Chemistry in New Zealand

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Articles and features

Other columns

Comment from the President

Welcome to the New Year and the first issue of *Chemistry in New Zealand* for 2018. It is an honour to serve as the President of the Institute this year and I hope I am able to continue the excellent work of the past two Presidents, Paul Plieger (2016) and Penny Brothers last year.

Penny and Paul (along with Council) have been attempting to modernise the NZIC and have been working hard to make some positive changes. Penny has been trying to strengthen links between the NZIC and some of our partner organisations – see the News section for further details. Hopefully strengthening these ties to other organisations will make the NZIC more visible and provide better outcomes for chemists in New Zealand. Additionally, Penny has advocated for a change from a one year to a two year term for the President and this rule change was voted in at the 2017 AGM. Penny and the NZIC Council hope that the new two year term for the President will allow for better continuity of leadership within the NZIC and allow the President, along with Council, to be more productive for you the members. As such I will be the last one year President of the Institute and Sarah Masters (the current 1st vice president) is set to become the first two year President in 2019.

Paul has been driving a project to modernise the Institute's IT platforms. He has been developing a new NZIC website that will be more functional and hopefully will become a new hub for chemical information for both the membership and the public. The new website will also modernise our subscription model moving from paper and mail to an online system for membership and membership renewals.

2018 will be another year of change for the Institute because we will have a new administrator and Honorary General Secretary. Richard Rendle, who has held both of these positions for the last many years, retired from the posts at the end of 2017. I would personally like to thank Richard for his years of tireless hard work. He has been an unsung hero of the NZIC, he has supported the President and Council and administered the membership renewals and the NIZC exams that school teachers use to prepare the next generation of chemists to pass their NCEA exams. For these efforts the NZIC Council voted to make Richard an Honorary Fellow (HonFNZIC) – the highest award the Institute can grant.

As an Institute we need to engage with the public and get the message out that chemistry remains relevant and important in our daily lives. There seems to be a large amount of chemical ignorance in the general public around many important issues, for example there is continued advertising of "chemical free" products on TV. This is of course driven by the public's impression that chemicals are bad for them. The NZIC needs to try to engage and educate the public and get the message out that chemistry is everywhere and largely responsible for the increases in both the standard of living and life span over the last century.

Something that may help improve the image of chemistry with the public is the high profile research that is being carried out around the country. There are many excellent chemists carrying out cutting edge research all around New Zealand in Universities, CRIs and industry. The NZIC Awards celebrate the achievements of some of those researchers. In 2017 all four of the Institute's awards were given out – see the News section for recipients. There was very strong competition for the each of the awards suggesting that chemistry in New Zealand is in good health. I congratulate the award winners and encourage you all to consider either nominating yourself or a deserving colleague for the 2018 awards. I look forward to a busy and productive year as the President of the Institute and hope to meet many of you during my branch visits throughout the year.

James Crowley
NZIC President

Biographical Note

James Crowley is an Associate Professor at the University of Otago**.** He obtained his BSc(Hons) and MSc from Victoria University of Wellington and completed his PhD at the University of Chicago under the direction of Professor Brice Bosnich (1999-2005). In 2005 he moved to Professor David Leigh's group at the University of Edinburgh, where he was awarded a British Ramsay Memorial Trust Fellowship (2006–2008), to carry out research on molecular machines. He started his independent career at the University of Otago, Department of Chemistry in 2008 and has since moved through the ranks to Associate Professor (2015). His major research interests are in catalysis, self-assembly, molecular recognition and the development of molecular machines. James has been a member of the NZIC since 1996 and has served as the Otago Branch Secretary (2008-2011) and Chairperson (2012-2013) and has been on the National Council since 2012.

New Zealand Institute of Chemistry

supporting chemical sciences

January News

NZIC News

Royal Society Te Apārangi Awards and Fellows

The Royal Society Te Apārangi Hector Medal was awarded to Professor *Sally* ***Brooker*** FRSNZ, FRSC, MNZM, University of Otago, for internationally recognised leadership in the design, synthesis and characterisation of chemical complexes that exhibit exceptional properties for sensing, memory, carbon-dioxide capture, selective fluorescence and catalysis. This medal is awarded for work of great scientific or technological merit that has made an outstanding contribution to the advancement of the particular branch of science.

The MacDiarmid Medal was awarded to Professor *Peter* ***Tyler*** FRSNZ FNZIC, Victoria University of Wellington, for the development of a new drug design technology which has been successfully applied to the invention, commercialisation and regulatory approval of Mundesine, a cancer drug used for the treatment of peripheral T-cell lymphoma. This medal is awarded for outstanding scientific research that demonstrates the potential for application for human benefit.

Professor *Jadranka* ***Travas-Sejdic***, School of Chemical Sciences, University of Auckland, was elected FRSNZ. Professor Travas-Sejdic has made significant contributions to the research field of biosensing, developing handheld, in-field detection systems using conducting polymers for fast sensing of biological molecules and small molecular targets of biological interest.

New Zealand Association of Scientists Awards

The NZAS Beatrice Hill Tinsley Medal was awarded to Professor *Christian* ***Hartinger*** from the School of Chemical Sciences, University of Auckland. This medal is awarded for outstanding fundamental or applied research in the physical, natural or social sciences published by a scientist under the age of 40. Professor Hartinger has pioneered original and creative research strategies which have led to anticancer agents with novel modes of action, and produced insights into the fate of such compounds in biological systems. His work has significantly improved understanding of the behaviour of metal-based anticancer agents at the molecular level.

New Zealand Institute of Chemistry Prizes

The **Maurice Wilkins Centre Prize for Chemical Science** was awarded jointly to Associate Professor *James* ***Crowley***, Department of Chemistry, University of Otago, and Professor *Jadranka* ***Travas-Sejdic***, School of Chemical Sciences, University of Auckland.

The **Shimadzu Prize for Applied and Industrial Chemistry** has been awarded to Professor *Cather* ***Simpson***, Departments of Physics and Chemical Sciences, University of Auckland.

The **ABA Resources Denis Hogan Prize for Chemical Education** has been awarded jointly to Dr *David* ***McMorran***, Department of Chemistry, University of Otago, and *Graham* ***Townsend***, Department of Chemistry, University of Canterbury.

The **Easterfield Medal** was awarded to Associate Professor *Sally* ***Gaw***, Department of Chemistry, University of Canterbury.

New Fellows

FNZIC

Richard ***Hartshorn*** and *Sarah* ***Masters*** (Canterbury Branch) were elected Fellows.

HonFNZIC

Richard ***Rendle*** was made an Honorary Fellow in recognition of his work in administering the affairs of NZIC over the last ten years.

News from Council

NZIC website

The website is being upgraded and should be functional when this issue goes to press. It will include a password protected interface that will allow members to access their personal information and subscription status.

Chemistry Teachers Group

A proposal to form a Chemical Educators of NZ (CENZ) group was received. The aim is to give secondary chemistry teachers a more formal voice. The group would operate within NZIC in a similar way to our Branches. A working group will present a formal proposal to the next Council meeting.

NZIC representation on external bodies

NZIC has a relationship with a number of organisations within New Zealand and internationally. Our profile with these organisations depends on having personal representation on the governing bodies.

High profile relationships:

IUPAC – *Richard* ***Hartshorn*** (Canterbury) is the IUPAC Secretary General, *Margaret* ***Brimble*** (Auckland) is President of the Organic and Biomolecular Division, *Gregory* ***Russell*** (Canterbury) is President of the Polymer Division and *Suzanne* ***Boniface*** (Wellington) serves on the Chemistry Education Committee.

Pacifichem – *Mark* ***Waterland*** (Massey) is our representative on the Pacifichem organising committee. We are one of seven Pacific Basin chemical societies which cosponsor the large Pacifichem conferences held in Hawaii every five years. As a sponsoring society we receive a share of the returns, resulting in a significant boost to NZIC funds every five years. The division of returns amongst the sponsoring societies was recently renegotiated and Mark was successful in securing a larger slice for the smaller societies (like NZIC) than was formerly the case.

Could do better:

Federation of Asian Chemical Societies (FACS) – *Penny* ***Brothers*** attended the FACS General Assembly at the RACI conference in July and it is an important forum for contributions to regional development of the discipline of chemistry. Council will look to have more significant input into FACS.

Asian Chemical Education Service (ACES) – NZIC is a partnership owner of *Chemistry An Asian Journal*, but has had little formal input. *Paul* ***Plieger*** attended the ACES meeting at the RACI conference and is now on a sub-committee of ACES.

Physical Chemistry Chemical Physics (PCCP) – PCCP is published by the Royal Society of Chemistry (RSC) and NZIC is a member of the ownership board but has had little formal input. Council has resolved to appoint a person to maintain closer links with PCCP. NZIC receives a dividend proportional to the number of papers from NZ published in these journals.

Royal Society Te Apārangi – NZIC is one of around 50 constituent member organisations. We have the opportunity to contribute through physical sciences, mathematical sciences, technology and engineering discipline-based forums, which the President or other nominee from NZIC is invited to attend. Our engagement with the RSNZ has also been low.

AUCKLAND

Events

The inaugural lecture by Professor Christian ***Hartinger*** entitled, *Disrupting paradigms – metals at the interface of chemistry, biology and medicine* was held on 5 October at the University of Auckland.

Green Chemistry Exhibition

The students of CHEM360: *Contemporary green chemistry* held a green chemistry science exhibition, aimed at communicating science to the general public, involving posters and interactive displays and experiments from the students covering different topics of green and sustainable chemical science. This is a new initiative from the Centre for Green Chemical Science to facilitate learning and to improve learning experiences and engagement. The students, who worked in groups of three, were responsible for identifying their exhibition topic, creating and designing their displays, and to deliver two interactive sessions to visitors of the exhibition.

On 17 November the University of Auckland hosted a joint RSC-NZIC seminar entitled *machine learning in drug discovery* by Professor Yu Zong Chen.

On November 21 the NZIC AGM was held at the University of Auckland with Professor *Penny* ***Brothers*** giving the Presidential address, *instructing molecules to do our bidding: three short stories*.

The inaugural lecture by Professor *Cather* ***Simpson*** entitled *more thoughts from an entrepreneurial academic* was held on 22 November.

Symposium on Pure and Applied Coordination Chemistry

On 22-24 November 2017 the University of Auckland hosted SPACC, focussing on aspects of coordination chemistry. There was a lot of support and interest from chemists from throughout Japan and New Zealand with over 80 participants, 36 oral presentations and 35 poster presentations. Thanks to *Christian* ***Hartinger*** and *James* ***Wright*** together with their Japanese counterparts and respective teams in organising the symposium.

BASF Kids Lab

The green chemistry science exhibition

NZIC AGM with (left) Penny Brothers and (right) Cather Simpson

On 22-23 November 2017, the Teaching Laboratories hosted the BASF Kids Lab. Thanks to *Katrina* ***Graaf*** and her team for a fantastic event. The BASF representative from Australia was very impressed with the way the laboratory was organised and run.

Congratulations

Congratulations to PhD student *Renjie Mike* ***Huang*** of the Leung Group for winning one of the three student poster prizes at the Queenstown Research Week QMB Proteins Satellite Meeting, held 7-8 September. The work that was presented in Mike's poster involved the application of virtual screening and biophysical techniques to discover new inhibitors of heat shock protein 90. This work was conducted in collaboration with the group of Dr *Jóhannes* ***Reynisson***.

Congratulations to the students in the School of Chemical Sciences for their success in the Faculty of Science postgraduate poster competition. Three posters received High Distinction: *Synthesis of biodegradable antimicrobial polymers with high selectivity* by *Chloe* ***Cho***, *the beauty of coupling characterization techniques* by *Andrew* ***Chan*** and *Phototherapy: using light to treat cancer* by *Nina* ***Novikova***. Two posters received Merit awards: *sniffing out the meth using capillary microextraction* by *Mansa* ***Nair*** and *intrinsically adhesive and conducting graft co-polymers* by *Min* ***Wang***. In addition, *Optimisation of the eco-friendly extraction of bioactive monomeric phenolics and useful flavour precursors from grape waste* by *Rebecca* ***Jelley*** was in the top 20. Well done to all those students!

RSC Inspirational Committee prizewinners left to right: Vladimir Golovko, John Spencer and Jóhannes Reynisson

Congratulations to *Michel* ***Nieuwoudt*** and *Cather* ***Simpson***, whose project to develop a rapid method for diagnosis of skin cancers featured in a very positive article in the NZ Herald (www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=11926350). Cather also made a brief appearance on TV3's *The Project*.

