Oakington* (A complete history and family tree of the Golding family of Oakington, Cambridgeshire from about 1650), 1992; and *Quantum Mechanics in Chemical Physics – an Exploration*, Common Ground Publishing, 2008.

Despite this full life, Ray was also Board Member/Director/Chairman of around 20 organisations from 1986. These include The Board of Senior School Studies NSW (1975-86), The Australian Festival of Chamber Music Pty. (1990-96), and The Australasian Marine Science Consortium (1984-2002). Apart from his FNZIC, he was a Fellow of the RACI, the Institute of Physics (UK), the Royal Society of Arts, the Australian Academy of Technological Sciences and Engineering, PACON International, and the Royal Astronomical Society.

Ray Golding always had time for colleagues, research fellows and students. He was never too busy to spend time carefully going through theory or discussing the detail of current research with them. Typically, he would set aside his Saturdays at UNSW and spend an hour or more with each student or research fellow in turn discussing progress, current stage of knowledge and future projections.

Following retirement from James Cook in 1996, Ray and wife Inge moved to a semi-rural property at Mooloolah, some 80 km north of Brisbane; *down on the farm* was the way Ray described it. At about this time, Ray was diagnosed with polymyositis, a rare degenerative muscular problem that affected his legs in particular. That hampered his movements to some extent but it did not stop him from cutting 2.5 Ha of lawn and generally tending to the *farm*, for some 12 years of retirement.

Ray is survived by wife Inge, two married daughters Tanya (Sydney) and Elke (Adelaide) and four grandchildren.

Craig Tennant

Article

Glycolipids and CD1: The Crossroad between Chemistry and Immunology

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Introduction

Research during the initial phase of the molecular biology revolution of the 1960s led to the paradigm that biological information, encoded in the genome, flows from DNA, to RNA, to protein. At the time, the understanding of the role of carbohydrates in living organisms was limited, with carbohydrates generally regarded as a source of energy or structural framework within cells and tissues.[1] However, over a decade later, the discovery of carbohydrates that play a vital role in key biological processes such as signalling, cell-cell communication, and molecular recognition opened a new field of research termed glycobiology.[2] A large number of polymers of two or more sugar units (oligosaccharides) decorate the plasma membrane of a cell and are responsible for cellular interactions and the recognition of pathogens. These oligosaccharides are connected to a non-carbohydrate portion, usually a protein or a lipid, giving rise to glycoconjugates known as glycoproteins and glycolipids, respectively.

Given that the immune system operates largely via receptor-ligand recognition, it is not surprising to find that glycoconjugates are capable of activating and modulating the immune response. Indeed, the blood group determinants, first noted by Karl Landsteiner over 100 years ago[3] but not structurally elucidated until the 1960s, are carbohydrate antigens found on the surface of red blood cells.[4] It is these carbohydrates, in the form of glycolipids and glycoproteins, that are responsible for the rejection observed during blood transfusion with incompatible blood groups.

Numerous bacterial cell wall glycolipids have also been found to have an important role in the immune response. In particular, the discovery that mycolic acid [a non-peptide lipid antigen from *Mycobacterium tuberculosis* (*MTb*)] stimulates T cells via a family of proteins called CD1, paved the way towards the discovery of a host of glycolipids that activate the immune system in a similar manner.[5] Subsequently, other glycolipid cell wall components of *MTb*, such as glucose monomycolate (GMM), phosphatidylinositolmannoside (PIM) and lipoarabinomannan (LAM) were found to be immunogenic.[6]

We present here some of the key glycolipids involved in regulating the immune response via their interaction with CD1 and T cells. Particular emphasis is placed on the glycolipid structure, the source of the glycolipid, and the specific type of CD1 protein with which the glycolipid interacts.

CD1 Proteins

CD1 molecules are proteins found on the surface of white blood cells including dendritic cells, macrophages and B cells. Collectively, these cells are known as antigen-presenting cells (APCs). In humans, the CD1 family consists of five members, CD1a-e, that are further classified into three major groups depending on their amino acid sequence. Thus, CD1a-c belong to group 1; CD1d to group 2; and CD1e to group 3. CD1 has a binding groove that is narrow and deep and consists of hydrophobic amino acids that are able to accommodate long alkyl chains of glycolipid tails.[7] In a CD1-glycolipid complex, the polar head group of the glycolipid protrudes from the CD1 binding pocket (Fig. 1).[8] This complex is recognised by T cells via the T cell receptor (TCR), and the interaction of CD1-glycolipid-TCR initiates a cascade of intracellular signalling which activates the T cells to produce signalling molecules, termed *cytokines*. The type of immune response generated is dependent on the cytokine profile produced.

The exact effect that the structure of the glycolipid has on CD1-glycolipid-TCR immune response is only known in a very general sense. It has been proposed that the stability of the glycolipid-CD1 molecule dictates the duration of T cell stimulation, which in turn influences the immune response. A prolonged TCR stimulation is thought to lead to a pro-inflammatory response whereas a transient TCR stimulation gives an immunomodulatory response.[9] Other processes such as CD1 and glycolipid trafficking into the cell, and glycolipid processing have also been found to affect the immune response.[10] Modification of the sugar head groups also affects TCR recognition of the glycolipid-CD1 complex, suggesting that the interaction between the TCR and the glycolipid-CD1 complex is highly specific. The ability to control the immune response via the development of specific CD1-binding glycolipids is a desirable research objective. It can be useful in the treatment of many diseases, including cancer, bacterial infections and autoimmune diseases such as multiple sclerosis and systemic lupus.

A CD1 molecule consists of two chains, the β_2-microglobulin chain and a heavy chain with three extracellular domains (α1-α3) (Fig 2A).11 The heavy α chains form hydrophobic binding pockets, A' and F', that are able to accommodate the lipid tails of glycolipids, as shown by the crystal structure of CD1d bound to the glycolipid α-galactosyl ceramide (Fig. 2B).[12] An extensive hydrogen bonding network holds the sugar head group in place for recognition by the TCR.

In a similar manner to CD1d, the human CD1a molecule possesses the A' and F' binding pockets (Fig. 2B). The human CD1b isotype, however, has four binding pockets, A', F', C' and T', and is thus able to accommodate alkyl chains up to 80 carbons in length.[13] To date, there are no high-resolution structural data for CD1c, but computa-

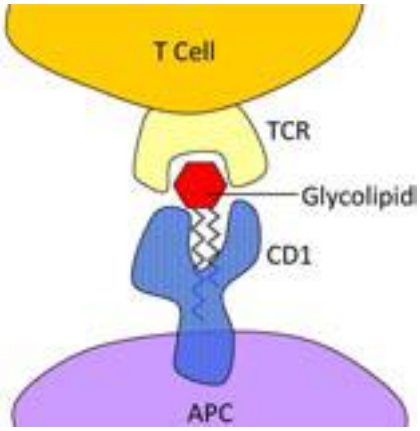


Fig. 1. Representation of CD1-glycolipid-TCR interaction during glycolipid antigen presentation.

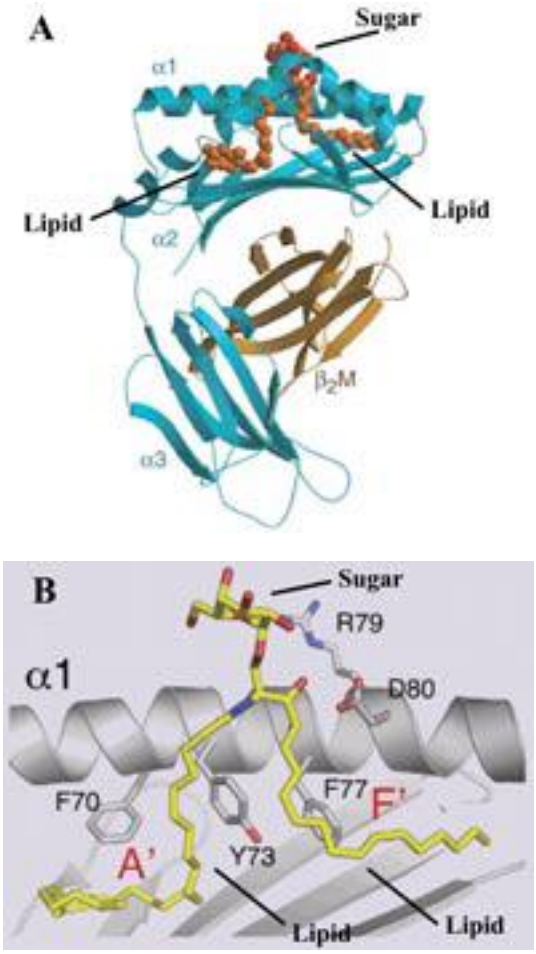


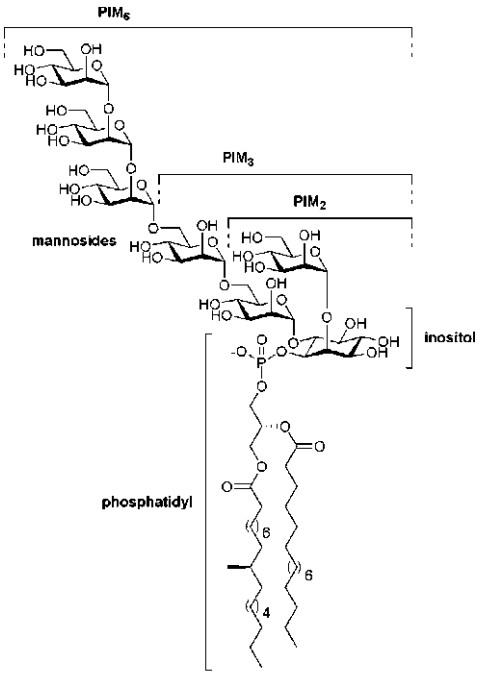
Fig. 2. Human CD1d complex with α-galactosyl ceramide: A) CD1d structure (α1–α3 domains, blue; β_2M, yellow); adapted with permission from Macmillan Publishers Ltd., Nat. Immunol - ref 1], copyright 2005; B) a side view of crystal structure of human CD1d in complex with α-GalCer. The α2-helix is removed for clarity and the side chains of some key amino acids are indicated. Reprinted from ref. 12 with permission; copyright 2007, Elsevier.

tional studies of it in a complex with a *MTb* glycolipid mannosyl-β1-phosphomycoketide (MPM) indicate that the enlarged F' pocket is responsible for binding bacterial polyketide with a multiply branched, unsaturated alkyl tail.[14] CD1e has low homology with other CD1 proteins. It has only a spacious single binding pocket but it can accommodate large lipid molecules. Unlike CD1a-d, which are expressed on the cell surface of antigen-presenting cells, CD1e is found primarily in the Golgi compartment and is believed to be crucial for glycolipid processing. Given the differences in structure of the CD1 molecules, it is not surprising that each shows some degree of specificity with respect to the glycolipids they bind.[8] Roughly, the CD1-binding glycolipids are divided into three classes: the phosphoglycolipids, the mycolates and the sphingoglycolipids. Each of these classes of compounds, and their effects on the immune response, is discussed below.