A profile of Professor *Cather* ***Simpson*** was featured in the most recent issue of NZ Geographic (www.nzgeo.com/stories/light-fantastic/?source=homepage). It includes a number of memorable quotes from Cather, including "Our job description is to think about things that don't exist".

Professor *Jadranka* ***Travas-Sejdic*** was elected as a Fellow of the Royal Society Te Apārangi. She was one of 16 new Fellows, and her citation states that Jadranka "has made significant contributions to the research field of biosensing. She has developed hand-held, in-field detection systems using conducting polymers for fast sensing of biological molecules and small molecular targets of biological interest." This is a great achievement, and reflects the respect that Jadranka has from her scientific peers. She joins Distinguished Professor *Margaret* ***Brimble***, Professor *Ralph* ***Cooney***, Professor *Juliet* ***Gerrard*** and Professor *David* ***Williams*** with this title.

The RSC Inspirational Committee prize 2017 was awarded to Dr *Jóhannes* ***Reynisson*** (University of Auckland), Professor *John* ***Spencer*** (Victoria University of Wellington) and Dr *Vladimir* ***Golovko*** (University of Canterbury). They are credited for "revitalising the New Zealand Local Section of the Royal Society of Chemistry and improving the engagement and activity of members throughout the country."

Congratulations to *Cather* ***Simpson*** and *Jadranka* ***Travas-Sejdic*** who have both been awarded prizes by the NZIC. Cather was awarded the Shimadzu Prize for Industrial and Applied Chemistry, while Jadranka was a co-awardee of the Maurice Wilkins Centre Prize for Chemical Science.

Congratulations to Professor *Christian* ***Hartinger*** who was successful in obtaining a Marsden grant and was also awarded the Hill-Tinsley medal by NZAS – well done. An article and link to an interview on Radio NZ are available at www.radionz.co.nz/national/programmes/ourchangingworld/audio/2018619867/using-noble-metals-to-kill-cancer

Christian is also featured as part of the University's Never Stop campaign – a large image of him and his group is on one of the hoardings in the Student Quad.

Christian Hartinger featuring in the Never Stop campaign

Congratulations to *Michael* ***Schmitz*** who was awarded a Professional Staff Development Award to attend the Australia & New Zealand Magnetic Resonance Society conference in Australia in early December, and the preceding Bruker User Group meeting. This was an excellent opportunity for Michael to learn about new NMR methods and ways to optimise use of our current instrumentation.

Congratulations to Dr *Erin* ***Leitao***, Dr *Michel* ***Nieuwoudt*** and Dr *Ben* ***Mallett*** who were appointed as Associate Investigators in the MacDiarmid Institute.

PhD candidates who have successfully presented and defended their PhD theses are:

Bincy ***Jacob*** *–Early cartilage degeneration: correlation of micro-structural and proteomic analysis* (supervisor: Dr *Viji* ***Sarojini***)

Guantian ***Li*** *– Functional properties and molecular structure of quinoa starch* (supervisor: Dr *Fan* ***Zhu***)

Chatchakorn ***Eurtivong*** *(Che) – In silico approaches in drug discovery and development of anticancer drug candidates* (supervisors: Dr *Jóhannes* ***Reynisson*** and Dr *Euphemia* ***Leung*** from the Auckland Cancer Society Research Centre). Che has landed a job as a molecular modeller at the Chulabhorn Research Institute, Bangkok, Thailand.

Charles ***Kong*** *– Studies towards the design, synthesis and analysis of antifreeze peptides and their potential applications* (supervisors Dr *Viji* ***Sarojini*** and Dr *Ivanhoe* ***Leung***).

CANTERBURY

Events

The annual *Trivia and Truffles* quiz was held at the University of Canterbury Club on 5 October. The winners were *We'll let you know* (Mike Reid, Don McNickle, Jan Wikaira, Sim Wikaira), second were *Fat kids always win at seesaw* (Amanda Inglis, Ellen Ashmore, Lynne Allen, Vic Chapman) and third were *Doctors with borders* (Dave Young, Will Kerr, Samantha Bodman, Bianca Sanderson). Thanks to Jimmy Whitmore for collating the results, the Branch committee for gathering sponsorship and helping on the evening, and the Club for their help setting up and clearing away.

The NZIC Council AGM and President's lecture by Professor *Penny* ***Brothers***, School of Chemical Sciences, University of Auckland, held on 26 October, were very well attended. The President's lecture, entitled *Instructing molecules to do our bidding: three short stories* comprised three vignettes of recent research that had as their common theme how to design and make molecules which have encoded "instructions" for particular applications. While their behaviour at the molecular level cannot be physically controlled, they can be "coded" with specific functional groups to try and achieve the desired outcomes.

University of Canterbury

Comings and Goings

We are very happy to welcome Professor *Brett* ***Robinson*** to our School. Brett writes…. "I'd like to briefly introduce myself to the many people in the Department who I've not yet met. I studied chemistry and biology at Massey University in the 1990s and completed my doctoral degree, under the supervision of the late *Robert* ***Brooks***, on the plant uptake of heavy metals from metalliferous soils. Robert encouraged and enabled me to complete part of my degree in Europe, which ultimately resulted in enduring collaborations in Italy, France, Spain, Switzerland and Austria. From 1998 – 2005, I worked under the guidance of *Brent* ***Clothier*** at HortResearch (now Plant & Food) on remediation of contaminated sites in New Zealand as well as in France and Spain. I moved to Europe in 2005 to work for *Rainer* ***Schulin*** in the Soil Protection Group at the Swiss Federal Institute of Technology in Zurich and returned to NZ in 2008, working at Lincoln University in the Department of Soil and Physical Sciences until late last year. My interest and passion is the investigation of contaminant fluxes in the water-soil-plant-atmosphere continuum. I'm excited by the prospect of engaging new minds and new equipment at UC to further elucidate chemical process that occur in the rhizospheres of plants growing in contaminated environments. Outside of work, I enjoy tramping, squash and tennis. I'm fortunate that my kids nag me to take them into the mountains on the weekend!"

Many friends and colleagues, from all over the University, gathered at the University of Canterbury Club to mark *Andy* ***Pratt's*** retirement. *Bryce* ***Williamson***, MC, presented Andy with a card and gift, and recounted some of the highlights and notable aspects of Andy's 25 years (to the day) as a member of the Department of Chemistry. Andy first came to UC as a sabbatical visitor in 1989. That visit is legendary: there are many stories about what a great visitor Andy was and especially about the cocktail party he hosted. *Jan* ***Wikaira*** commented that it was the best cocktail party she's ever attended. In 1992, Andy left his position at Oxford University and joined the staff at UC. Bryce and others spoke about the many and very varied contributions Andy made to UC. Andy was recognised as an inspirational teacher, often shouldering a very high teaching load. He has an immense knowledge of broad areas of chemistry and biochemistry, conveyed in class through his unique peripatetic lecturing style. Andy's research into the origin of life fitted perfectly with his wide scientific interests and creativity. Andy also took on major administrative roles, with his final task being the almost single-handed development (with the associated piles of paperwork) of our six new 300-level papers to be launched in 2018. Andy's time at UC is also very notable for his involvements beyond our Department. He was a long-term active and hard-working contributor to the Faculty, served on the Academic Board and was an academic representative on Council for many years. The latter role is testament to the high regard and respect he earned from his fellow staff. Andy was recognised as someone who cared about the direction of the University and was not afraid to exercise his rights as a critic and conscience of society (and of the University). Finally, Andy was always very interesting to talk to about many, many things beyond work, including (but not limited to) philosophy, literature, music, tramping and sport. His neck massages were much appreciated and will be missed, but we will look forward to shorter meetings!! Andy, thanks for everything. It's great to know you intend to keep in touch with us while pursuing your many other interests.

Congratulations

Professor *Paul* ***Kruger*** and his team have been awarded an MBIE 2017 Catalyst Strategic grant worth $1.5 million over three years.

Outreach

Dr Graham's *Blow up science* show on 19 July, sponsored by the Royal Society Te Apārangi, was aimed at primary school children and their families. Two shows were held in the Jack Mann Auditorium in the morning, before Dr *Graham* ***Walker*** (ANU) and *Debbie* ***Woodall*** (Royal Society NZ) left Christchurch for Greymouth (the next show). Thanks to *Sarah* ***Masters*** and *Jan* ***Wikaira*** for assisting with logistics and support for this event.

MANAWATU

We welcome Shikeale Harris, Liam McGarry and Brodie Matheson as summer students. Shikeale is working with Professor *Shane* ***Telfer*** on *Various discrete structures and extended networks using chiral truxene precursors*, Liam with Associate Professor *Gareth* ***Rowlands*** on C-H activation chemistry, and Brodie with Associate Professor *Paul* ***Plieger*** on *Developing a pyrazine based ligand for metal-metal communication*.

Holly White has been working on a research paper over the summer semester with Professor *Dave* ***Harding*** on a project studying methods to improve topical penetration of anaesthetics. In New Zealand, it is becoming increasingly necessary to use anaesthetics to perform any painful operations on animals. Topical application coupled with rapid penetration of fast acting anaesthetics is seen to be a desirable alternative to multiple injections for operations such as horn removal from deer.

Jenna Buchanan has graduated with her MSc titled, *The computational investigation of a dinuclear manganese complex with Jahn-Teller compression and elongation*.

Adil Alkas presented a poster at the EuroMOF conference in Delft, Holland in November.

Massey University welcomed several speakers:

Bill ***Hawkins*** from the University of Otago gave a presentation titled, *One ring to rule them all: the synthesis of biologically relevant compounds from cyclopropanes*.

Sarah ***Masters*** from the University of Canterbury presented on, *Gas-phase molecular imaging using electrons*.

Associate Professor *Micheal R.* ***Mucalo*** from the University of Waikato gave an overview of his last 30 years of research in a talk titled, *Research forays in biomaterials, colloids, drug delivery and spectroelectrochemistry*.

Neil W Barnett from Deakin University gave his presentation due to being awarded the 2017 Royal Society of Chemistry Australiasian Lectureship.

Robert ***Keyzers*** from Victoria University presented his work on, *NZ algal natural products; bioactivity and mass spectrometry guided isolations*.

OTAGO

This years High School Chemistry Quiz (the 15th so far) saw 30 teams from schools around Dunedin and further afield meet in Otago Museum's Hutton Theatre to battle for the Bunsen Burner of Wisdom. After the usual feed of pizza from Poppas Pizzas, and an initial round of *oxidants and reductants* things got down to business with five rounds of questions of both a chemical nature as well as general knowledge. Teams also contributed Chemical Haiku for extra prizes. Quizmaster *Dave* ***McMorran*** is to be commended for a fantastic quiz and especially for keeping a theatre full of high-school students on task and entertained! Prizewinners were: First: *BOB* (Logan Park High School); Second: *No Ho P Es* (James Hargest College); Third: *Technically alcohol is a solution* (Otago Boys' High School).

University of Otago, School of Pharmacy

Siddharth ***Matikonda***, in the group of Allan Gamble successfully defended his thesis, *Development and application of strategies in prodrug chemistry*, which was also placed on the Division of Health Sciences Exceptional PhD Thesis List. Well done, Sid!

University of Otago, Department of Chemistry

The Department of Chemistry had great success in the latest round of Marsden Fund grants. *David* ***Larsen*** and colleagues from the Department of Pharmacology and Toxicology were awarded $910,000 for the grant titled, *Polymer-immobilized carbon monoxide donors: agents for tissue protection*. *Claudine* ***Stirling*** received $960,000 for her grant, *How does the Earth stop global warming? Testing climate stabilisation during 'hyperthermal' events*, which she will complete with international collaborators. *James* ***Crowley*** and colleagues *Christian* ***Hartinger*** and *James* ***Wright*** from the University of Auckland received $910,000 for the project, "*Blossoming of bioinspired supramolecular architectures: towards applications in catalysis, drug delivery and materials science*". Well done to you all!

Top: High School Chemistry Quiz winners, team BOB from Logan Park High School: Tarrin Loughran, Louis Whitburn, Hamish McKinlay, Benjamin Dubyk. Bottom: The appropriately-themed prize-winning trophy.

The Department celebrates the recent success of two staff at the 2017 NZIC awards. *Dave* ***McMorran*** has been awarded the Denis Hogan prize for Chemical Education and *James* ***Crowley*** has been awarded the Maurice Wilkins Centre prize for Chemical Science. Dave was also recently awarded an Otago University Students Association Teaching Excellence award and James was a finalist in the Otago University Students Association Supervisor of the Year award. Well done to you both for some very well-deserved recognition!

Sally ***Brooker*** has been awarded the RSNZ Hector Medal. As she was unable to attend the RSNZ awards dinner, DVC Professor Richard Blaikie accepted it on her behalf and then kindly organised a local celebration in which the VC, Professor Harlene Hayne, presented her with the medal. This is a huge honour – well done Sally!

In the last of the awards news of this issue, the Department of Chemistry was successful in the 2017 Division of Sciences Awards. *Eng Wui* ***Tan*** received the Industry Links award, the *Keith* ***Gordon*** research group won Research Group of the Year, *Bill* ***Hawkins*** received the Early Career Researcher award and *Keith* ***Hunter*** was awarded the Distinguished Service prize. What a haul, great job everyone!

The department welcomes a large cohort of summer students this year, who have brought great energy and enthusiasm to the department. Summer students are: *Ioan* ***Fuller****,* *Hamish* ***Stafford****,* *Lachlan* ***Gaudin****,* *Elliot* ***Tay****,* *Sian* ***Stables****,* *Kaleb* ***Winefield****,* *Brianna* ***Nally****,* *Ray* ***Yang****,* *Charlie* ***Ruffman****,* *Calum* ***Gordon****,* *Harriet* ***Love****,* *Ruth* ***Warren****,* *Joseph* ***Mapley****,* *China* ***Payne****,* *Emma* ***Barnes****,* *Jacob* ***Harrison****,* *Melenaite* ***Tohi****,* *Jeffrey* ***Evans****,* *Jake* ***Ward****,* *Cam* ***Keelty****,* *Brianna*

***Thompson**, Sam **McIntyre**, Alice **Craig**, Simon **Petrie** and David **Rubin**.*

The Supramolecular and Polymer Group (*Stephen* ***Moratti*** and *Lyall* ***Hanton***) welcomes the arrival of *Marianne* ***Kurzur*** from Tuttlingen, Germany, on a 6-month internship. The ENT gel developed in the group has just been granted FDA approval for sale in the US, which was noted in many newspapers as well as in a radio interview on Radio Pacific. As well, the mechanically stimulated drug release gel developed by *Eng Wui* ***Tan*** and *Stephen* ***Moratti*** was just highlighted in Doctor (NZ) magazine.

In the Plant Extracts Research Unit, *Ioan* ***Fuller*** is working as a summer student, carrying on his successful 3rd year project on herbicidal activity of natural products in mānuka foliage. This work is contributing to the Outreach project *Mānuka chemistry in the community*, funded by MBIE's *Unlocking curious minds* fund. *Elaine* ***Burgess***, working with *Dave* ***Warren*** and *Nigel* ***Perry***, has developed an experiment in which school students collect their local mānuka, extract foliage and test herbicidal activity. Samples are also sent to Plant & Food Research for GC-MS chemotyping, to add to knowledge of mānuka variation around New Zealand. Nigel and Elaine are just starting another MBIE-funded project, with *Monika* ***Gerth*** in the Department of Biochemistry, on fighting kauri dieback caused by pathogenic *Phytophthora*. Mātauranga Māori (Māori knowledge) will be used to identify native plant species with bioactive, antipathogen characteristics. The PFR team will extract and fractionate, with Biochemistry running *Phytophthora*assays to direct the isolation of active natural products.


Left to right: VC Professor Harlene Hayne, Professor Sally Brooker with the Hector Medal, and DVCs Professor Helen Nicholson and Professor Richard Blaikie, University of Otago, November 2017. Photo: Sharron Bennett.


Brookers Bunch with their three 2017 awards, the RSNZ Hector Medal, RACI Burrows Award and Queens Birthday honour MNZM. Back: Humphrey, Ross, Fola, Santi, Stuart. Middle-Front: Fabrice, Sandhya, Sally, Abdullah. Absent: Hannah and Michael. Photo: Sharron Bennett.

Jaydee ***Cabral*** received a $5,000 travel award and was selected as a NZ delegate to the MBIE Catalyst funded Texas Medical Centre (TMC) Delegation. The delegation will travel to Houston in March 2018 for a week long programme. Jaydee was selected as one of seven NZ researchers to attend. The Houston Medical Precinct is the world's largest medical complex with 56 co-located institutions, including 3 medical schools, 21 hospitals, and 8 world-class research and academic institutes. The aim of the delegation is to meet a broad range of influential research leaders and industry representatives to showcase NZ's R&D capabilities in the relevant fields and initiate potential science collaborations.

The Ocean Foundation, Secretariat of the Pacific Regional Environment Programme (SPREP) and the University of the South Pacific in Fiji recently hosted a series of courses on ocean acidification monitoring and research. *Kim* ***Currie*** from the NIWA / University of Otago Research Centre for Oceanography in Dunedin joined scientists from the National Oceanic and Atmospheric Administration (NOAA) to train participants from Pacific Island nations in the analytical and field skills necessary to initiate and implement an ocean acidification monitoring and research programme. An introductory course involved lectures, lab and field work; this was followed by an applied course providing hands-on training. A parallel course focused on policy development. This suite of skills will enable the participating nations to work towards enhancing resilience of local marine environments to changing ocean chemistry resulting from uptake of anthropogenic carbon and other stressors. These include coral reefs, mangroves and sea grass beds which are of social and economic importance to our South Pacific neighbours.

The spin-out company of *Carla* ***Meledandri***, Silventum Limited, was incorporated on 15 September 2017. Carla was a keynote speaker at the Society for Pure and Applied Coordination Chemistry Symposium (SPACC24) in Auckland and an invited speaker at the MacDiarmid Institute's Emerging Scientists Association (MESA) Soft Matter Bootcamp in Kaiteriteri in November. Carla, *Gemma* ***Cotton*** and *Dagmara* ***Jaskólska*** all gave talks at the MacDiarmid Insitute's Cluster Hui on Nanoclusters at Kinloch, also in November. The Meledandri group also welcomes Liam Parke who has just stared as an MSc student in the group after successful completion of his honours degree.

Anna ***Garden*** organised the MacDiarmid Institute's Cluster Hui on Nanoclusters at Kinloch where students *Geoffrey* ***Weal***, *Charlie* ***Ruffman***, *Ray* ***Yang*** and *Caitlin* ***Casey-Stevens*** gave contributed talks. A great meeting was had by all and the post-hui tramp in the Caples Valley was definitely a highlight! Charlie and Anna both spoke at the Otago Energy Research Centre Symposium and Geoff presented a poster. *Caitlin* ***Casey-Stevens*** was an invited speaker at the eResearch@Otago day in October. *Ray* ***Yang***, *Anna* ***Garden***, *Santi* ***Rodriguez-Jimenez***, *Sally* ***Brooker*** and *Ian* ***Stewart*** published a paper in *J. Am. Chem. Soc.* about using simple calculations to predict spin state in solution. Santi was first author and this is Ray's first paper. Well done to both students for some great work!

There is lots of news from the group of *Keith* ***Gordon*** (KCG). *Sara* ***Miller*** presented a poster 'of excellence' which also included an oral presentation on the *Vibrational spectroscopy for ex vivo detection of coeliac disease – a proof of principle study towards point of care diagnosis*" at GASTRO 2017 in Auckland. Work by *Jonathan (Jono)* ***Barnsley***, in collaboration with *Nigel* ***Lucas***, and fellow KCG members was presented on the front cover of the October edition of *ChemPhotoChem* (the October 2017 issue) and as a case study for the New Zealand eScience Infrastructure (NeSI). Congratulations to Jono as this is his 12th paper from his PhD work. Geoffrey Smith was awarded a TeachNZ science scholarship for his upcoming *Masters of teaching and learning* course at the University of Otago College of Education. *Jeremy* ***Rooney*** published a paper in the Journal of Raman Spectroscopy entitled, *Submicron Raman spectroscopy mapping of serpentinite fault rocks* and was a co-author of a paper in Solid Earth titled, *Structural disorder of graphite and implications for graphite thermometry*. Jeremy presented results from his main research project to paint suppliers at New Zealand Steel in late October. *Georgina* ***Shillito*** had a paper entitled, *Cyclometallated platinum(II) and palladium(II) complexes containing 1,5-diarylbiguanides: synthesis, characterisation and hydrogen bond-directed assembly* published in *CrystEngComm*. *Joseph* ***Mapley*** completed his honours on *A computational and spectroscopic study of β-indandione substituted zinc porphyrins* and is currently working as a summer intern in the KCG labs and is planning on starting his PhD in February.

Keith ***Gordon*** gave a plenary lecture at the XIVth International Conference on Molecular Spectroscopy, Białka Tatrzańska, Poland, September 4 – 6, 2017 where he talked about generating long-lived charge-separated excited states from blended organic, inorganic chromophore systems: a spectroscopic and computational study. He also presented an invited talk at SciX in Reno where he described the group's work on using low frequency Raman spectroscopy to understand order in metal-organic frameworks and solar cell polymers and he presented, with *Sara* ***Miller***, on their findings in meat analysis at the Ruakura Research Centre in Hamilton in November. Keith also gave a keynote lecture at the 24th International SPACC Symposium in Auckland in November.

Brookers Bunch have celebrated the submission of three PhD theses by *Ross* ***Hogue***, *Santi* ***Rodriguez-Jimenez*** and *Stuart* ***Malthus***. Ross's thesis was placed on the Division of Sciences exceptional theses – so huge congratulations to him. Both Ross and Santi graduated in person in December, and Stuart's oral examination was held in December.

Ross Hogue (top) and Santi Rodriguez-Jimenez (bottom) with their final, hard bound, PhD theses. Photos: Sally Brooker.

Ross ***Hogue*** was awarded the prize for best energy related talk by a student at the Otago Energy Research Centre Symposium in November. Great job, Ross! *Sven* ***Porath***, a visiting PhD student from Bielefeld

University, has successfully completed his 11 month internship in the Brooker group and returned to Germany. Three new PhD students have started in Brookers Bunch: *Sandhya* ***Singh*** (MSc from IISER Mohali, India), *Sunday Folaranmi* (known as Fola) ***Akogun*** (MSc from Lanzhou Jiaotong University, China), and *Abdullah* ***Abudayeh*** (MSc from Bradford University, UK).

Sally ***Brooker*** was invited to present her collaborative research with Professor Annie Powell (Karlsruhe Institute of Technology), on the MacDiarmid Institute 'desk', to the German President, Dr Frank-Walter Steinmeier, his advisors, and the new NZ Minister for Science, Research and Innovation, Dr Megan Woods, on the occasion of the German President's state visit to New Zealand marking the 40th anniversary of Scientific and Technological Cooperation between NZ and Germany, in Wellington on 6 November.

New PhD students in Brookers Bunch (left to right): Sandhya, Abdullah and Fola

Top: Dr Megan Woods, President and Mrs Steinmeier, with a model of the Brooker, Feltham and Powell macrocyclic Single Molecule Magnet, kindly made by Garth Tyrell (Otago). Bottom: Sally and Renee Goreham cracking a joke with the dignitaries. Photos: Nicola Gaston.

WAIKATO

University of Waikato

Nearly 150 students from the greater Waikato region and Bay of Plenty participated in the annual ChemQuest competition, held recently by the Department of Chemistry. This was a fun-filled evening for students studying NCEA level 2 chemistry. It was a very close contest with only three marks separating first place from fifth place and a playoff required to decide fourth and fifth places. Prizes were awarded as follows:

1st Place: Hamilton Boys' High School (Patrick Dowd, Immo Frank, Joshua Monteiro)

2nd Place: Te Puke High School (Ayden Mackie, Travis Moke, Ashleigh Ngow)

3rd Place: Hamilton Boys' High School (Alex Chen, Jason Mace, Varin Malhotra)

4th Place: Katikati College (Ben Douglas, Ethan Frazer, Jacob Topp)

5th Place: Hillcrest High School (William Harlow, Gabriel Pan, John Vos)

The quiz was generously sponsored by the Waikato Branch of NZIC (major sponsor), Hill Laboratories and the Faculty of Science and Engineering, University of Waikato. Question master was *Michèle* ***Prinsep***, ably assisted by numerous other staff and students from the Department.

Hill Laboratories

Hill Laboratories has a new Hamilton site. After a three year search for the perfect spot to house 300 staff from four different laboratory locations in Hamilton, a 7000m^2 former New Zealand Post sorting office in Frankton was chosen as the site for Hill Laboratories' growing operation. Only one year ago, it was a full blown construction site but it is now a world-class, state-of-the-art laboratory. The move to Frankton was both strategic and born out of necessity. "Within the past five years alone, Hill Laboratories has experienced 33 percent revenue growth and 22 percent increase in staff numbers. As we continue to grow it is fitting that we consolidate staff and resources into one central location," CEO Dr Matt Glenn explained. As of mid-November, all Hamilton based staff had moved across to Frankton from sites in Melville, Hamilton East and Ruakura. Although missing the Hamilton East coffee and eateries, staff are positive about the change, and confident that customers will soon reap the benefits from the efficiencies gained.