Phosphoglycolipids

Phosphoglycolipids are glycolipids that contain a hydrophilic polar head group (a sugar moiety) connected to one or more phosphate groups, which in turn, are connected to a hydrophobic tail comprised of two fatty acyl chains. They are commonly found in cell membranes and can form lipid bilayers. Phosphoglycolipids that bind to CD1 and induce T cell responses are phosphatidylinositol mannosides (PIMs; **1**) mannosyl-*β*1-phosphodolichol MPD; **2**) and mannosyl phosphomycoketides (MPM; **3**).

Phosphatidylinositol mannoside



1a, PIM_2; **1b**, PIM_3; **1c**, PIM_6

Fig. 3. Phosphatidylinositol hexamannosides (PIM_2-PIM_6).

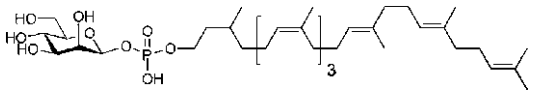
The PIMs **1** were first isolated from *MTb* in 1930,[15] and were characterized in 1960 by Ballou and colleagues.[16] *MTb* contains several PIM structures, including PIM_1, where the inositol residue of phosphatidyl-*myo*-inositol (PI) is mannosylated at the C-2 position, and PIM_2 (**1a**) where PIM_1 is further mannosylated at C-6 position of the inositol moiety. Further α-1,6 mannosylation of PIM_2 gives rise to PIM_3 (**1b**) and PIM_4 – the common precursor of PIM_5 and PIM_6 (**1c**), which are made by consecutive α-1,2 mannosylation of PIM_4.

In 2004, PIMs were shown to be a natural antigen for CD1d-restricted T cells.[17] In this study, a number of mycobacterial lipids were tested, but only a mixture of

different PIMs stimulated NKT cells via CD1d binding, and triggered an antigen-specific IFN-γ production and cell-mediated cytotoxicity. The structural parameters for CD1d binding included the need for two acyl chains on the phospholipid (PIMs may also contain a lipid at the C-6' position of PIM_2, but this is not necessary for CD1d binding), and the presence of a polar head group was required for recognition by T cells. Interestingly, CD1e activates lysosomal mannosidase in order to break down larger PIM analogues, *e.g.* PIM_6, into PIM_2 that can then be identified by CD1d.[18] PIMs have potential to be used as adjuvants, as seen in studies by Painter and co-workers,[19] where it was found that PIM ether analogues activate immature bovine dendritic cells. The first total synthesis of PIM_2 and PIM_6 was reported in 2006,[20] followed shortly thereafter by the synthesis of an alternatively acylated analogue.[19]

Mannosyl-β-1-phosphodolichol

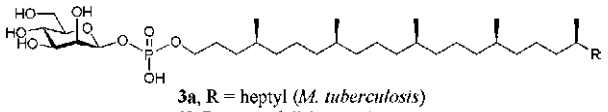
Mannosyl-*β*-1-phosphodolichol (MPD) belongs to the family of glycosyl-1-phosphopolyprenols that are found in all cells. Amongst different organisms, the long chain isoprenoids differ in length, saturation, phosphorylation and glycosylation. MPD consists of a mannosyl *β*-1-phosphate moiety attached to a partially saturated polyprenoid lipid. Multicellular organisms have the longest ($C_{90\text{-}100}$) dolichols, while fungi and protozoa have shorter chain lengths ($C_{70\text{-}90}$ and $C_{50\text{-}65}$, respectively).[21] Synthetic MPD, with shorter chain lengths ($C_{30\text{-}34}$), have been shown to stimulate T cells,[22] while no activation was observed for lipids with longer chains ($C_{55\text{-}95}$). MPDs with a chain length similar to those found in Mycobacteria ($C_{30\text{-}35}$) give the strongest T cell response.



2

Mannosyl-β-1-phosphomycoketide

Mannosyl-*β*-1-phosphomycoketides (MPMs, **3**) are potent mycobacterial antigens, and have been isolated recently from *MTb* (**3a**) and *M. avium* (**3b**).[21] These phospholipids contain a mannosyl-*β*-1-phosphate moiety similar to that found in **2**; however, the lipid portion consists of a pentamethylpentacosyl unit which is fully saturated and was first reported by Crich and Dudkin[23] in 2002, and more recently by Van Summeren and colleagues.[24]



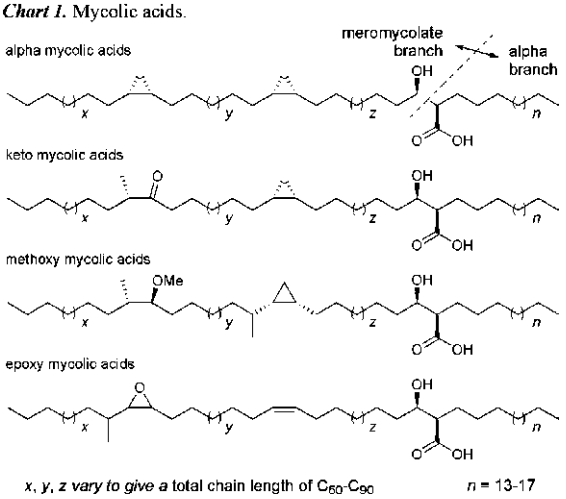
3a, R = heptyl (*M. tuberculosis*)
3b,R = pentyl (*M. avium*)

MPD and MPM are the two classes of antigens that are presented by CD1c molecules. The presence of repeating isoprenoid units in both antigens and their binding to CD1c isoforms indicates that methyl branching is an isoform-specific motif for CD1c-presented antigen.[21] Indeed, in recent work by Jong *et al*.[22] it was shown that methyl branching in MPM and MPD contribute to T cell activation. It is thought that the repeating units may help retain the lipid inside the CD1c groove, in the same way as straight chain lipids interact with the unbranched A′ pocket of the CD1a molecule.[22] Studies of MPM from mycobacterium strains show that the lipid portion is the important moiety that allows CD1c-restricted T cells to distinguish between self MPDs and foreign MPMs.[25] Since polyisoprenoid lipids are made by all mammalian cells, T cells have been shown to be specific for particular branched antigens, such as those synthesised by disease-causing *Mycobacteria* species which consist of a *β*-carbohydrate linkage, a C_{30} branched lipid chain containing five methyl groups, phosphates, and mannose groups of *S*-stereochemistry.

Glycosyl Mycolates

Mycolic acids (Chart 1) are *α*-alkyl, *β*-hydroxy fatty acids that are present in most mycobacterium species and also in related taxa-like *Corynebacterium* and *Nocardia*.[26] Mycolic acids from different taxa vary in the number of carbon atoms present: 30-36 for *Corynebacteria*, 40-60 for *Nocardia*, and 80-90 for *Mycobacteria*. The first such acids isolated were obtained by Stodola and colleagues in 1938 from human tubercle bacillus.[27]

Chart 1. Mycolic acids.

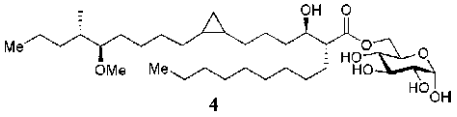


In 1950, Asselineau and Lederer showed that mycolic acids are high molecular weight β-hydroxy fatty acids with a long alkyl chain at the α-position. Subsequent studies revealed that they have at least two stereogenic centres that are located α and β to the carboxylic acid, each with *R* stereochemistry.[28] There are two distinct motifs in mycolic acid: the meromycolate branch and the alpha branch. The alpha branch is similar in every mycobacterial mycolic acid and differs only in chain length. The meromycolate branch, however, is more variable and different acids are classified according to the functionalities found in the meromycolate region.[29] Mycolic acids are restricted to binding to CD1b molecules and were the first lipid antigens found to induce T cell activation via binding to CD1b molecules.[5] Some of these acids have recently been synthesised.[30]

Glucose-monomycolate

Glucose-monomycolate (**4**, GMM), a glycolipid consisting of mycolic acid attached to the 6-position of glucose, is present in numerous bacterial species including *Mycobacterium*, *Rhodococcus* and *Nocardia*. It is a known potent ligand for human T cells when presented by group 1

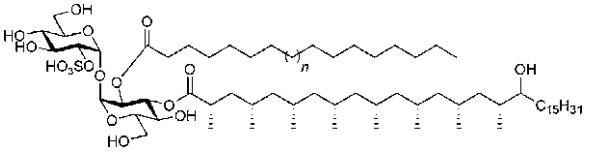
CD1 molecules. Studies have shown that the recognition of GMM by CD1b-restricted T cells is highly specific for the glucose moiety, the *R*,*R* configuration of the mycolic lipid, and the linkage of the mycolate to the glucose unit.[31-33] Variations in the lipid chain of GMM did not change the T cell response to GMM.[31] *Mycobacteria* are unable to synthesise GMM outside the host cell since a non-mycobacterium source of glucose is needed. Accordingly, GMM is only produced by a pathogenic mycobacterium after infection of the host cell.[32] The crystal structure of the CD1b-GMM complex has been solved and shows that both the acyl chains are buried in the antigen binding groove of CD1b, thus leaving the glucose unit exposed to the surface for recognition by TCR.[34] Similar to the CD1a crystal structure, the CD1b-GMM structure shows that a portion of the acyl chain protrudes from the F' pocket.[35]