WELLINGTON

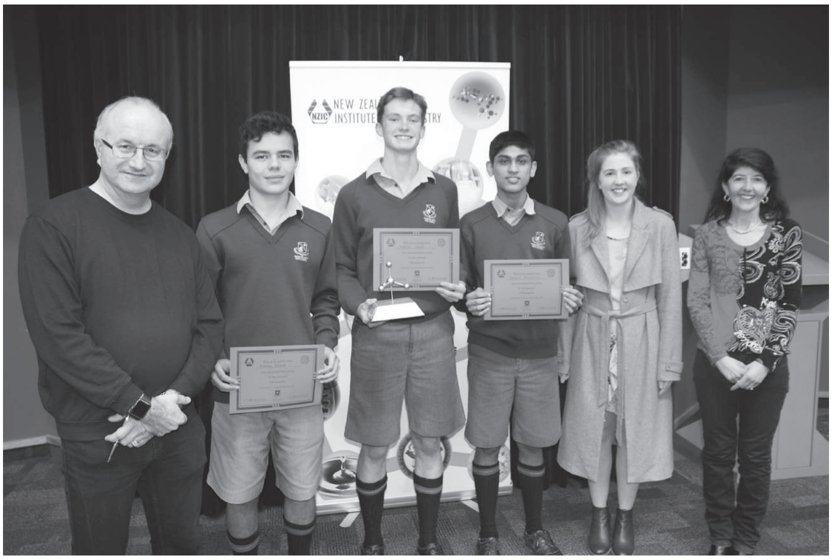
In September, *Ken* ***Clarke*** spoke about some of his experiences as compliance manager at Responsible Care NZ, a complex role with many facets! A student careers evening was offered for students at all levels and this year the varied speakers included ex-students *Eldon* ***Tate*** from Inhibit Coatings, *Teresa* ***Vaughan*** from the Environmental Protection Authority, *Richard* ***Kleingeld***, science teacher at Samuel Marsden College and *Pauline* ***Calloch*** from Callaghan Innovation.

A site visit to the Resene factory in Naenae in October was attended by about 20 students, who were entertained by Resene employee and chemistry graduate *Sam* ***Mallia***. The visit began with an introduction to the history of Resene, then the group was shown where paint was mixed and stored, as well as a small lab for quality testing and an accelerated weathering testing lab. The students appreciated the opportunity to experience a local employer (Resene hires about 30 chemists!). The visit ended with shared pizza before a return to the city.

This year's Wellington Branch named lecture was the Halton Lecture, held in November and given in celebration of Emeritus Professor *Brian* ***Halton***'s many contributions to chemistry - in New Zealand and worldwide - through his research of strained organic molecules, through his teaching of many students at Victoria University, and through his commitment to the NZIC, at both the branch and national levels. The Halton Lecturer was a previous PhD student of Brian's, Professor *David* ***Officer***, who is at the University of Wollongong in the Intelligent Polymer Research Institute and the Australian Research Council Centre of Excellence for Electromaterials Science. David spoke about *Shining light on new materials: molecules to devices*; the audience was led through some of the past and present research highlights in light harvesting, saw droplets of photoactive material move in response to light, and heard delightful stories of personalities in chemistry from the dawn of organic chemistry through to recent times!

The Wellington Branch congratulates *Ian* ***Miller*** on being elected as a Fellow of the Royal Society of Chemistry. Congratulations also to *Peter* ***Tyler*** on being awarded the 2017 MacDiarmid Medal - a recent Stuff article featured his medal award and the recent success of a drug created by Peter and collaborators: https://www.stuff.co.nz/national/health/97734408/A-coup-for-Kiwi-medicine-Peter-Tyler-honoured-for-work-developing-aggressive-lymphoma-drug

A number of Branch members have attended and presented at confer-



Prize winners: The winning team from Hamilton Boys' High School, Immo Frank, Patrick Dowd and Joshua Monteiro with Kate Leach from Hill Laboratories (right), organiser Michèle Prinsep (far right) and the chairperson of the Waikato branch of the NZIC, Associate Professor Michael Mucalo (left)

The new Hill Laboratories site

ences nationally and internationally. *Gavin* ***Painter*** attended the CD1-MR1 Immunology conference in Napa Valley, USA. *Robin* ***Fulton*** and *Martyn* ***Coles*** presented at the 24th International Society of Pure and Applied Coordination Chemistry conference in Auckland. *Suzanne* ***Boniface*** presented at the Australian Conference of Science and Maths Education in Melbourne. *Ralf* ***Schwoerer*** travelled to York, UK, on a Royal Society International Exchanges Scheme award and spent 2 months with Martin Fascione working on the automated synthesis of oligosaccharides. The synthesiser in York is the third of four commercial units (Glyconeer) currently operating worldwide. *Dennis* ***Page*** and *Joanne* ***Harvey*** visited Canberra in November for the 50th Anniversary of the Research School of Chemistry at the Australian National University. The events marked achievements of the School, its alumni and staff, a tour of the new chemistry building and the Birch Lecture.

VUW

In September, *Michelle* ***Cook*** successfully defended her chemistry PhD thesis under the supervision of *Jim* ***Johnston*** (primary) and *Robin* ***Fulton*** (secondary). In October, *Helen* ***Woolner*** defended her chemistry PhD, supervised by *Peter* ***Northcote***.

In November, students from Massey and Victoria met in Palmerston North for the annual Massey-Vic student symposium, and were treated to short seminars by students at both institutions.

In addition to his Halton Lecture, David Officer (Wollongong) also gave a more technical seminar on *Developing nanostructured electromaterials for bio and energy applications.* Chemistry department seminars were given by *Jadranka* ***Travas-Sejdic*** (Auckland) on *Grafted conducting polymers: towards intrinsically self-healing and stretchable polymer electronics*; *David* ***Barker*** (Auckland) on diverse syntheses of both complex natural products and versatile polymers, and *Shane* ***Telfer*** (Massey) about successes, challenges and utility of metal-organic frameworks. Anthony Carroll from Griffith University in Brisbane visited and spoke on the discovery of new natural products from the Australian flora.

Wellington hosted the first First-Year Science Educators' Conference (FYSEC) in November, which attracted attendance from academics, professional staff and school teachers from around New Zealand and Australia.

Simon ***Hinkley*** was successful in the last MBIE round. He is leading a team that has been awarded $6.2 million over five years to generate new compounds for use in products that accelerate bone and tissue repair. *Kai* ***Chen*** was awarded a Marsden Fast-Start grant for the project *Photoluminescence shines a light on the exemplary optoelectronic properties in hybrid organic-inorganic perovskite*.

Victoria University hosted professional development days for chemistry teachers in both Wellington and Auckland during November, highlighting aspects of current chemistry research and other chemical topics of interest, including the NZIC Spectra Database.

BRANZ

Catherine ***Nicholson*** presented a training module on materials durability and performance to students from the NZ Institute of Building Surveyors in Christchurch on 19 September. On 9 November she attended the *Innovating with light forum* held in Auckland. This was organised by *Bridget* ***Ingham*** from Callaghan Innovation and was an excellent opportunity to learn more about synchrotron methods and how the process for accessing the Australian synchrotron works for NZ-based researchers.

Wellington branch NZIC members at Resene in Lower Hutt

One of the many mixing vats at the Resene site

Synthesis of deuterium labelled sesquiterpenes for a convenient GC-MS analysis

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Keywords*: sesquiterpenes, isotopic labelling, deuterium, terpenoids*

Introduction

Sesquiterpenes, members of the terpenoid family of compounds, are an important class of compounds that have been isolated from a variety of natural sources.[1] Despite all sesquiterpenes being comprised of three isoprene units, thus having an empirical formula of $C_{15}H_{24}$, over 5000 sesquiterpenes have been isolated. Sesquiterpenes have been implicated in a number of biological roles, including plant growth regulation,[2] signalling[3] and defence mechanisms.[4] Furthermore, there has also been postulation that sesquiterpenes contribute to flower pollination.[5]

In other, therapeutic-related benefits, sesquiterpenes have been cited for their beneficial medicinal properties, exhibiting a number of activities including anti-inflammatory and anti-proliferative actions.[6-8] As over 90 different sesquiterpenes have been found in a range of grape varieties and grape-related products, there has been great interest in sesquiterepenes in relation to wine science and the potential benefit of wines that contain these compounds.[9-11]

The biogenesis of sesquiterpenes is related to that of monoterpenes for which the current knowledge is far more extended. While some steps, such as the importance of the 1-deoxy-D-xylulose 5-phosphate (DOXP) and mevalonic acid pathways to the biosynthesis of sesquiterpenes is known, their biogenesis is far less understood.[12-14] Sesquiterpenes possess a hydrocarbon skeleton – these backbones are highly diverse and complex which makes identification and quantification of these compounds very difficult. Even in the most recent and advanced studies, significant limitations on their chemical detection were encountered, with several sesquiterpenes only tentatively identified.[15-21]Additionally, almost no sesquiterpenes were quantitatively detected because of the lack of available and suitable standards.

Isotopically labelled precursors have previously been used to study the biogenesis of sesquiterpenes, as well as to investigate the enzymes responsible for the cyclised products.[14,22-24] These studies, however, fall short in the identification and quantification of other labelled species that could potentially have been formed. While the total synthesis of a number of sesquiterpenes has been widely reported,[25,26] however these syntheses have not proven useful in terms of identification and quantification of these species in plant tissues as no labelled sesquiterpenes were also synthesised.

If pure, isotopically labelled analogues of sesquiterpenes were available, they would be beneficial in the study of the formation and evolution of these molecules in complex biological matrices, as has been shown in the study of other classes of compounds.[27-30] To this end, instead of introducing labelled sesquiterpene building blocks, which would lead to the formation of a number of sesquiterpenes without the possibility of definitively resolving them, we proposed synthetic strategies that would allow us to obtain new, isotopically labelled sesquiterpenes. These compounds could then be used for analytical purposes in MS-based SIDA (Standard Isotope Dilution Analysis) approaches. Herein we report our research into the synthesis of a number of labelled sesquiterpenes and their application in the analysis of grape and wine matrices.

Synthesis of labelled sesquiterpenes

Our approach was based on obtaining commercially available sesquiterpenes or sesquiterpenoids and then introducing deuterium atoms to these compounds. The introduced deuterium atoms were required to be sufficiently stable to be retained in some of the fragments formed during ionisation in MS or MS/MS analyses. The use of deuterium labelling was chosen over the use of ^{13}C labelled compounds as this allowed commercially available, non-labelled compounds to be utilised as starting materials for the synthesis. ^{13}C labelled sesquiterpenes have recently been reported for use in mechanistic studies on this class of compounds. However, they require *de novo* synthesis from more expensive, labelled precursors.[31,32]

Synthesis of linear oxygen-containing sesquiterpenes

Initially, we directed our attention to the synthesis of a set of standards of linear sesquiterpenes (Fig. 1). To this end, the first commercially-available sesquiterpene to be used was (*E*,*E*)-farnesol **1**. (*E*,*E*)-Farnesol **1** and its derivatives, (*E*,*E*)-farnesyl acetate **2** and (*E*,*E*)-methyl farnesoate **3** are all known wine aroma compounds, although their contribution to wine aroma has not been explored due to the aforementioned difficulties in their quantification in biological matrices. We first wished to synthesise deuterated standards of each of these compounds.