4

Diacyl trehalose sulfates

The two diacyl trehalose sulfates ($Acyl_2SGL$) **5a** and **5b** have been recently identified as a new mycobacterial antigens that are able to stimulate T cells through CD1 binding.[36] They consist of a trehalose core that is acylated at the 3-position by a hydroxyphthioceranoic acid and at the 2-position by stearic or palmitic acid to give **5a** and **5b**, respectively. In a study by Gilleron *et al*., the addition of $Acyl_2SGL$ to T cells infected with the virulent *MTb* strain H37Rv resulted in intracellular killing of the bacteria via release of IFN-γ. This occurred by stimulation of CD1b-restricted human T lymphocytes by $Acyl_2SGL$, suggesting that $Acyl_2SGL$ or its analogues could be used as subunits in vaccines against tuberculosis.[37] Guiard and co-workers investigated the T cell activation of $Acyl_2SGL$ by varying the length, position, and structure of the fatty-acid residues. The analogues able to stimulate T cells had a saturated or monounsaturated polymethylated fatty acid and the stereocentres at the 3-position of the trehalose were of *S*-configuration. Naturally occurring $Acyl_2SGL$ was most potent in T lymphocyte activation.[38] The length of the fatty acid chain at the 2-position also influences antigenicity. Analogues with C_{16} acyl chains at the 2-position and multi-branched $C_{22\text{-}24}$ lipids at the 3-position stimulated T cells. However, compounds with a short fatty acid chain (C_8) did not lead to T cells stimulation.[39] These studies suggest that $Acyl_2SGL$ can be used as a subunit vaccine against tuberculosis and also in designing lipids that could be used in these vaccines. The first synthesis of diacyl trehalose sulfate and its analogues were reported by Guiard and colleagues[38] in 2008.



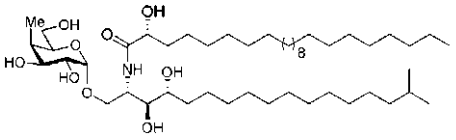
5a, $n = 1$; **5b**, $n = 3$

Glycosphingolipids

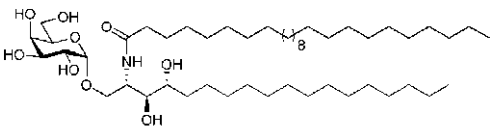
Glycosphingolipids consist of a carbohydrate portion and a ceramide lipid that contains a fatty acid and a sphingosine chain. Aside from α-galactosyl ceramide (α-GalCer), most glycosphingolipids are self antigens able to induce an auto-reactive T cell response. The presentation of self antigens to T cells differs greatly from the presentation of antigens from mycobacterial glycolipids. Glycosphingolipids are presented to T cells without internalization by antigen-presenting cells and they bind to CD1 molecules at physiological pH without the use of chaperone proteins. In multiple sclerosis (MS), an autoimmune response against glycolipid components of myelin, potentially could contribute to disease pathogenesis. It has been shown that T cells of MS patients are more reactive to glycolipids compared to healthy individuals. Self glycolipids, such as sulfatides (*vide infra*), potentially could be the autoantigens that are recognised by T cells in autoimmune diseases.[40]

α-Galactosyl Ceramide (α-GalCer)

In 1993, the pharmaceutical division of Kirin Breweries isolated a series of novel α-galactosyl ceramides from the marine sponge, *Agelas mauritianus*.[41] Of the series, agelasphin-9b (AGL-9b, **6**) was found to be the most potent anti-tumour agent.[42] AGL-9b consists of a galactosyl moiety α1-linked to a ceramide portion containing an *N*-acylated phytosphingosine backbone. Structural optimisation by Morita *et al*.[43] later identified analogue KRN7000 (**7**) as a more suitable candidate for clinical use. The anti-tumour activity of **6** and **7** are comparable, however **7** lacks the hydroxyl group on the acyl chain and the methyl branch on the phytosphingosine backbone. Consequently, its chemical synthesis is more straightforward, thus making it a better drug candidate; KRN7000 is now widely known as α-GalCer.



6, Agelasphin-9b (AGL-9b)

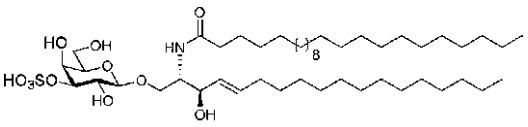


7, KRN7000 or α-galactosyl ceramide (αGalCer)

α-GalCer has been reported to have potential in the treatment of several diseases including cancer, malaria, type 1 diabetes, and multiple sclerosis.[44] The mechanism by which α-GalCer exerts its therapeutic effect only became known with the discovery that it binds to CD1d and activates a subset of T cells called invariant natural killer T (*i*NKT) cells.[45] α-GalCer is the first agonist found to activate the CD1d-restricted *i*NKT cells that express an invariant TCRα chain (Vα24Jα18 in humans and Vα14Jα18 in mice). The first chemical synthesis of α-GalCer was reported by Morita *et al*.[46] in 1995 but subsequently optimised by others.[47,48] Much effort is currently being made to develop derivatives of α-GalCer with improved anti-tumour activity, particularly within the context of cancer immunotherapy, an area of research in which we are particularly interested.

Sulfatide

Sulfatides, illustrated by **8**, are the 3-*O*-sulfate esters of galactosyl cerebrosides and are mainly present in the myelin tissue of mammals (nervous tissue in the central nervous system), although trace amounts are also found in other tissues. The sulfatide glycosphingolipids are essential to myelin and consist of several molecular species that differ in the extent of unsaturation and hydroxylation of the amide-linked fatty acid on the ceramide backbone, and also in the length of the acyl chain.[49]



8, a representative sulfatide

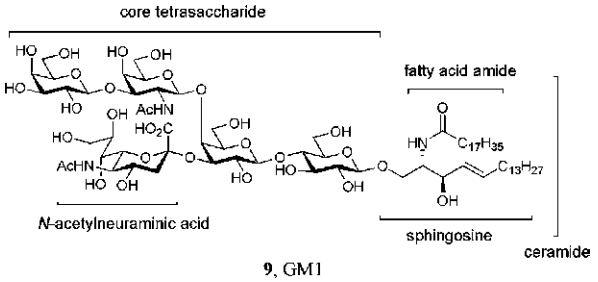
Sulfatides are interesting since they are able to bind to all CD1 isoforms and induce an immune response.[50] CD1a-CD1c all load sulfatides on the cell surface without processing. The sulfatide-CD1a complex persists longer in living cells than the CD1b and CD1c complexes. While the A' pocket in the CD1a binding groove is structured to accommodate alkyl chains (C_{18-23}), the F' pocket (which accommodates the protruding polar head group and most of the fatty acid lipid) is more open and more in contact with the receptor surface of the T cell of the CD1a binding groove, and this likely explains this.[51] CD1a is specially designed to recognize and bind the lipid backbone rather than the head group.

Sulfatide can also bind to CD1d and stimulate natural killer T (NKT) cells. The 3-*O*-sulfate group on the galactose is required for the activation of sulfatide-specific NKT cells, and it has been shown that these are specific for β-linked (but not α-linked) sulfatides.[52] The recognition of sulfatide by the CD1d-restricted NKT cells is important in autoimmune diseases of the central nervous system, particularly multiple sclerosis.[49] The synthesis of sulfatide analogues has been reported by Franchini *et. al*.[52]

Gangliosides

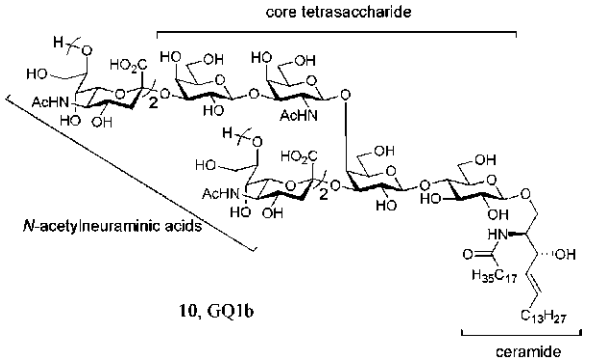
Gangliosides are complex glycosphingolipids found in eukaryotic cells and consist of oligosaccharide chains incorporating *N*-acetylneuraminic acid (NeuNAc) that are attached to a ceramide lipid. They have a β-glucosyl moiety is linked to the primary hydroxyl of the ceramide moiety, and, in turn, a β-galactose is coupled to the glucose 4-position. The structural diversity of this class of compounds results from differences in the sugar moieties that are attached to the β-galactose residue.

GM1:- GM1 (**9**) is the most abundant ganglioside found in human myelin. It consists of the β-galactosyl-β-glucosyl ceramide, to which a β-galactosyl-*N*-acetyl-galactosamine is linked at the 4-position, and an *N*-acetylneuraminic acid residue at the 3-position. Unlike most glycolipids that form the glycolipid-CD1 complex intracellularly, GM1 binds to CD1b on the cell surface at neutral pH without prior internalization.[53] GM1 contains the minimum epitope for recognition by T cells for it was found that gangliosides with head groups smaller than GM1 were not stimulatory, while those with larger head groups fully activated T cells. CD1b-GM1 complexes can stimulate T cells to release cytokines such as TNF-α and IFN-γ.[53] Additionally, it has been shown that ganglioside-specific T cells can discriminate between small differences in the carbohydrate portion of the glycolipid and that the terminal galactose of GM1 is important for recognition by T cells.[40] Lyso-GM1 (which lacks the fatty acid amide on the sphingosine backbone) was unable to stimulate T cells, suggesting that both the acyl and sphingosine group of GM1 are required for the binding to CD1b. GM1 binding to CD1b is highly reversible such that other ceramide-containing glycosphingolipids can displace it.