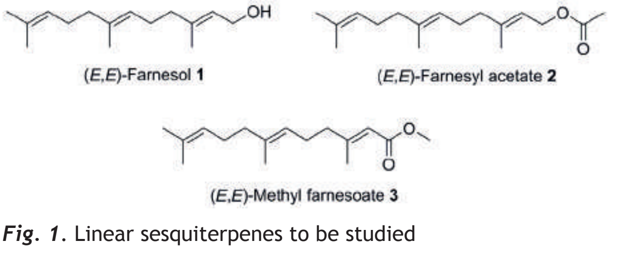
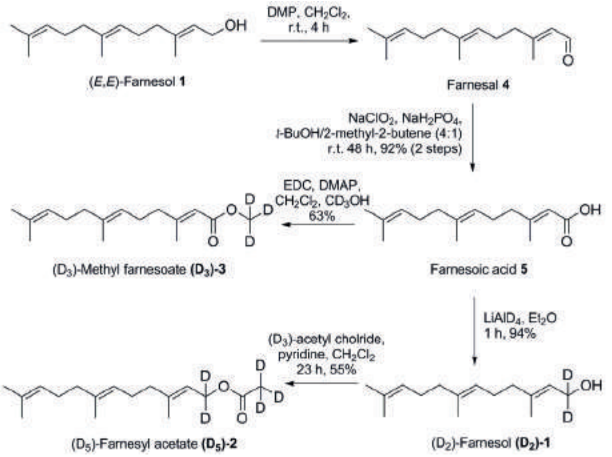


Fig. 1. Linear sesquiterpenes to be studied

Starting with (*E*,*E*)-farnesol **1**, the primary alcohol was reacted with acetyl chloride to provide (*E*,*E*)-farnesyl acetate **2**. Replacing acetyl chloride with (D_3)-acetyl chloride was a simple strategy to generate a deuterium labelled analogue. However, although easy to introduce, these acetyl deuterium labels can be easily lost in fragmentation during mass spectrometry techniques which would result in the majority of the standards' fragments being identical to the unlabelled derivative. We therefore revised the synthesis to allow for introduction of deuterium atoms into the backbone of (*E*,*E*)-farnesyl acetate **2**.

Thus, in a revised synthesis, (*E*,*E*)-farnesol **1** was oxidised to farnesal **4** which was then converted to farnesoic acid **5** in 92% yield (over two steps) using a Pinnick oxidation[33] (Scheme 1). (D_2)-Farnesol **(D_2)-1** was then produced from farnesoic acid **5** in 94% yield through reduction using lithium aluminium deuteride. **(D_2)-1** was then converted to (D_5)-farnesyl acetate **(D_5)-2** when reacted with (D_3)-acetyl chloride. Finally, a deuterium-labelled (*E*,*E*)-methyl farnesoate **3**, **(D_3)-3** was synthesised from farnesoic acid **5** via esterification using (D_3)-methanol and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in 63% yield.



Scheme 1. Synthesis of labelled linear sesquiterpenes

Synthesis of cyclic sesquiterpenes

The next set of standards was made from two commercially available cyclic sesquiterpenes; (+)-aromadendrene **6** and (-)-carophyllene oxide **7** (Fig. 2). Both **6** and **7** contain a single terminal alkene and, apart from the epoxide present in (-)-carophyllene oxide **7**, no other functional groups. Our approach to introduce deuterium atoms to these compounds was through the oxidation of the terminal alkene functionalities to generate the ketone derivatives, which could then undergo a Wittig reaction with a suitably labelled Wittig reagent – this would result in the original sesquiterpene with the terminal alkene protons replaced with deuteriums.

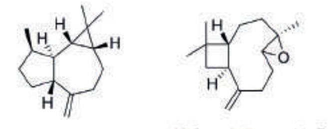
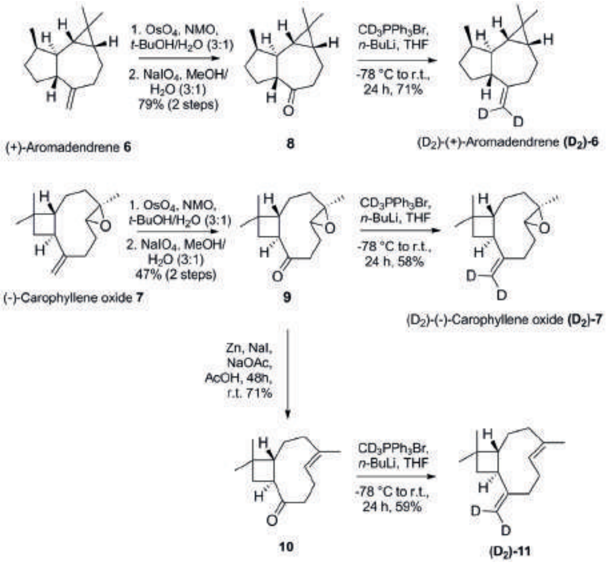


Fig. 2. Cyclic sesquiterpenes to be studied

We initially tried to convert the alkene functionality to a ketone through the use of ozone but this gave significant amounts of side products. Fortunately, we were able to use a two-step dihydroxylation/periodate cleavage procedure on **6** and **7** to give the desired norsesquiterpenes **8** and **9**, respectively, in good yields and with little unwanted side products (Scheme 2). For the Wittig reaction, the deuterated Wittig reagent was freshly prepared by stirring methyl triphenylphosphonium bromide in excess deuterium oxide with sodium deuteroxide for 4 h.[34] The optimum stirring time for the preparation of 1 g of deuterated reagent was 4 h using 0.50 mL of sodium deuteroxide (30 wt.% in D_2O) in 10 mL of D_2O. The reaction time and molar equivalent of sodium deuteroxide were optimised so as to maximise the percentage of deuterium exchange, while minimising the formation of the ylide. Although formation of the ylide is desired for the Wittig reaction, its formation during the deuterium exchange step is undesired since the reactive ylide degrades with prolonged storage. Applying standard Wittig reaction conditions to ketones **8** and **9** gave the D_2-labelled sesquiterpenes **(D_2)-6** (71%) and **(D_2)-7** (58%) respectively, with approximately 95% deuterium incorporation.



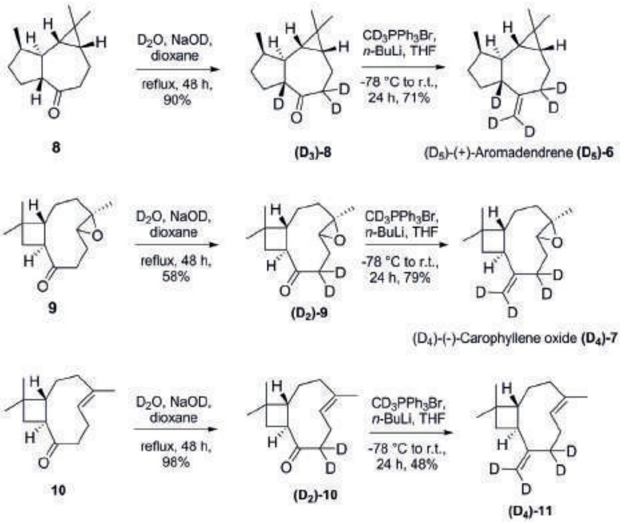
Scheme 2. Synthesis of deuterium-labelled cyclic sesquiterpenes

Another sesquiterpene was prepared from (-)-carophyllene oxide ketone derivative, kobusone, **9**; de-epoxidation of the iodohydrin intermediate of **9** gave a 5.5:1 ratio of the *trans* isomer **10**, over the *cis* isomer (isocarophyllene). The aforementioned Wittig reaction was then carried out on β-carophyllene ketone derivative **10** to give the D_2-labelled product, **(D_2)-11** in 59% yield.

Synthesis of additionally labelled cyclic sesquiterpenes

As these labelled compounds would be used as analytical standards in an EI-MS method, we considered the structural lability of compounds bearing a deuterated methylene group. There is a potential for these terminal alkenes to be easily fragmented therefore we decided to also introduce additional deuterium labels to the carbon backbone on the carbon adjacent to the terminal alkene. This was possible by exchange of the acidic α-protons of the previously prepared ketone intermediates, **8-10**.

Following a previously reported method by Tkachov *et al.*[35], ketones **8-10** were heated at reflux in dioxane with D_2O and NaOD to efficiently provide deuterated analogues, **(D$_3$)-8**, **(D$_2$)-9** and **(D$_2$)-10** (Scheme 3). Deuteration of ketones **9** and **10** resulted in exchange of the α-protons on the 9-membered ring only. This was not the case for ketone **8**, however, where not only were the α-protons on the 9-membered ring exchanged, but also the α-proton at the bridging carbon of the cyclobutane ring. It should be noted that **(D$_3$)-8**, **(D$_2$)-9** and **(D$_2$)-10** are also useful in SIDA MS/MS as standards as these norsesquiterpenes have all been identified as either natural products or of particular interest as a synthetic starting material.[36-38] The Wittig reaction was once again utilised with these ketones to produce **(D$_5$)-6**, **(D$_4$)-7** and **(D$_4$)-11** in 48-79% yields, now containing deuterium labels on both the cyclic and exocyclic carbons.



Scheme 3. Synthesis of additionally-labelled cyclic sesquiterpenes

Use of labelled sesquiterpenes in the analysis of grape matrices

Preliminary studies in grape and wine matrices based on GC-MS and GC-MS/MS were then performed. Optimisation of the MS conditions has allowed us to focus on the molecular ion and exploit the 3-5 Da m/z shift caused by the isotopic labelling. The prepared standards were used as internal standards in SIDA-MS/MS studies which enabled the accurate quantification of sesquiterpene levels in biological samples.

Based on limited information available in the literature on the content of sesquiterpenes in grape,[39] detection limits obtained with these methods were suitable for the analysis of these molecules.

Sauvignon blanc grape samples were analysed for their sesquiterpene content. Three sesquiterpenes, namely caryophyllene oxide **7**, farnesol **1**, and farnesyl acetate **2**, were identified and quantified in four grape matrices, Chardonnay, Merlot, Pinot Grigio, and Sauvignon blanc.

Conclusions

The methods presented herein provide a robust route to the synthesis of a number of deuterated sesquiterpenes with various levels of deuteration, as required. The use of these labelled sesquiterpenes was successfully shown in the quantitative analysis of grape matrices, allowing for further study of these notable natural products.

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Improving the efficiency of organic solar cells using supramolecular chemistry

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Introduction

The development of sustainable, low-cost and scalable technologies for the production of energy is one of the most urgent challenges facing modern society. Annual global energy consumption is predicted to reach 860 exajoules (EJ) by the year 2040 – an increase of 48% since 2012.[1] A switch from fossil fuels is necessitated by a number of factors. These include: increasing global population, increased demand for energy and environmental deterioration caused by over-reliance on organic fuels.[2]

Solar energy capture remains one of the most promising foundations for alternative energy technologies, and is a vibrant and truly interdisciplinary research area. Of the current options available for solar energy, photovoltaics (devices which convert light into electrical energy via the photovoltaic effect, see below) show considerable potential for development as a solution to the energy problem.[2] The field of photovoltaics is itself incredibly diverse, with different technologies typically characterised by the materials from which they are made. Prominent examples include: traditional inorganic (usually Si-based), dye-sensitised, perovskite and quantum dot solar cells.[3] Another possibility is the use of organic photovoltaics (OPV), where the photoactive component of the device is made solely from organic materials (either polymeric or small molecule). The highest certified power conversion efficiencies (PCE) for a range of photovoltaic technologies are given in Fig. 1.[3]

It is clear from Fig. 1 that the performance of so-called "emerging PV" technologies is currently dwarfed by established crystalline silicon photovoltaics, with the exception of high-performance perovskite solar cells. However, the quantity of solar energy incident on Earth within a single hour is approximately equal to the energy required by the global population for an entire year.[4] A more relevant consideration is the fact that the theoretical potential of solar energy, although difficult to assess accurately, has been estimated as being within the range of 1,575-49,837 EJ annually.[5] With these values well in excess of annual energy consumption, PCE is clearly not the only metric by which the viability of photovoltaic technologies should be judged. Other important considerations include production/installation costs, cell lifetime and environmental impact.[2] In particular, low-cost production is vital if solar technologies are to compete with fossil fuels. It is in this context that OPV devices reveal themselves as an attractive option. The low material costs of OPV devices and the compatibility of organic materials with high-throughput, solution-phase production techniques such as roll-to-roll printing represent a key advantage of OPVs over many other photovoltaic technologies.[2]

The charge generation process in organic photovoltaics

The process by which light is converted into electricity in organic photovoltaic devices is fundamentally different to that of inorganic solar cells. One of the primary reasons for this is that organic materials typically exhibit lower dielectric constants than inorganic materials.[6] This means that charges are less effectively shielded from one another. The result is that, in organic materials, absorption of light leads to the formation of an electrostatically-bound charge pair known as an *exciton*. This is in contrast to silicon-based solar cells, in which charges are immediately free to separate from one another following promotion of an electron to the conduction band. Because of this key difference, OPV devices are normally prepared as two-component organic films with a bulk heterojunction (BHJ) morphology (Fig. 2). The organic film present in OPV devices is called the "active layer". In a BHJ device, the active layer is composed of two interpenetrating organic materials, termed the "donor" and "acceptor" in accordance with their roles in photocurrent generation (see below). The donor can be either a polymeric or a small molecule-based material. The acceptor is typically fullerene-based (although the development of non-fullerene acceptor materials is currently a subject of much investigation). The active layer is sandwiched between two electrodes. By necessity, one of the electrodes must be transparent in order to allow light to reach the active layer. This is most commonly achieved by the use of a tin-doped indium tin oxide (ITO) anode.[2]