9, GM1

GQ1b:- GQ1b (**10**) is another ganglioside that was found to complex with CD1b and activate T cells. It possesses a core tetrasaccharide to which four *N*-acetylneuraminic acid residues are linked. GQ1b is abundant in the mammalian central nervous system and participates in physiological activities such as toxin binding, modulation of protein phosphorylation, cell adhesion and growth, and apoptosis.[54] In 2001, it was shown that the GQ1b-CD1b complex stimulates T cells and induces the production of cytokines IL-2 and IFN-γ.[55] The first total synthesis of this ganglioside was accomplished in 1994.[56]



10, GQ1b

Conclusion

Glycolipids are important molecules that play a major role in biological processes such as signalling, cell-cell communication, and molecular recognition. In particular, a number of the glycolipids that bind to CD1 have been identified. These include:

- the phosphoglycolipids such as phosphatidylinositolmannoside (PIM), mannosyl-β-1-phosphodolichol (MPD), and mannosyl-β-1-phosphomycoketide (MPM),
- the mycolates, typified by the mycolic acids, glucose-monomycolate (GMM) and diacyl trehalose sulfate ($Acyl_2SGL$), and
- the glycosphingolipids, *e.g.* GM1, GQ1b, sulfatides,

and α-galactosyl ceramide (α-GalCer).

The therapeutic role of glycolipids that modulate the immune system via interactions with CD1 and subsequent T cell activation is still in its infancy. However, much progress is being made in understanding CD1-glycolipid-T cell binding and this has the potential for use of the glycolipids in the treatment of diseases.

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Article

Colour Tuneable Photoluminescent Quantum Dots for Ink-Jet Printing of Security Documents and Labels

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Introduction

Zinc sulfide (ZnS) is a well known semi-conductor material with a band gap, E_g, of about 3.6 eV, which is within the energy range of UV light. When it is in the form of nanocrystalline particles, the particles are referred to as a quantum dots. The ZnS quantum dot lattice can be doped with transition metal ions and, when the doped material is excited by UV light, it exhibits photoluminescence in the visible region with the colour depending on the nature and level of the transition metal ion dopant. When doped with Mn^{2+} ions, UV irradiation gives a red-orange colour at about 600 nm, and when doped with Cu^{2+} ions a green-blue colour is seen at about 530 nm. In ambient light they are invisible. The dopants act as recombination centres for the excited electron-hole pairs, resulting in strong and characteristic photoluminescence.[1] The size of the quantum dots does have an effect on the fluorescence quantum yield Φ of the doped quantum dots, and is given by Eq. 1:[2]

$$\Phi = \frac{1}{1 + \beta D^2} \quad \text{..... Eq. 1}$$

where D is the diameter of the quantum dot and β is the ratio of the non-radiative and radiative decay lifetimes. It shows that the smaller the particle size, the larger the fluorescence or photoluminescence yield. Doped ZnS quantum dots are typically 2 nm in size while the Bohr radius for ZnS is 2.5 nm.

A stable colloid of doped ZnS quantum dots is colourless as the particles are too small to scatter light in the visible region but it exhibits the sharply defined characteristic photoluminescence colour in the visible region when viewed under UV irradiation. This is due to the nature of the particular transition metal ion used as the dopant. Colloid stability is usually achieved by using a capping agent, such as the citrate ion, which coats the individual quantum dot nanocrystals and prevent agglomeration. The ability to form stable colloids of photoluminescent quantum dots opens up the exciting possibility for their use as photoluminescent inks in security documents and labels in both single colour and full colour characters and images, and also in novel flexible photoluminescent displays and advertising.

Preparation of Doped ZnS Quantum Dots

The zinc sulfide quantum dots doped with Mn^{2+} and Cu^{2+} were synthesised using a chemical precipitation method from AR grade reagents and double distilled water for all solutions.[3] In a typical synthesis of Mn^{2+} doped ZnS, 10 mL each of 1.0 M $ZnCl_2$, 0.01 M $MnCl_2$ and 0.5 M sodium citrate solution were mixed and stirred for 10 minutes and then 10 mL of 1 M Na_2S solution was added dropwise from a burette. A white precipitate of ZnS/Mn^{2+} quantum dots formed and the resulting suspension was centrifuged and washed with distilled water and redispersed in 40 mL of distilled water to provide a colloidal suspension. Several experiments were conducted using different concentrations of Mn^{2+} ranging from 1-10 mol % to determine the optimum photoluminescence yield.[3]

In a similar way, the Cu^{2+} doped ZnS quantum dots were prepared from 10 mL each of 1.0 M $ZnCl_2$, 0.01 M $Cu(OAc)_2$, 0.5 M sodium citrate and 0.5 M sodium thiosulfate solution to give the colloidal suspension. The dopant concentrations here were adjusted from 0.2-1.0 mol % to determine the optimum photoluminescence yield.[3] The photoluminescent spectra of the doped quantum dot colloids were measured on a Perkin-Elmer LS-55 Photoluminescence Spectrometer over a range of 300-800 nm using an excitation wavelength of 320 nm and with a filter to remove the excitation line from the emission spectra.

The quantum dot colloids were incorporated into an ink-jet formulation and ink-jet printed onto paper and textile substrates using a 2811 Dimatix Materials digital printer. The requirements for the quantum dot ink-jet formulation needed to be matched as closely as possible to those of commercial inks and these are shown in Table 1. In order to approximately match these requirements and to ensure stability of the ink formulation, mercaptosuccinic acid [HO_2C-CH(SH)-CH_2-CO_2H – MSA] in a mole ratio of MSA:Zn = 8:1 for Mn^{2+} doped ZnS and MSA:Zn = 4:1 for Cu^{2+} doped ZnS was used.

Table 1. Property match for ink for ink-jet printing.

Property	Value
Viscosity	10-12 centipoise at 60 °C
Surface tension	28-33 dynes at 60 °C
Low volatility	bp < 100 °C
Density	Specific gravity > 1 g/mL
Filtration	Filtered to 0.2 μm

Results and Discussion

The photoluminescence spectrum of Mn^{2+} doped ZnS is shown in Fig. 1. A peak is observed in the visible range at *ca.* 600 nm that gives rise to the fluorescent red-orange colour. This is due to the presence of Mn^{2+} in the host ZnS lattice, which produces localized energy levels ($^4T_1 - {}^6A_1$). Incident UV light, with energy greater than the band gap, promotes an electron from the valence band to the conduction band. This then decays back to the valance band via a pathway involving a transition from the intermediate $^4T_1$ to the $^6A_1$ energy levels, giving rise to the emission of light in the visible region red-orange colour.[2] The emission at about 400 nm (Fig. 1) is due to S^{2-} vacancies in the ZnS lattice.[4] A similar mechanism takes place for Cu^{2+} doped ZnS where the transition is between the ^2E and $^2T_2$ energy levels. The emission occurs at about 530 nm and gives rise to the blue-green colour (Fig. 2).[5] The emission from the S^{2-} vacancies is not observed in this case as there are fewer S^{2-} ions available due to the use of $S_2O_3^{2-}$ in the reaction.

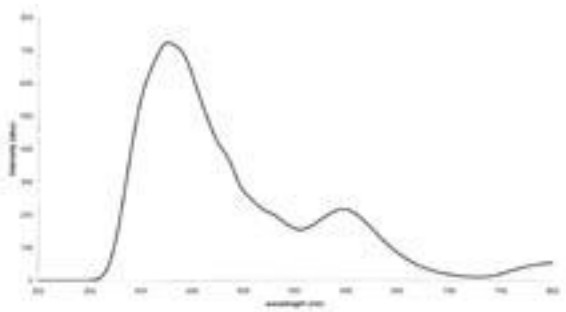

Fig. 1. The photoluminescent emission spectrum of Mn^{2+} doped ZnS quantum dots under UV light –see ref. 3.

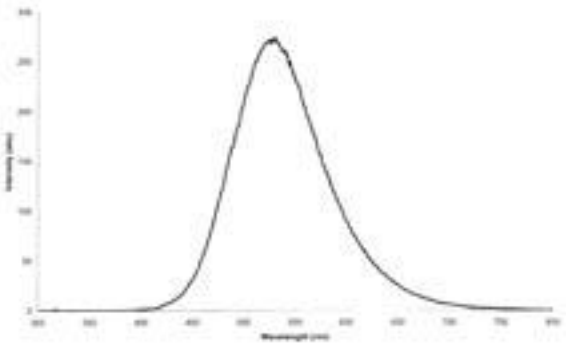

Fig. 2. The photoluminescent emission spectrum of Cu^{2+} doped ZnS quantum dots under UV light – see ref. 3

The Mn^{2+} doped ZnS quantum dots (using MSA as the colloid stabiliser) were ink-jet printed onto photocopy paper and photo quality ink-jet paper. The drop spacing was adjusted to give the highest ink loading without smearing in order to achieve the brightest image. A 15 micron drop spacing proved to be ideal. Furthermore, the image brightness could be enhanced by printing a number of passes. Similar print conditions were used for Cu^{2+} doped ZnS quantum dots.[3]

A simple rectangle printed with Mn^{2+} doped ZnS quantum dots is shown in Fig. 3. Under visible light (Fig. 3, left) the paper appears characteristically off-white and no image is discernible. However, when viewed under UV light (Fig. 3, right), the rectangle is clearly visible due to the light emission from the $^4T_1 - {}^6A_1$ transition. The paper itself appears blue due to photoluminescence under the UV light. Fig. 4 shows a more complex image of the VUW logo printed with Mn^{2+} doped quantum dots. It gives an orange image under UV light (Fig. 4, left) whereas the Cu^{2+} doped quantum dots give a green image under the same conditions (Fig. 4, right). Two passes of printing were used for the Mn^{2+} doped ZnS quantum dots and one pass for the Cu^{2+} doped ZnS quantum dots. Fig. 5 shows a printed circuit pattern printed with orange Mn^{2+} doped quantum dots.[3]

These images show that a good level of print quality and print resolution can be achieved with the quantum dot ink formulations developed here. Thus, there is excellent potential for the use of such photoluminescent quantum dots for printing images of different colours that are only visible under UV light.

Conclusion

The research has shown that photoluminescent doped zinc sulfide quantum dots have been successfully prepared and formulated into a stable ink-jet formulation. It has been used successfully to print digital characters and images that are invisible in ambient light, but are visible in different colours when viewed under UV light. The colour depends on the nature and level of dopant metal ion contained in the host ZnS lattice. Mn^{2+} doped ZnS (red-orange) and Cu^{2+} doped ZnS (green-blue) have been used here. This new technology opens up significant potential applications in the ink-jet printing of security documents and labels in single colour and full colour characters and images, and also in novel flexible photoluminescent displays and advertising.

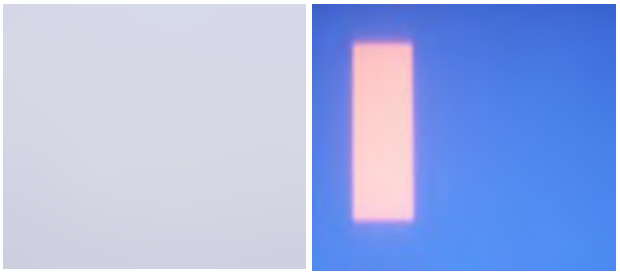

Fig.3. Photo quality ink-jet paper printed with a rectangle on Mn^{2+} doped quantum dots and viewed under ambient light (left) and UV light (right) – see ref. 3.

Fig. 4. Ink-jet paper printed logo with two passes of Mn^{2+} doped quantum dots (left) and with one pass of Cu^{2+} doped quantum dots (right) viewed under UV light – see ref. 3.

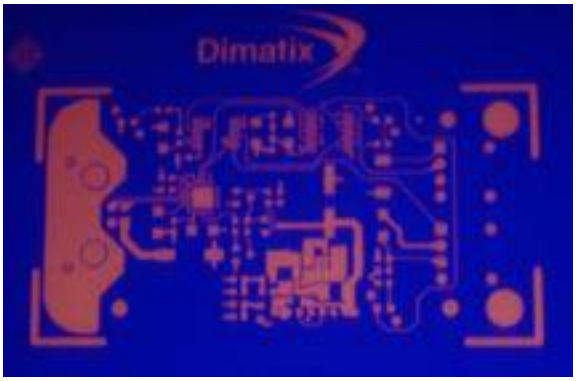

Fig. 5. A detailed ink-jet printed image of a printed circuit board template on photo quality ink-jet paper using Mn^{2+} doped ZnS quantum dots, viewed under UV light – see ref. 3.

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Dates of Note

The 10th of April 1910 saw the first night airplane flight (made in the US by *Walter R.* ***Brookins*** in Montgomery, Alabama), while on the same day in 1950 the first US jet passenger international trip was made from Toronto, Canada, to New York City.

Percy L. ***Julian***, the African-American chemist whose 100 patents include the synthesis of cortisone, hormones, and other products from soybeans, died on 19 Apr 1975. *Aleksandr* ***Oparin***, the Russian biochemist noted for his studies on the origin of life from chemical matter, died on 21 Apr 1980.

April 24 marks the 20th anniversary of the launch of the space shuttle *Discover* that carried the Hubble space telescope (deployed the following day), while on the same day in 1970, the People's Republic of China became the fifth nation with a satellite in orbit. *Wolfgang* ***Pauli***, the Austrian-born American winner of the 1945 Nobel Prize for Physics for his discovery of the *Exclusion Principle*, was born on 25 Apr 1900, the same day as *Charles* ***Richter***, inventor of the Richter Scale.

Carl ***Bosch***, the German industrial chemist who directed development of the industrial scale process for production of ammonia from atmospheric nitrogen at BASF, died on 26 Apr 1940. April 27 marks 40 years since the discovery of hahnium was announced at an American Physical Society meeting in Washington, DC.

29 Apr 1925 was the day that the first woman was elected to the US National Academy of Sciences (*Florence Rena* ***Sabin***, a histologist of Baltimore, Maryland), while, in 1820, *Thomas* ***Hancock***'s first patent for the application of rubber in clothing was dated. April 30, 1955 was the day that the artificial element mendelevium was announced by a team that included *Glen* ***Seaborg***.

May 1 is the 75th anniversary of the completion of the Boulder Dam. This day in 1825 saw *Johann Jakob* ***Balmer*** born. He was the Swiss mathematician and physicist who discovered a formula basic to the development of atomic theory. Although a mathematician, Balmer's most important work was in giving a formula relating the wavelengths of the spectral lines of the hydrogen atom 125 years ago (1885) at age 60. While his prediction agreed with observation it was not understood why until after his death with the theoretical work of *Niels* ***Bohr*** (1913).

English chemist *William* ***Nicholson*** was the first to produce a chemical reaction by electricity, discovering the electrolysis of water on May 2, 1800; he died on 21 May 1815. Sir *Alastair* ***Pilkington***, the British industrialist and inventor of the float glass process, died on May 5 in 1995. On the same day in 1930, *Amy* ***Johnson*** left Croydon on the first solo flight by a woman between England and Australia.

Johann Joachim ***Becher***, the German chemist, physician and adventurer, who gave an early theory of combustion (1669) in which all flammable objects were supposed to contain a substance that was released when the object burned. Becher called it *terra pinguis* (L. fatty or combustible earth). He was born on May 6, 375 years ago (1635). The *penny black* and *twopenny blue* adhesive postage stamps, showing the profile of Queen Victoria, went on sale on 6 May 1840. *William* ***Lever*** (1st Viscount Leverhulme), the British soap manufacturer and philanthropist, died on May 7 in 1925 while on the same day in 1660, *Isaack B* ***Fubine*** of Savoy patented macaroni in The Hague.

The 8th of May represents 220 years since the French National Assembly decided to create a simple, stable, decimal system of measurement units. The earliest metre unit chosen was the length of a pendulum that gave a half-period of one second. On 30 Mar the following year (1791), after a proposal by the Académie des Sciences, the Assembly revised the definition of the metre to be 1/10 000 000 of the distance between the North Pole and the equator. On 7 Apr 1795, the Convention decreed that the new *Republican Measures* were to be henceforth legal measures in France. The metric system adopted prefixes: Greek for multiples and Latin for decimal fractions.

Joseph Louis ***Gay-Lussac***, died on May 9, 160 years ago (1850), the day 50 years ago (1960) that the US Food and Drug Administration approved a pill as safe for birth control use. *François-Marie* ***Raoult***, the French chemist known for his law on solutions, was born 10 May 1830, while *John Wesley* ***Hyatt*** died on the same day in 1920. Wyatt was a US inventor and a pioneer of the plastics industry who discovered the process for making celluloid. In the 1860s he became interested in finding a substitute for ivory to make billiard balls. With his brother Isaac, he improved the techniques of moulding pyroxylin (partially nitrated cellulose) with camphor by dissolving in an alcohol/ether mixture to make it softer and more malleable. This he called *celluloid* and trademarked it on 14 Jan 1873. It was the first synthetic plastic, for which he took out a patent in 1870.

Stanislao ***Cannizzaro***, known for the reaction named after him, died 100 years ago on May 10. On this same date 150 years ago, in 1860, the discovery of caesium was announced by German chemists, *Robert* ***Bunsen*** and *Gustav Robert* ***Kirchoff*** to the Berlin Academy of Scientists.

Dorothy Mary Crowfoot ***Hodgkin***, the crystallographer of distinction, was born 100 years ago on May 12. Nylon stockings went on general sale for the first time in the US 70 years ago on May 15; four million pairs were sold in several hours. This same day 75 years ago (1935) saw *Albert* ***Einstein*** awarded the Benjamin Franklin Medal for his outstanding fundamental contributions to theoretical physics, especially his relativity theory.

May 16, is the 50th anniversary of the first operation of a synthetic ruby crystal laser at Hughes Research in Malibu. *Kasimir* ***Fajans***, the Polish-American physical chemist

who discovered the radioactive displacement law simultaneously with Frederick Soddy, died on 18 May 1975. On the same day in 1980, following a week-long series of earthquakes and smaller explosions of ash and smoke, the long-dormant Mount St. Helens volcano erupted, and on this day 100 years ago (1910), Halley's Comet was visible from Earth, moving across the face of the sun; Earth passed through the tail the day after.

T.E. ***Lawrence***, (Lawrence of Arabia), died 75 years ago on May 19, 1935. The same day in 1885 (125 years ago) saw the first mass production of shoes in the US. *Eduard* ***Buchner***, the German biochemist (1907 Nobel Prize for Chemistry for demonstrating that the fermentation of carbohydrates results from the action of different enzymes contained in yeast and not the yeast cell itself) after whom the funnel is named, was born 150 years ago on May 20.

Georges ***Claude***, the French engineer, chemist, and inventor of the neon light, died 50 years ago on 23 May (1960). 225 years ago this day (1785), a letter from *Benjamin* ***Franklin*** documented his invention of bifocal glasses. He was writing from France to a friend describing the solution to carrying around two pairs of glasses to see objects at different distances, with the comment that *I have only to move my eyes up and down as I want to see far or near*.

John ***Davy***, the English chemist and doctor who first prepared, named and characterised the gas phosgene, was born 24 May 1790; he was the younger brother of Humphry Davy. 75 years ago on this day (1935), the first spectrophotometer was sold by General Electric Co. It distinguished and charted up to two million different shades of colour by using a photo-electric device to receive light alternately from a sample and from a standard. 25 May 1940 saw one of the most famous animal tests in medical history; eight mice were inoculated with a lethal dose of streptococci and then four of them were injected with penicillin. Next day the four mice given streptococci alone were dead, the four with penicillin were healthy.

Robert ***Koch***, the German physician and a founder of the science of bacteriology, discovered the tubercle bacillus (1882) and the cholera bacillus (1883). He died 100 years ago on May 27. Masking tape was patented on May 27, 1930.