In an OPV device, the photovoltaic process occurs as follows (Fig. 2).[6-8] First, a photon is absorbed by a molecule in the active layer (normally a donor molecule), forming an exciton. Second, the exciton diffuses to the donor/acceptor boundary. Upon reaching the interface, the exciton dissociates *via* electron transfer from the donor to the acceptor. This results in the formation of negatively charged species in the acceptor material and a positively charged species (a "hole") in the donor material. The resultant charge pair is called a charge-transfer (CT) state. It is important to note that at this stage, the electron and hole are still subject to electrostatic attraction toward one another. The energy required to separate the charges is called the CT-state binding energy, denoted by E_{CT}. The charges then separate from one another and diffuse to the electrodes. Although not the focus here, it is worth noting that the precise mechanism by which the charges in a CT-state are able to separate from one another is still being actively investigated.[9-11]

This description of the photovoltaic process, together with the fact that the exciton diffusion length is typically

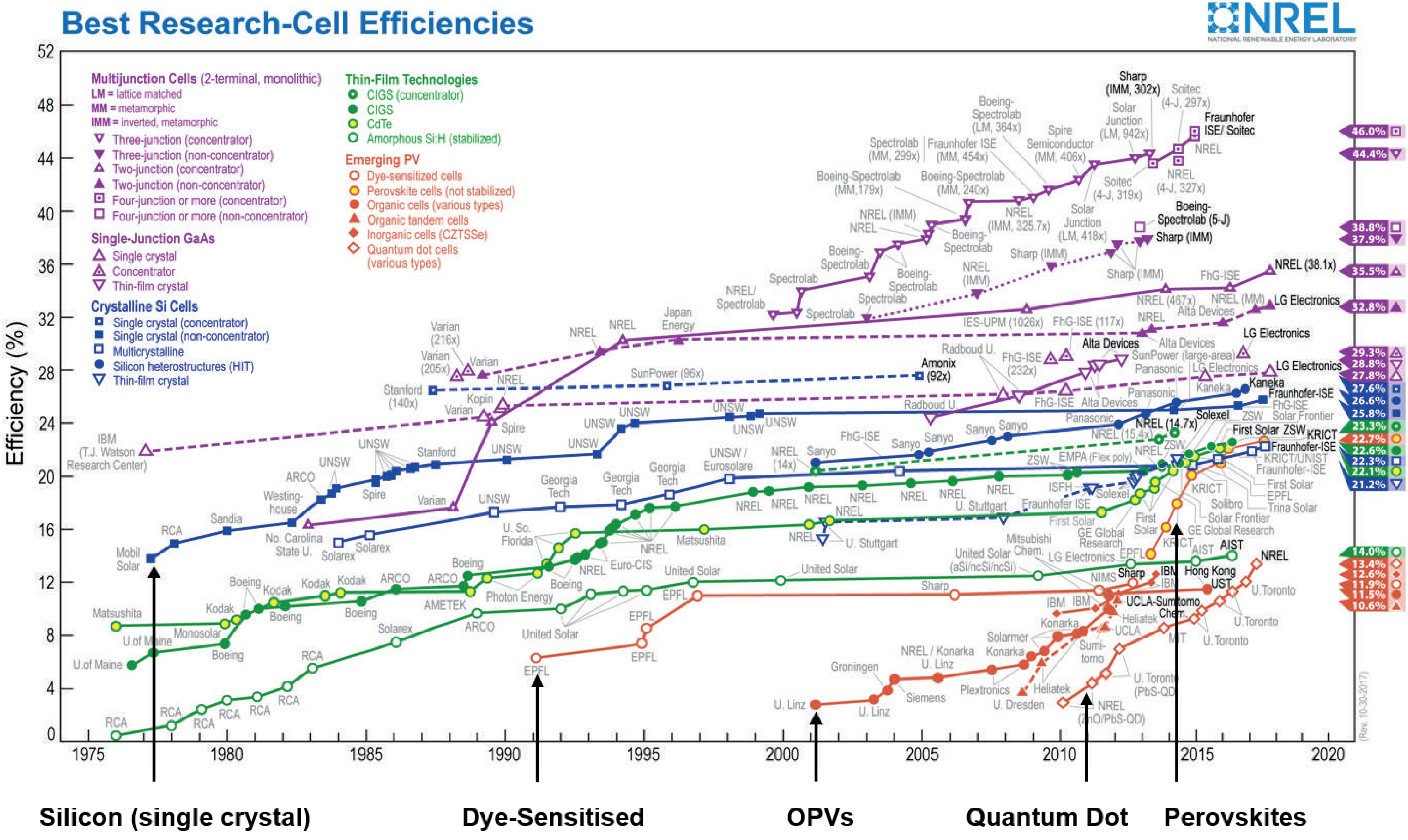


Fig. 1. Highest certified efficiencies for different photovoltaic technologies.[3]

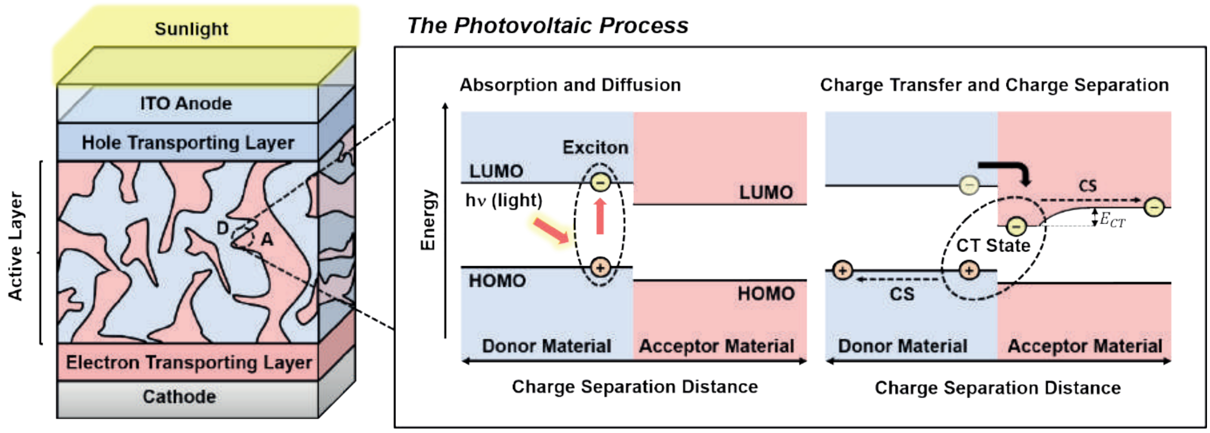


Fig. 2. Typical device architecture for a bulk heterojunction (BHJ) organic solar cell and simplified overview of the photovoltaic process. D = donor, A = acceptor, HOMO = highest occupied molecular orbital, LUMO = lowest unoccupied molecular orbital.

only 10-20 nm, makes clear the rationale behind a) the use of two-component organic films, and b) the use of BHJ active layer morphologies. A second molecular component is required to separate the exciton into charges via an electron transfer process while BHJ morphologies reduce the distances that excitons need to travel before reaching the donor/acceptor interface, where they can separate.[6,12] An ideal BHJ organic solar cell possesses nanoscale donor/acceptor domain sizes, while retaining continuous charge transport channels (often called “charge percolation pathways”) through which separated charges may be transported to the electrodes without re-crossing the donor/acceptor boundary.

Effects of intermolecular interactions on OPV efficiency

Historically, the design of new active layer materials has largely focussed on optical tuning of the donor and acceptor molecules (or polymers).[13] Adjusting the HOMO and LUMO levels by varying molecular structure provides compounds with absorption maxima at wavelengths corresponding to regions of high solar flux. Control of the frontier molecular orbitals also ensures that the offset between the donor and acceptor LUMO levels is sufficient to drive the dissociation of the exciton to form a CT state.[6,7] Finally, the “open-circuit voltage” V_{OC} (defined as the voltage required to stop current when the device is under solar illumination) can be roughly correlated with the difference in energy between the donor HOMO level and the acceptor LUMO level in the gas phase.[9,10]

However, there are many factors that influence device performance other than the gas phase energy levels of the materials employed. These include the degree of molecular order and packing structure in the active layer, the donor/acceptor blend morphology, thermal stability and solubility.[6,10,13,14] Critically, each of these factors depends on intermolecular interactions which, although difficult to control, constitute an under-utilised design consideration in the field of OPV. The most obvious example of the use of intermolecular interactions in the context of OPVs is π–π stacking, which is ubiquitous. However, beyond optical tuning and π–π stacking of chromophores, the rational design of new OPV materials by chemists is rare.[13] Current strategies targeting intermolecular interactions that have been shown to improve device efficiency include hydrogen bonding,[15-17] dipolar interactions,[18-20] and donor/acceptor shape complementarity.[21,22] It is the goal of this article to provide a brief overview of these different strategies, illustrating the key design principles by means of a small number of selected examples. For ease of representation, this article will focus on small molecule donor materials.

Hydrogen bonding

Other than π–π stacking, the use of hydrogen bonding interactions is the most common way of enhancing molecular organisation in the active layer of organic solar cells. One of the best examples of the use of hydrogen bonding in the context of OPV is motivated by the seminal work of Iqbal and co-workers, who reported the preparation of *t*-butyloxycarbonyl (Boc) protected diketopyrrolopyrrole (DPP) **1** (Fig. 3).[16] In keeping with common practice for DPP-based dyes, masking of the amide functionality with a Boc group drastically improved the solubility in organic solvents, enabling preparation of thin films by solution-based methods (i.e. spin-coating). Subsequent heating of the organic films to approximately 180°C led to spontaneous cleavage of the Boc groups, regenerating the parent DPP **2** and extruding CO_2 and isobutene. Removal of the amide protecting groups during heating thus enabled the hydrogen bonding interactions between adjacent molecules to be re-established.

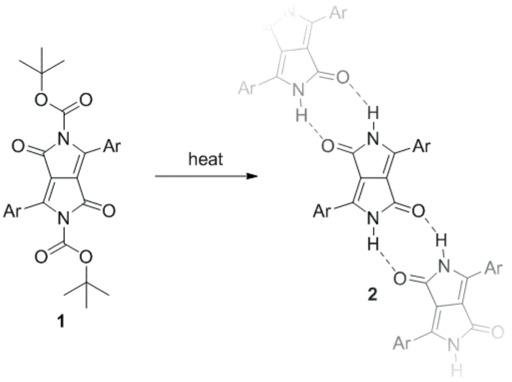


Fig. 3. Thermal cleavage of DPP **1** to give **2**.[16] The diketopyrrolopyrrole (DPP) framework is highlighted in blue.

Although not originally discovered in the context of solar energy capture, the same approach has since been adopted in the context of OPV by several research groups.[17,23] In general, thermal annealing of Boc-protected DPP derivatives has been found to result in significant improvements in photovoltaic efficiency (up to 20-fold compared with the protected compound).[17] These improvements in performance were found to be due to a combination of two factors. First, charge-carrier and exciton mobility in the active layer (i.e. conductivity) was improved due to the formation of crystalline DPP aggregates upon reactivation of hydrogen-bonding.[17] Second, the formation of hydrogen-bonding networks provided a favourable active layer morphology characterised by interpenetrating crystalline domains, thereby enhancing the probability that excitons are generated in proximity to a suitable interface where dissociation can occur.[17,23]

A second example of the use of hydrogen bonding interactions in the field of OPV can be found in the work of Stupp *et. al.*, who reported the preparation of compound **3** (Fig. 4).[24] The performance of photovoltaic devices employing **3** as the donor and phenyl-C_{71}-butyric acid methyl ester ($PC_{71}BM$) as the acceptor were investigated.[24] Under appropriate conditions, compound **3** was shown to undergo self-assembly *via* a combination of hydrogen bonding and π−π stacking to form well-defined donor nanowires. The efficiency of OPV devices incorporating these nanowires was 400 times greater than that of devices prepared by simple mixing of **3** and $PC_{71}BM$, which did not result in the formation of nanowires. More importantly, the efficiency of devices containing nanowires of **3** were 54% higher than analogous devices fabricated using the isolated chromophore (highlighted in blue) as the donor and $PC_{71}BM$ as the acceptor.[24]

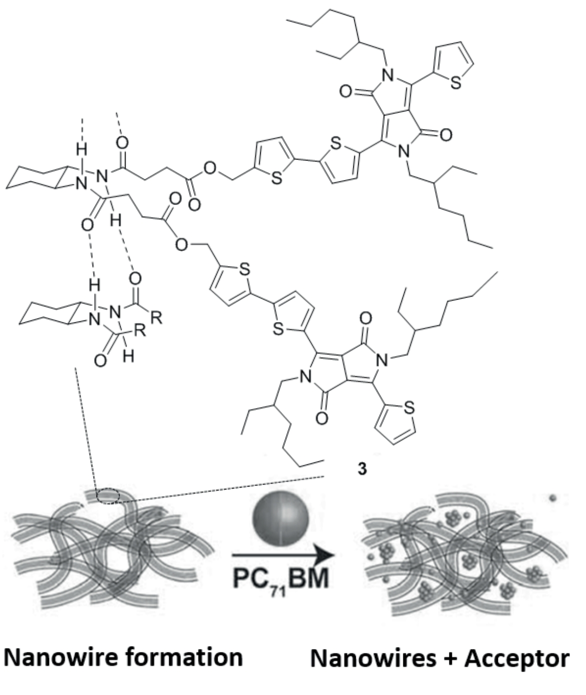
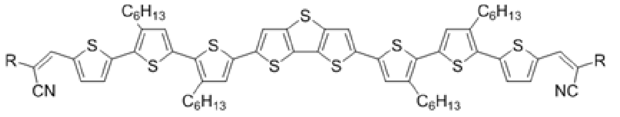


Fig. 4. Nanowire formation due to cooperative hydrogen bonding and π−π stacking.[24] Reproduced with permission of the Royal Society of Chemistry.