June 2, 1850 saw the birth of *Jesse* ***Boot*** (1st Baron Trent), the English chemist who founded Boots Company Ltd. *Robert* ***Noyce***, who with Kilby invented the integrated circuit, died on 3 June 1990. 70 years earlier (3 June 1920) had *Ernest* ***Rutherford*** speculate on the possible existence and properties of the neutron in his second Bakerian Lecture: *The Nuclear Constitution of Atoms*.

Johan ***Gadolin***, the Finnish chemist who discovered the element yttrium (1794) and after whom gadolinium is named, was born 250 years ago on June 5. On June 6 in 1880, the first funicular to transport passengers up an active volcano was inaugurated on Mount Vesuvius. When opened to the public June 10, visitors could travel up a steep rail in an 8-seat carriage. The song *Funiculi, Funicula* was inspired by this inauguration.

June 8 marks 55 years since *Tim* ***Berners-Lee***, died – he was the inventor of the world wide web. It is also the day 70 years ago that the element neptunium was announced by McMillan and Abelson working at the University of California-Berkeley.

June 11 signifies the 100th anniversary of the birth of *Jacques-Yves* ***Cousteau***, the oceanographer, marine biologist and ocean explorer. The next day, June 12, 175 years ago (1835), *Edward* ***Troughton*** died; he was the English scientist and instrument maker who established himself as the inventor and improver of instruments. June 16, 1980 saw the US Supreme Court rule that a patent could be issued for a genetically-engineered bacterium, while the 17th is the day in 1970 that *Edwin* ***Land*** patented the Polaroid camera.

Per Teodor ***Cleve*** died on June 18 in 1905. He was the Swedish chemist and geologist who discovered the elements holmium and thulium. The 100th anniversary of the birth of *Paul J.* ***Flory*** is on June 19. He was the American physical chemist and recipient of the 1974 Nobel Prize for Chemistry for his investigations of synthetic and natural macromolecules. June 22, 1675 is the day that Charles II created the Royal Greenwich Observatory by Royal Warrant. The building was designed by Sir Christopher Wren who was appointed the first Astronomer Royal upon its completion in 1676.

Jonas Edward ***Salk***, who developed the poliomyelitis vaccine, died on 15 June 1995. *Johannes* ***Wislicenus***, the pioneer of the importance of the spatial arrangement of atoms within a molecule, was born 175 years ago on June 24, the day in 1930 that aircraft were first detected by radar.

Roy J. ***Plunkett***, the American chemist and inventor of Teflon, was born on June 26, 1910. Chlorophyll *a* was first synthesized by *Robert Burns* ***Woodward*** and reported on 27 June 50 years ago. The first virus reported in crystalline form was 75 years ago on 28 June 1935; Prof *Wendell* ***Stanley*** received the 1946 Nobel Prize in Chemistry for his work on the tobacco mosaic virus.

29 June is the 120th anniversary of the death of *Alexander* ***Parkes***. He was a multi-talented British industrial chemist, expert in electroplating and able to silver-plate such diverse objects as a spider web and flowers. He patented a method of extracting silver from lead ore by adding zinc in 1850 and produced the first plastic, which he called Parkesine, in 1855 by dissolving cellulose nitrate in alcohol and camphor containing ether. The resultant hard solid could be moulded on heating, but he could find no market for the material. It was rediscovered in the 1860s by *John Wesley* ***Hyatt*** (see 10 May above) who named it *celluloid* and successfully marketed it as a replacement for ivory.

William ***Oughtred***, the English mathematician who invented the earliest form of the slide rule, died 350 years ago on 30 June 1660, the day 100 years ago that the US first investigated dropping bombs from an aeroplane.

The 150th anniversary of the death of *Charles* ***Goodyear***,

Merck Relocates New Zealand Warehousing and Logistics Operations

In the interest of providing you with continuity of excellent service, we have relocated our warehousing and logistics operation to Auckland. We have ceased despatching goods from Palmerston North and as of Monday 15th March began the despatch of all orders from the new site in Auckland. Our normal Customer Service continues to be available.

There is no change to our overall business commitment in New Zealand. Our key focus will continue to be providing you with the highest level of service. Our Sales Team, along with our Customer Service staff, will maintain usual levels of contact with you. There are no changes to our main telephone lines, fax number or web and email address.

The one change you will notice is that Chemfreight have now taken over the national delivery of our products. They have an excellent reputation for providing innovative solutions to client's changing needs and the flexibility to act quickly. Chemfreight will be delivering Merck products to you, no matter where you are located in New Zealand.

As a sign of our appreciation of your business, we have taken the step of offering to all our New Zealand customers a **"free into store" delivery service** effective from the 15th March to 30th June 2010.

Please be assured that we have the best interests of all our customers in mind and we are confident that these changes will add value to your business. If you wish to contact me personally regarding this, please do so on +61 418 246 207.

Peter Sommers
Managing Director

MERCK

2011 ROYAL SOCIETY OF CHEMISTRY AUSTRALASIAN LECTURESHIP

Applications are called for the 2011 Royal Society of Chemistry Australasian Lectureship - closing date 31 August 2010

The lectureship, financed by an annual grant from the RSC to Australia and New Zealand, is held by a New Zealand resident every fourth year. The 2007 lecturer was Prof Peter Schwerdtfeger (Massey University). The 2008-2009 lecturers were Profs Martin Banwell (Australian National University) and Cameron Kepert (University of Sydney).

The lectureship involves lecture tours in Australia and New Zealand, coordinated by the respective RSC Local Representatives: Prof. Graham Bowmaker (University of Auckland) and Prof. Alan Bond (Monash University).

The selection panel for the 2011 Lectureship will be Prof. Graham Bowmaker (Auckland), Prof. John Spencer (Wellington), Prof. Leon Phillips (Christchurch) and Dr. Mark Waterland (NZIC President).

Applications must include a CV and an account of the work to be covered in the lectures. The major part of the work should have been carried out in New Zealand.

Applications should be sent to:

Prof. G.A. Bowmaker
Department of Chemistry
University of Auckland
Private Bag 92019
Auckland

Or email: *ga.bowmaker@auckland.ac.nz* by the closing date of 31 August 2010.

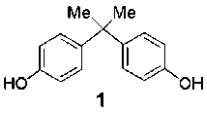
Chemistry in the News

Bisphenol A and Melamine Food Contamination Science Updates

Our 'Behind the News' sections of *Chemistry in New Zealand* have previously dealt with the topics of Melamine Food contamination (Jan 2009) and Bisphenol A (BPA) used in baby bottles (July 2008).

Both issues are once again in the news and so I thought it would be interesting to look at the recent updates for these items.

1. Bisphenol A (BPA)



1

Bisphenol A (**1**) has been used in baby bottles and some baby feeder cups, and is also found in epoxy resins, which are used as the protective linings inside food cans. It is synthesized by the condensation of acetone with two equivalents of phenol *via* acid catalysis. A large excess of phenol is required to ensure complete condensation.

$$Me_2CO + 2PhOH \longrightarrow (p\text{-}HOC_6H_4)_2CMe_2 + H_2O$$

The worry is whether levels of BPA, which can leach out of these plastics, could be dangerous if ingested by infants or babies.

Following on from the article in 2008, in January of this year the US Food and Drug Administration (FDA) decided that BPA was *of some concern* to the health of babies and young children. The FDA advised that scratched and worn-out baby bottles should be thrown out as the BPA may leach from these scratches. They also suggested that very hot liquids should not be used in children's drink containers made from BPA.

The FDA, working with the National Toxicology Program (NTP), has committed to performing studies over the next 18-24 months at the National Centre for Toxicological Research in Arkansas to *clarify certainty about potential risks of BPA*.

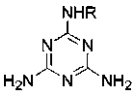
The American Chemistry Council issued a statement in relation to BPA (15/01/2010) also suggesting that more research was required and stated: *Extensive scientific studies have shown that BPA is quickly metabolized and excreted and does not accumulate in the body. BPA is one of the most thoroughly tested chemicals in commerce today*.

BPA has been linked to increased risks of cancers, diabetes and reproductive disorders along with cardiovascular problems. Infants and children are therefore vulnerable as their reproductive organs are not fully formed.

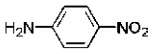
Two studies (one funded by the makers of BPA) have been published in 2010 in the *Journal of Toxicological Studies* stating no neurological problems were seen in rats fed BPA during pregnancy but both studies have been disputed by other scientists in the field. The research and debate on BPA continues.

2. Detecting Melamine Contamination in Food

The BBC news recently reported that melamine-tainted (**2**) milk products have once again been found on sale in China and that the search is on to find over 100 tonnes of melamine-containing milk. The powder is thought to be from a batch recalled in 2008. The scandal erupted when over 30,000 infants were taken ill after drinking melamine-containing milk products.



2



3

Methods to detect the presence of melamine contamination in food have included the use of mass spectrometry and colorimetric techniques utilizing gold nanoparticles. However, the former method relies on the use of expensive equipment and the latter requires a stabiliser which is difficult to synthesize.

Researchers in China have recently developed a new silver nano particle sensor which changes colour from yellow to dark green in the presence of melamine. The silver particles are modified with *p*-nitroaniline (**3**, *p*-NA). Aggregation of silver particles occurs due to the electron donor-acceptor interactions between the melamine and the *p*-NO_2 nitrogen atom of **3** and this is what produces the colour change.

The researchers Cuiping Han and Haibing Li at the Central China Normal University, Wuhan state: *The unique instrument-free detection feature of this colorimetric method could allow for on-site detection of melamine and offers great potential for household diagnostic applications*. Their results were published in the *Analyst*.

Anthea Lees

Conference Calendar

New Zealand International Science Festival

Dunedin, 6 – 11 July 2010

New Zealand's only international science festival, which explores real issues to debunk myths, challenge perceptions and open up the world of science to everyone. In 2010, the seventh biennial festival theme is "food for thought" featuring six days of fun and truly stimulating experiences.

Gordon Research Conference on Green Chemistry

Davidson College, North Carolina, USA, 25-30 July 2010

Applications for this meeting must be submitted by 4 July, 2010. Please apply early, as some meetings become oversubscribed (full) before this deadline.

www.grc.org/programs.aspx?year=2010&program=greenchem

XXIVth European Colloquium on Heterocyclic Chemistry

Vienna University of Technology, 23-27 August 2010

Covers all aspects of heterocyclic chemistry with special focus on novel methods in heterocyclic synthesis and the application of heterocycles in medicinal chemistry, agrochemistry, sustainable chemistry, and materials.

Abstracts deadline: 11 April 2010.

www.echc2010.net/scientific-program.html

21st International Symposium on Medicinal Chemistry (ISMC 2010)

Brussels, Belgium, 5 -9 September 2010

This symposium traditionally attracts experts in drug research and development, in particular medicinal and synthetic chemists, combinatorial chemists, molecular modelers, pharmacologists, as well as development chemists.

www.ismc2010.org/

2nd Asia Pacific Conference on Ionic Liquids and Green Processes

Dalian Golden Pebble Beach Resort, Liaoning Province, China, 7-10 September 2010

The program will feature a wide range of plenary and invited papers covering various topics in the emerging field of Ionic liquids. For the first time this conference will give young scientists (PhD students, PostDoc) a unique opportunity to present their work in a special session during this conference. Deadline for abstract submission: 30 April 2010

www.apcil.org/

Nucleic Acid Conference - NACON VIII: 8th International Meeting on Recognition Studies in Nucleic Acids

University of Sheffield, Sheffield, United Kingdom, 12-16 September 2010

Themes of the Conference will be devoted to interactions between: Nucleic Acids:Nucleic Acids; Small molecules:Nucleic Acids; DNA:Proteins; RNA:Proteins

Deadline for abstracts: 9 July 2010

www.nacon.group.shef.ac.uk/

Dalton Discussion 12: Catalytic C-H and C-X Bond Activation

Durham University, United Kingdom, 13- 15 September 2010

The meeting will highlight the importance of catalytic bond activation in cross-coupling chemistry

Poster Abstracts deadline: 16 July 2010

www.rsc.org/ConferencesAndEvents/RSCConferences/dd12/index.asp

Organic Process Research & Development

Barcelona, Spain, 13-15 September 2010

Unlike other conferences, practically all our speakers are experts from industry, which means the ideas and information you take home will be directly applicable to your own work.

www.scientificupdate.co.uk/conferences/scheduled-conferences/details/74-Organic-Process-Research-and-Development-Europe.html

Drug Analysis 2010

University of Antwerp, Antwerp, Belgium, 21- 24 September 2010

This symposium will cover all aspects of pharmaceutical and biomedical analysis, including emerging domains, such as 'omics', process analytical technology and green analysis.

www.ldorganisation.com/produits.php?langue=english&cle_menus=1238740593

3rd International Symposium on Green Processing in the Pharmaceutical and Fine Chemical Industries

University of Massachusetts Boston, Boston, MA, USA, 30 September - 1 October 2010

Focus Areas: Green organic synthesis, Biotransformations and biological drug processing, Enabling technology platforms. Sponsorship opportunities are now available.

https://guidinggreen.com/Pharm_FineChem.html

Polymer Chemistry Conference

Puerto Morelos, Mexico, 19-22 November 2010

This conference will focus on polymer chemistry and materials science applied to biological problems of current relevance. Topics will include synthesis of functional polymers, integration of biomolecules, biohybrids, hydrogels, tissue engineering, controlled polymer synthesis, protein-sugar interactions, hybrid materials for disease diagnostics, biomaterials synthesis, and drug delivery.

www.zingconferences.com/index.cfm?page=conference&intConferenceID=66&type=conference

2012 International Symposium on Macrocyclic and Supramolecular Chemistry (ISMSC-2012)

The University of Otago, Dunedin, New Zealand, 29 January - 2 February 2012.

Please register your interest via our website *www.otago.ac.nz/ismsc2012/*

Grants and Awards

Bilateral Research Activities Programme - call for applications

Applications are now invited to the 2010-11 Bilateral Research Activities Programme (BRAP) of the International Science & Technology (ISAT) Linkages Fund.

Please note that this call is for collaborations with all countries EXCEPT Germany and Spain.

Deadline: 4.00pm Tuesday 20 April 2010

Both the guidelines and application forms are available for downloading at *www.royalsociety.org.nz/site/funding/isat/default.aspx*

Bilateral Research Activities Programme - call for applications - SPAIN

Applications are now invited to the 2010-11 Bilateral Research Activities Programme (BRAP) of the International Science & Technology (ISAT) Linkages Fund.

Please note that this call is for collaborations only with SPAIN.

Deadline: 4.00pm Tuesday 20 April 2010

Both the guidelines and application forms are available for downloading at *www.royalsociety.org.nz/site/funding/isat/default.aspx*

RSNZ Charles Fleming Fund

Travel Award Up to $6,000 (total fund) is available annually and is likely to be split between a number of applicants to provide partial funding support to scientists or technologists to travel and attend scientific congresses, assemblies, or committees for the furtherance of science or technology

Senior Scientist Award Up to $10,000 p.a. available to support the research of a senior scientist at a university in New Zealand, and that of their research group

Publishing Award Up to $2,000 p.a. to support the preparation of scientific books and relevant publications

Award for Environmental achievement Up to $2,000 p.a. for the continued support ($6,000 every 3 years) of the Society's triennial Charles Fleming Award for Environmental Achievement.

All applicants must be permanent residents of New Zealand.

Deadline: 1 May 2010

www.royalsociety.org.nz/site/funding/charlesfleming/default.aspx

RSNZ Teacher Fellowship

This Scheme, funded by the Government and administered by the Royal Society of New Zealand, offers primary, intermediate and secondary teachers the opportunity to improve their teaching through experience in technological, scientific or social sciences practice.

Awarded Teacher Fellowship

A one-year Fellowship in which the teacher designs their own project and identifies their own host organisation. The Awarded Teacher Fellowship Scheme gives teachers the opportunity to gain practical experience and up to date knowledge by working on a project of their own design in the areas of science, mathematics and technology.

Application forms and guidelines for 2011 will be available by April 2010.

If you are thinking of applying please contact either Gillian Ransom or Joanna Leaman on 04 472 7421.

Applications close on 16 July 2010.

Primary Teacher Fellowship

A six-month fellowship designed to create potential science curriculum leaders in the primary sector.

Closing date: 12 April 2010.

Email: *PSTF@royalsociety.org.nz* or phone Joanna Leaman or John Auty 04 472 7421

Fulbright New Zealand Travel Awards

Fulbright New Zealand Travel Awards are for New Zealand academics, artists or professionals to visit the US for 12 to 90 days in order to present their work to American audiences.

Travel Award exchanges must include at least one major presentation. Grantees are encouraged to maximise the impact of their award by supplementing their main proposed activity with others including additional public talks, collaboration with American colleagues, visits to sites of interest etc.

Approximately twelve awards are offered each year.

Deadlines 1 April, 1 July and 1 November each year.

www.fulbright.org.nz/awards/nz-travel.html

RSNZ Talented School Students Travel Award

This is funded by the Ministry of Research, Science and Technology and administered by the Royal Society of New Zealand. It has been established to support Yr9 – Yr13 school students, providing funds to help cover the direct travel costs to nationally recognized science and technology based events outside New Zealand.

Enquiries to: Debbie Woodhall

Phone 04-470 5762 Fax: 04-473 1841 or

Email:debbie.woodhall@royalsociety.org.nz

www.royalsociety.org.nz/Site/teachersstudents/Medals_and_special_awards/talent/default.aspx

RSNZ International Conference Fund

Provided by the Minister of Research, Science and Technology and administered by the Royal Society of New Zealand. It is funding to assist organisations and institutions to host major international conferences in New Zealand. No closing date for applications.

www.royalsociety.org.nz/site/funding/int_conf/

Three Great Patented Inventions

Katherine Hebditch and Tim Stirrup

Baldwins Intellectual Property, PO Box 5999, Wellesley St, Auckland
(e-mail: *katherine.hebditch@baldwins.com* or *tim.stirrup@baldwins.com*)

Since the first patent was issued, there have been patents granted for many great inventions. Below we discuss just three of these inventions and some of the issues encountered by the patentee.

The Post - it™ note - the invention we didn't even know we needed.

In 1970 a patent was filed on behalf of 3M for an invention titled *Acrylate Copolymer Microspheres*.[1] The invention detailed in the patent specification was developed accidentally by research chemist Spencer Silver while working for 3M. Silver had developed a low tack, reusable adhesive; essentially glue that barely stuck!

Silver thought there must be a use for this glue and promoted it within 3M. However, it wasn't until 1974 that a colleague of Silver's - Art Fry - having heard about Silver's invention came up with the idea of using the glue to hold the bookmark in his hymnbook in place.

3M encourages its technical staff to spend up to 15% of their time on projects of their own choosing. Art Fry used this time to develop and refine his idea. At one stage during the development process Fry wrote a note to a colleague on one of his bookmarks and it came back with the answer written below on the same note. This prompted Fry to develop the product as more than just a sticky bookmark.

Initial marketing of the new sticky memo pad gave disappointing results. As there was no known equivalent product on the market, customers didn't yet realised the usefulness of the product. It wasn't until 1978 when 3M gave out free samples of the product and the public loved them that it really took off.

3M has since developed and patented various modifications and improvements to their famous product, but that original patent was filed without knowing quite how widely used the invention would become.

Viagra™ – the infamous invention.

Back in 1991 Pfizer filed patents for a series of compounds with properties useful in the treatment of cardiovascular disorders.[2] At the end of patent specifications there are a series of *claims* that define what the owner of the patent has a monopoly over. The claims of Pfizer's patents described the active compounds. These claims gave Pfizer a monopoly to make and sell these active compounds (and products containing them). Many of these original patent applications were granted and are in force in many countries in the world.

In 1993 Pfizer discovered that the compounds also had other quite different properties. Patent applications were filed which included claims to a method of treatment of erectile dysfunction using the active compounds of the earlier patents.[3] However, in a more daring move, the patents also included broader claims to a method of treating erectile dysfunction using any compound which was a cGMP PDE_V inhibitor.