While the preceding examples indicate that hydrogen bonding interactions can be harnessed to improve OPV efficiency, it is important to note that such intermolecular interactions can also have adverse effects on device performance. For example, Wong and co-workers[25] have reported that the efficiency of organic solar cells incorporating compound **4** and phenyl-C_{61}-butyric acid methyl ester ($PC_{61}BM$) was decreased relative to analogous devices containing compound **5**, which cannot form hydrogen bonds with itself (Fig. 5). In this case, the hydrogen bonding interactions between molecules of **4** result in the formation of large donor domains of approximately 28-50 nm (compared with 17-30 nm for **5**) leading to inefficient transport of excitons to the donor/acceptor interface.[25] Intermolecular hydrogen bonding of **4** also disrupted the π−π stacking interactions between neighbouring donor molecules, lowering the charge-carrier mobility relative to compound **5**.



4, R = $CONHC_8H_{17}$
5, R = $CO_2C_8H_{17}$

Fig. 5. Compounds investigated by Wong and co-workers.[25]

Finally, it should also be noted that intermolecular donor-acceptor hydrogen bonding can also be used to control the photophysical properties of organic blends relevant to organic solar cells. However, to date, the use of this approach in a device context is rare.[26]

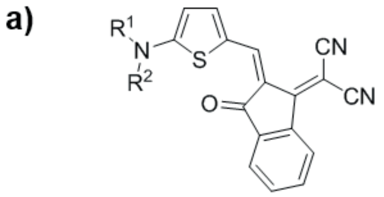
These examples illustrate that while hydrogen bonding interactions can be advantageous for OPV performance, whether or not this is the case depends on the precise nature of the molecular/polymeric species employed, in addition to other factors, such as processing conditions. In particular, any positive effects of hydrogen bonding must be carefully balanced against the effects on active layer morphology and other (possibly competing) intermolecular interactions.

Dipole-dipole interactions

Until relatively recently, the design and development of materials for OPV technologies was highly influenced by the Bässler model.[20] Briefly, this model predicts that molecules with dipole moments are unlikely to be successful in organic electronics due to an increase in energetic disorder associated with a random alignment of dipole moments. This energetic disorder would then impede charge-transport, adversely affecting device performance. The acceptance of this model meant that new donor molecules were often designed to be either centrosymmetric or to possess a high degree of symmetry. Over the past decade this perspective has been challenged, most notably by the group of Würthner.[18,27] Two examples of the highly polar merocyanine dyes developed by Würthner *et al*. are given in Fig. 6.[18] Compound **6** has a ground-state dipole moment of 8.6 Debye and is therefore not suitable as a material for organic electronics according to the Bässler model. However, solution-processed BHJ solar cells incorporating compound **6** (and related dyes) as the donor and $PC_{61}BM$ as the acceptor show impressive performance. Specifically, the non-optimised power conversion efficiency for the **6** / $PC_{61}BM$ material system was shown to be 2.3%. The authors also optimised the power conversion efficiency of the best performing dye of the series, compound **7**. The optimised efficiency of devices incorporating compound **7** was within the range 4.5-5.1% (in 2011).

The high efficiency of OPV devices based on **6** and **7** was rationalised with reference to the X-ray crystal structure of compound **6** (a quality diffraction pattern for **7** could not be obtained). In the crystal, molecules of **6** are arranged in discrete stacks with an antiparallel arrangement of molecular dipole moments (Fig. 6b). The authors rationalised that a similar packing arrangement is operative in devices incorporating compound **6**. The large dipole moment, together with the lack of bulky substituents capable of impeding close contact between adjacent molecules, means that molecules of **6** are able to self-assemble into well-defined centrosymmetric dimers. Dimerisation effectively eliminates the molecular dipole moment at the dimer level and above. This means that an increase in energetic disorder is avoided, allowing the construction of high-performance devices.

This work represented a significant challenge to the status quo regarding design principles for organic electronics, especially OPVs. However, it should be noted that careful design is again crucial to the success of these materials; the dipole moment must be sufficiently large to control molecular alignment, while the steric bulk associated with any solubilising groups must not significantly impair molecular organisation. The importance of unimpeded packing of molecules is also apparent when the π-framework of the central molecule is distorted. For example, the X-ray crystal structure of compound **8** reveals that bending of the aromatic framework interferes with formation of antiparallel molecular stacks (Fig. 7). This is manifested in increased π–π stacking distances and decreased overlap of adjacent chromophores. This structural disruption is accompanied by low efficiencies (1%) of devices incorporating **8**.



6, R^1 = *n*-butyl, R^2 = *n*-butyl
7, R^1 = *n*-butyl, R^2 = ethyl

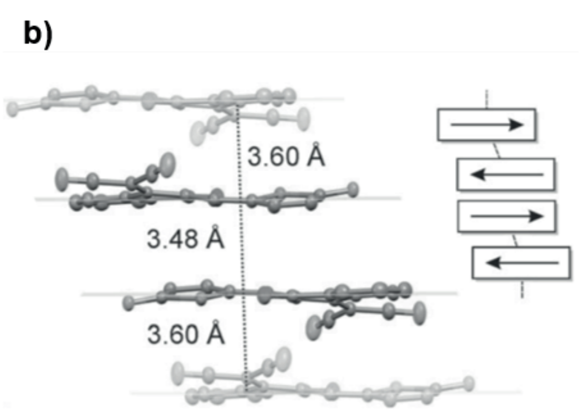
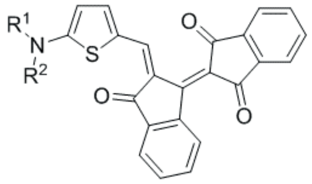


Fig. 6. (a) Highly dipolar merocyanine dyes **6** and **7**. (b) X-ray crystal structure of compound **6** showing antiparallel packing structure.[18] Reproduced in part with permission of Wiley-VCH Verlag GmbH & Co. KGaA.

Another example of dipole-dipole interactions enhancing photovoltaic performance comes from the work of Heeger *et al.*, who reported a marked improvement in performance using compound **9** (and two isomers) when compared with compound **10** (Fig. 8).[28] The optimised device efficiency of **9** in combination with $PC_{70}BM$ was 6.7%. In contrast, compound **10** was unable to generate any significant photovoltaic response. Given that these molecules differ from one another only by exchange of two equivalent carbon atoms for nitrogen, this difference in efficiency was surprising. The authors rationalised the



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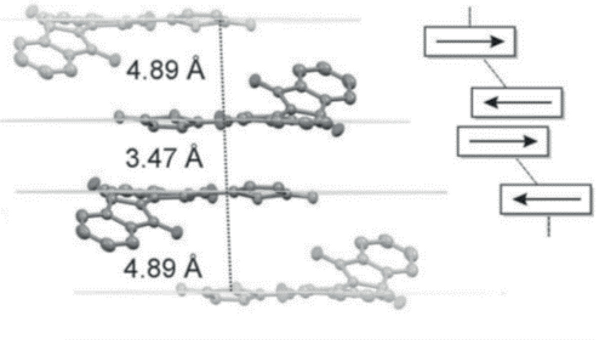
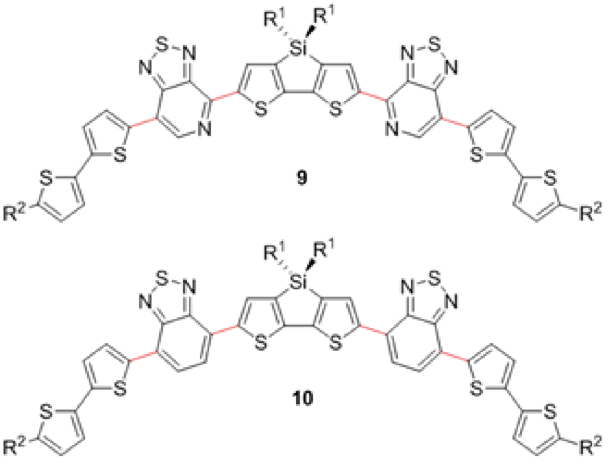


Fig. 7. Distorted merocyanine dye **8** and X-ray crystal structure showing disrupted aromatic stacking.[18] Reproduced in part with permission of Wiley-VCH Verlag GmbH & Co. KGaA.



R^1 = 2-ethylhexyl
R^2 = hexyl

Fig. 8. High-performance donor molecules prepared by Heeger *et al.*[28]

change in performance by considering the effects of changing the conformation of the molecule (about the red single bonds in Fig. 8) on the dipole moment. Quantum chemical calculations indicated that the presence of the nitrogen atom in **9** resulted in a smaller variation in the direction and magnitude of the dipole moment than **10** as the conformation of the molecule was changed. Compound **9** also appeared to exhibit a "conformational locking" effect due to non-bonding interactions between the pyridyl nitrogen atoms and the proximal sulfur atoms. These two factors were proposed to be responsible for enhanced antiparallel π-π stacking of **9** compared to **10**, leading to better self-assembly and improved photovoltaic performance. In addition to the difference in device performance, this hypothesis was supported by detailed morphological characterisation (grazing-incidence wide angle X-ray scattering, high resolution transmission electron microscopy and dark-field transmission electron microscopy) which indicated a greater degree of molecular order in films of **9** compared to **10**.

Shape complementarity

Given that OPV cells typically use fullerene acceptor materials such as C_{60}, one interesting approach to improving efficiency is the use of donor molecules capable of forming supramolecular donor-acceptor complexes due to shape complementarity. Towards this end, Nuckolls and co-workers[29] reported the preparation of a series of contorted hexabenzocoronenes (HBCs) and dibenzotetrathienocoronenes (DBTTCs) which readily co-crystallise with C_{60} or C_{70}-based fullerene acceptors.[21,22] The parent HBC, compound **11**, is shown in Fig. 9.[29] The unusual, doubly-concave structure of **11** enables the formation of bi-directional "ball and socket" co-crystals with C_{60}. Using a combination of grazing-incidence X-ray diffractometry and surface sensitive photoelectron and absorption spectroscopies, it was shown that even when using a bilayer device morphology, compound **11** and C_{60} formed small co-crystalline domains at the donor/acceptor interface. Bilayer devices fabricated using **11** and C_{60} exhibited power conversion efficiencies of up to 1.04%. These values are surprisingly high, considering the bilayer morphology employed and the fact that the absorption spectrum of compound **11** does not match well with solar illumination. Indeed, the authors found power conversion efficiencies of up to 5.7% when devices were irradiated with narrow wavelength range UV light. This suggests that the efficiency of such devices could be improved by optical tuning of the donor molecule. The key role of the donor-acceptor complex was highlighted by the preparation of devices incorporating a non-contorted HBC incapable of forming ball and socket complexes that were otherwise similar to compound **11** in terms of molecular and electronic structure and photo-physical properties. These otherwise analogous devices exhibited markedly decreased performance, clearly implicating the donor-acceptor shape complementarity as a key factor in the high performance of devices containing compound **11**.