Patents only give a monopoly in each country they are granted. However, Pfizer filed their patent applications in approximately 23 countries around the World.

When Eli Lilly wanted to market their rival product Cialis, the broader claims of these patents became the subject of litigation in many countries.

The multitude of court cases have demonstrated how patent laws and their application can differ between countries. For example, in the Federal Court of Australia the patent was initially found to be invalid in relation to two aspects. Firstly, that the invention defined by these much broader claims was obvious in relation to what was known to a person skilled in the field at the time of filing, *i.e.* not inventive. Secondly, the patentee was deemed not to be entitled to claim such broad subject matter.[4] However, on appeal the invention was found to be inventive, but the patent was still found invalid due to the broad subject matter.[5]

In contrast, at the Court of Appeal in the UK, the patent was found invalid because the invention defined in the claims was found to be obvious.

In the United States, the patent has been undergoing re-examination by the patent office. The Board of Patent Appeals has recently issued their decision, which rejected the broader claim for, among other reasons, not being novel.

Given the huge commercial significance of these cases, they may not stop there.

While the invention defined in the claims of the patent must be novel and inventive for the patent to be valid, how these and other criteria of validity are assessed in the courts of each country can vary.

Aspirin – the invention that just keeps getting better.

In the 18th and 19th centuries there was considerable interest from scientists and doctors in the properties of willow bark extract. This extract, which was later found to contain the compound salicylic acid, was found to reduce pain, fever and inflammation. However, it also had the unpleasant side effect of causing gastric irritation, which in some cases could be severe.

The compound acetylsalicylic acid, now commonly known as aspirin, was first discovered by Charles Gerhardt in 1853 while conducting research into ways to reduce the unpleasant side effects of salicylic acid.[6]

In 1898, Felix Hoffmann, a chemist working for Bayer, developed a more efficient method of making acetylsalicylic acid from salicylic acid and acetic anhydride. Bayer tested and then marketed the drug and was granted a patent for Hoffman's manufacturing method.[7]

Aspirin has been used as a painkiller for over 100 years, but more recently it has been found to have many other useful properties. Many patients who have previously had a stroke or heart attack now take low doses of aspirin as an anti-co-

agulant to reduce the chance of further damaging episodes. Studies of the use of aspirin to treat many other diseases are ongoing.

The use of a known compound as a new treatment for a disease poses problems when applying for patent protection. In many countries, including New Zealand, it is not possible to claim a monopoly for a method of treating a disease in humans. In court cases in New Zealand, it has been deemed that it would be morally objectionable to restrict methods of medical treatment. The person that would infringe such a claim in a patent would be the person treating the disease, such as doctors and medical staff.

Consequently, there is an issue of what a patent can claim in this type of situation. The compound itself can't be patented because it is not novel. Additionally, the new method of use can't be patented because the courts have deemed it will not be allowed.

However, in a case at the New Zealand Court of Appeal in 1999,[8] the court found this type of situation could be covered in a so called *Swiss-style* patent claim, so named because it was first used in Switzerland. Such claims take the form of, for example, *The use of aspirin in the manufacture of a medicament, for the treatment of heart disease*.

This type of claim doesn't claim the method of use as such; it claims the use to make a medicine for a specified purpose. If you see convoluted wording such as this in the claims of a patent, think of the example of Aspirin.

A reminder: if you have any queries regarding intellectual property related matters (including patents, trademarks, copyright or licensing), please contact us.

References

1. United States Patent Number 3,691,140.
2. First patent application GB909013750; equivalent in New Zealand NZ238586.
3. Patent Cooperation Treaty publication number WO94/28902.
4. Federal Court of Australia, Eli Lilly and Company *vs* Pfizer Overseas Pharmaceuticals [2005] FCA 67.
5. Federal Court of Australia, Pfizer Overseas Pharmaceuticals *vs* Eli Lilly and Company [2005] FCAFC 224.
6. C. Gerhardt, *Ann*. **1853**, 87, 149.
7. United States Patent Number 644,077.
8. Pharmaceutical Management Agency Ltd *vs* Commissioner of Patents (1999) 46 IPR 655.

Katherine Hebditch and Tim Stirrup of Baldwins Intellectual Property in Auckland specialise in chemistry and biotechnology patents. Katherine obtained her PhD in organic chemistry from the University of Manchester in the UK in 2004. She is currently working towards registration as a patent attorney. Tim obtained his PhD in molecular biology from the University of Southampton in the UK in 2007. He is also working towards registration as a patent attorney.

Book published to celebrate 350th anniversary of the Royal Society of London.

A new book entitled *Seeing Further: The story of Science and the Royal Society* edited and introduced by the American author Bill Bryson was released in January this year to celebrate the 350th anniversary of the establishment of the Royal Society of London.

The Royal Society first met in 1660, when a number of men met at Gresham College to listen to the, then young, Christopher Wren give a lecture on astronomy. It is the oldest scientific academy in existence and Isaac Newton, Charles Darwin, Albert Einstein, Robert Hooke, Robert Boyle, Joseph Banks, Humphry Davy, Isambard Kingdom Brunel, John Locke and Alexander Fleming were all fellows.

This book contains contributions from scientists including Richard Dawkins (on Darwin), John Barrow (on cosmological physics), Steve Jones (on biodiversity) and Phillip Ball ('making stuff' in the practice of science) along with popular authors such as Margaret Atwood (who traces the TV origin of 'the mad scientist'). Other authors cover topics including aeronautics, systematic biology, climate science, X-ray crystallography, Bayesian distribution and Bakelite, and complexity theory.

David Attenborough remarks that *As we approach the 350th anniversary in 2010 we have an opportunity to build on the work of these great scientists. The discovery of the electron, the splitting of the atom, the computer, the double helix and the World Wide Web were all works of fellows of the society*.

A live webcast to celebrate the launch of the book can be seen at the following website: *http://royalsociety.org/Event_WF.aspx?pageid=4294969660&terms=bill+bryson*

The President of the Royal Society of London, Martin Lord Rees, was a visitor to New Zealand in March of this year. He is a successor of Sir Isaac Newton and Ernest Lord Rutherford and came to New Zealand as the Rutherford Memorial Lecturer. He gave a lecture in Wellington entitled *The world in 2050* and another in Christchurch entitled *The Next 20 Years in Astronomy: Probing the Big Bang, Galaxies and Planets*.

Honorary Doctorates for NZ Chemists

Both Canterbury and Victoria University are awarding Honorary Doctorates in Science to chemists. At Canterbury, former Chancellor Dr ***Robin Mann***, ONZM, FNZIC, will receive his honorary degree in the April ceremonies, while at Victoria former student Prof ***Martin Banwell***, FAA, Hon. FRSNZ, FRACI, (Australian National University) is to be recognised on May 18.

Canterbury's Dr Mann served as chancellor from 2003 to 2008, said he '*felt greatly honoured but humbled by the award*' and that '*it is not something I feel I deserve nor did I expect to receive. Having said that I must say I am delighted to accept the recognition in the spirit it is given*'. He completed three degrees in chemistry at the then Canterbury College of the University of New Zealand – BSc (1957), MSc (Hons) (1959) and PhD (1962) and worked as a part-time lecturer at the University before embarking on a distinguished career in industry and management.

In 1961 he joined G L Bowron and Co. Ltd., as a research chemist. He was appointed production director in 1969 and Managing Director and Chief Executive officer from 1984 until his retirement from there in 2000. He was also general manager of tanning for Waitaki International Ltd. (1987-89) and senior director and Vice-President of the Japanese Maruhachi Mawata and Co. Ltd., from 1998 to 2000.

His NZIC Fellowship was for services to industry. He is also a Fellow of the NZ Institute of Management, a Distinguished Fellow of the NZ Institute of Directors and life member of both the NZ Tanners' Association and the Canterbury Manufacturers Association. In 2003 he was made an Officer of the New Zealand Order of Merit for services to business and the community.

Dr Mann was co-opted to the University Council in 2001, soon after his formal retirement, and was appointed Pro-Chancellor in short order and Chancellor in 2003. Since stepping down from Council at the end of May 2009, Dr Mann has continued serving the University in his role as Chairman of the UC Foundation, the registered charitable trust.

Victoria University's honorary doctorate is to go to Prof Martin Banwell, Director of the Research School of Chemistry at the Australian National University. Since graduating with a PhD (Organic Chemistry) in 1979 from Victoria University, he has made seminal contributions to the discipline as detailed in some *ca*. 250 publications and patents. He is now one of Australasia's most highly cited organic chemists with research outcomes exploited by several pharmaceutical companies in their drug development projects. Many of his former students and postdoctoral fellows hold significant positions in industry and academia throughout Australasia, North America and Europe, and this includes VUW's Dr. Joanne Harvey.

Professor Banwell achieved worldwide recognition from his contributions to the total synthesis of biologically active natural products that featured the novel deployment of strained organic molecules or the use of chemoenzymatic techniques. Several dozen such targets have been reported, many of which his group prepared for the first time. In accompanying work, a number of the synthesized compounds have been subject to detailed biological evaluation that has revealed novel properties and hitherto unrecognized structure-activity relationship patterns. The Banwell synthesis of the alkaloid colchicine solved, for the first time, profound problems of regiochemical control that had dogged all earlier studies. These include one led by the Harvard-based Nobel Laureate R. B. Woodward. His synthesis of lamellarin K, a rare marine natural product isolated from a sponge found on the outer reaches of the Great Barrier Reef, is now being used by a European-based drug development company for the creation of new anti-cancer agents that will be used to treat rare forms of lung cancer. The German-based chemical giant BASF is also collaborating in the development of new and environmentally benign agrochemicals. This work hinges on the exploitation of new synthetic methodologies, developed within the Banwell Group, that allow for the rapid assembly of polyheterocyclic frameworks from open-chain precursors. More recently, Professor Banwell completed an abbreviated and enantioselective synthesis of the structurally novel and potent new antibiotic platencin, a natural product that was first reported in 2007 (by the Merck Pharmaceutical Company) and which is now regarded as one of the most important recent discoveries in the whole area of anti-infective agents.