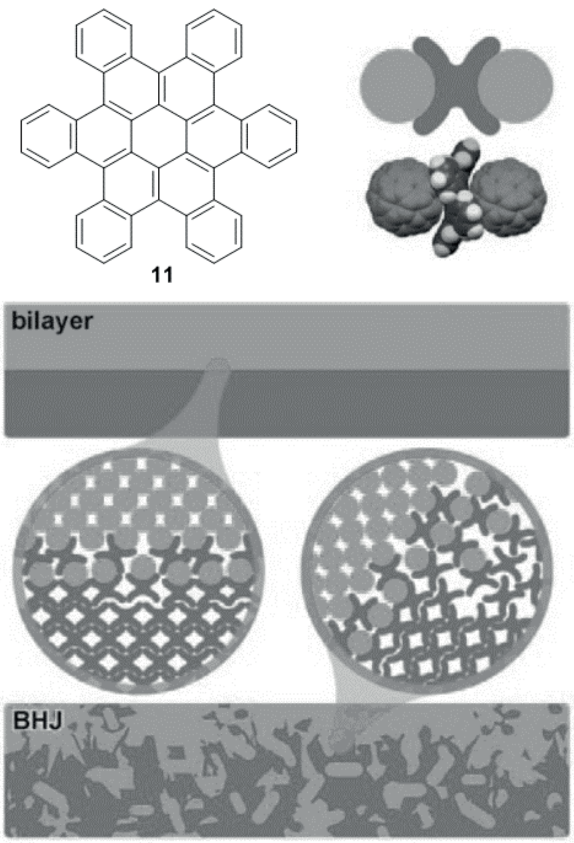
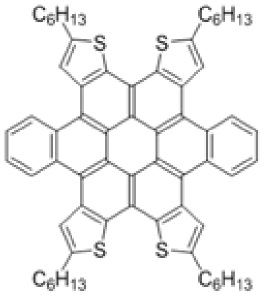


Fig. 9. Contorted HBC **11** and depiction of formation of bidirectional "ball and socket" complexes with C_{60}.[29] Reproduced in part with permission of Wiley-VCH Verlag GmbH & Co. KGaA.

Although the use of a bilayer morphology enabled detailed confirmation of the formation of molecular complexes between **11** and C_{60} in a device context, this morphology necessitated the use of physical vapour deposition for formation of the active layer. Ideally, organic solar cells should be solution-processable. With this in mind, Nuckolls and co-workers reported the fabrication of solution-processed organic solar cells incorporating contorted DBTTC **12** and $PC_{71}BM$ (Fig. 10).[22] The cells exhibited power conversion efficiencies of up to 2.7 %, which is again surprising due to the relatively low absorbance of compound **12** in wavelength regions corresponding to high solar flux. Compound **12** is expected to form similar donor-fullerene adducts as compound **11**. This is supported by the fact that the optimal mixing ratio of donor to fullerene (either $PC_{71}BM$ or $PC_{61}BM$) was found to be 1:2, with device performance sharply declining upon deviation from this ratio. Interestingly, on the basis of grazing incidence wide angle X-ray scattering experiments, the authors propose that **12** and $PC_{71}BM$ are completely mixed at the molecular level in their solution-processed devices. Such a morphology would not be expected to contain efficient charge percolation pathways. Although the efficiency of the devices is impressive in this light, this highlights the importance of achieving the correct balance between donor-donor and donor-acceptor interactions.

Conclusions

It is clear from the examples herein that the use of supramolecular interactions is a promising strategy through which chemists are able to contribute to the development of improved OPV technologies. However, it is also the case that such approaches are not yet the norm in



12

Fig. 10. Contorted DBTTC **12** prepared by Nuckolls *et al.*[22] Reproduced with permission.

the field of OPV.[30] The optimisation of bulk properties such as active layer morphology, charge-carrier mobility and disorder remains largely empirical. This is unsurprising, since photovoltaic performance is a multi-factorial optimisation problem and OPVs are still in their infancy compared with established technologies. However, as our understanding of both the photovoltaic process and supramolecular chemistry grows, improved control over OPV performance can be expected to follow.

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Shedding light on conservation of art in New Zealand

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Abstract

Interrogation of art materials with light reveals valuable information about their composition and properties for the art conservator. Raman and mid-IR FTIR spectroscopy are non-destructive methods that probe vibrational behaviour and can rapidly and non-invasively characterise the media and pigments in paints. Time-resolved UV-Vis spectroscopy can yield important information about the dynamics of photodegradation. This article highlights some examples of how time-resolved UV-Vis, Raman and FTIR spectroscopy have assisted art conservators in New Zealand and helped to determine appropriate treatment methods and preventative conservation strategies.

Introduction

The identification of materials as well as their response to illumination, are important for an understanding of works of art and their conservation. Not only does it shed light on the artistic choices and intentions, it also assists in the development of appropriate conservation strategies for care and treatment.[1] Studies into the unique choices made by New Zealand artists have been carried out alongside those of international art in public collections. A variety of techniques have been applied to examining the composition of the materials in these artworks, which may comprise complex mixtures or layers of natural and synthetic organic media such as drying oils, proteins or synthetic polymers as well as organic and inorganic pigments and fillers. Analysis of the artworks include examination of the surfaces under UV and IR light [2,3] microscopic and elemental examination of cross-sections using SEM-EDS,[4] X-ray powder diffraction,[5] pyrolysis with GC-MS[6] and HPLC-MS.[2] However, analysing the chemical composition of these artworks presents a number of challenges. In many cases the artworks are fragile and only very small fragments can be removed for analysis. Tiny fragments from paintings can comprise more than one layer of different media, each ranging anywhere between 1 – 100 µm in thickness, as well as heterogeneous mixtures of one or more different pigments and fillers. Analysis of the materials within each individual layer is often impossible using chromatographic methods.

Vibrational spectroscopy provides an alternative method for analysing art materials and has been extensively used for characterising a wide variety of materials such as modern paint media, pigments and forgeries in paintings, ancient artefacts, rock art and patina on steel sculptures.[7-12] In addition, time-resolved spectroscopy allows us to probe the mechanism of photodegradation of some highly coloured organic pigments. These types of studies allow us to explore the detailed response of the photoactive components in artworks to illumination. Results of time-resolved UV-Vis can guide decision-making about how best to balance the beneficial and destructive impacts of lighting upon the art itself. It gives insight into the details of the degradation of pigments, varnishes and other light-absorbing components.[13-15]

Vibrational spectroscopy employs both FTIR (far, mid or near-IR) and Raman spectroscopies as complementary techniques, each having particular advantages and disadvantages. Raman analysis would be preferred for samples where water or hydrated chemical species would dominate the mid-infrared spectrum, or where modes below 400 cm^{-1} are required, such as the lattice modes of many inorganic pigments and fillers. This region is particularly useful for differentiating polymorphs, such as the rutile, anatase and brookite forms of titanium oxides,[3] or different iron oxide or other inorganic pigments. Raman spectroscopy would also be the preferred method for molecules with low or no polarity such as graphite or carbon black, as more symmetrical vibrations such as aromatic breathing modes, C-C and S-S stretching modes feature more strongly in Raman spectra. Also, the fluorescence emission which is the main disadvantage of the Raman technique can be avoided or minimised using laser excitation at longer wavelengths in the near-infrared region of the electromagnetic spectrum. FTIR spectroscopy would be the preferred method if differentiation of compounds is based on highly polar functional groups in the paint media, for e.g., acetates, alkyd resins, oils and proteins, where the main groups of interest would be –OH, COO-, C=O or N-C=O.

The energy range of mid-IR radiation (155-413 meV, wavelengths 3 – 8 µm) corresponds to the fundamental translational, rotational, and vibrational energy transitions of molecules. Molecules will absorb energy in this energy range if they undergo a change in dipole moment during a normal mode of vibration of the molecule. Since the energies of these transitions are unique to the structure of the molecule, measurement of the absorption energies provides a powerful tool for characterising the different compounds in paint media. Using different sampling modes such as ATR (attenuated total reflectance) allows one to measure only selected surface layers to depths of 3 – 10 µm, depending on choice of crystal material. Analysis of selected layers in cross sections of paint fragments is enabled with FTIR spectrometers with microscope attachments that can record spectra from areas as small as 50 x 50 µm. In Raman spectroscopy, measurement is made of the inelastic scattering of monochromatic radiation resulting from its interaction with molecular vibrations. The incident monochromatic radiation can range anywhere from the UV to near infrared, typically 350 nm - 1064 nm. For a vibration to exhibit Raman scattering there must be a change in polarisability of the molecule during the normal mode of vibration. The frequencies of Raman bands are measured as wavenumber shifts from the exciting radiation. Raman spectrometers coupled with a microscope or a fibre optic probe enable analysis of areas as small as 0.5 µm. The spectra of both the Raman and mid-IR techniques can be subdivided into three regions:[12]

1. ~ 3600–2500 cm^{-1}, associated with X–H stretching vibrations, (where X = C, O, N or S. For X= P, cumulative double bonds (e.g., NCS) and triple bonds (e.g., CN) the range is 2500 - 2100 cm^{-1})
2. ~ 2000–1500 cm^{-1}, with double bond stretching vibrations (e.g., C=O, C=C, C=N)
3. ~1500 - 400 cm^{-1}, referred to as the fingerprint region where subtle differences occur between quite similar molecules, reflecting, for example, differences in polymorphic form, degree of crystallinity, extent of orientation or state of hydration.

The spectrum of a compound exhibits a number of bands from each of these regions, corresponding to the fundamental vibrational modes. These occur at frequencies characteristic of the composition and structure of that compound and are measured as wavenumbers (cm^{-1}) or in the case of Raman, wavenumber shift from the excitation wavelength (cm^{-1}). Definitive characterisation of the compound therefore requires matching more just than one of the bands, as well as their relative intensities. Spectral databases such as iRUG[16] and UCL Raman spectroscopic library[17] provide libraries of FTIR and Raman reference spectra of commonly used pigments and different media used in paints which can help to identify the compounds in paint samples. In addition, both Raman and FTIR spectroscopy can be used to map selected areas of the surface, providing chemical images of the material.

This article describes some examples where vibrational spectroscopy has been used to identify materials in paintings and a work on paper, to assist conservators from the Auckland Art Gallery Toi o Tāmaki. The results have contributed to understanding of the artist's techniques, as well as informing the treatment and preservation of these works from public collections. It is hoped that this article will stimulate interest in wider use of vibrational spectroscopy for the analysis of New Zealand's cultural heritage, as currently it is very difficult for conservators in this country to access the expertise required.

Methods

FTIR spectra of paint fragments were recorded using a Continuum FTIR microscope and Nicolet 8700 Thermo Electron FTIR spectrometer with DTGS detector, performing 64 scans at 4 cm^{-1} resolution. Samples that were small or thin enough for collecting spectra in transmission mode were placed on a NaCl window, or compressed between two diamond widows of a diamond compression cell, with KBr crystal as reference. Areas of 30-100 µm could be analysed in transmission mode using the 15x Reflachromat objective. The surfaces of some samples were analysed in ATR mode using the Smart Orbit accessory of the spectrometer with diamond window and single bounce at 45 degrees, sampling to a depth of 4 µm. All spectra were analysed using OMNIC spectroscopic software (Thermo Fisher).

Raman spectra were recorded using a Renishaw System 1000 microprobe in backscattered mode with a x50 objective, N.A. 0.75. The spectrometer grating was 1200 g/mm, slit width 50 µm. An HNF filter was used to remove Rayleigh scattered light. Excitation was the 785 nm line of a solid state diode laser with exit power of 25 mW which could be reduced if needed to avoid thermal degradation or minimise fluorescence for some of the materials. The laser was focused onto the surface to a spot size of 2 µm and spectra were recorded for between 20 – 120 s. Spectra were analysed using Grams 32 software (Galactic Industries).

Results and discussion

Characterisation of media and pigments in paint fragments

Analysis of modern materials

New Zealand artist, Ralph Hotere (1931-2013), created his series of *Black Paintings* in the 1960s and 70s. The artist experimented with industrial paints and techniques to produce paintings with high gloss surfaces intersected with lines, but the smooth surfaces are very easily damaged. The project for the 2008 Marylyn Mayo Intern at the Auckland Art Gallery, Lydia Gutierrez, was to identify the materials and techniques used for these paintings as this will assist conservators in treating them.[18] Analysis of a 50 µm x 50 µm area in a paint fragment from one of his *Black Paintings* (Fig. 1) confirmed his preferred use of nitrocellulose, which conveyed a translucent and polished appearance to the painting.[18] Other components identified in the FTIR spectrum of the 50x50µm white area of the paint fragment were the calcite polymorph of calcium carbonate ($CaCO_3$) and talc ($Mg_3Si_4O_{10}(OH)_2$) used as fillers. Additional bands not accounted for by these three compounds were a close match to an alkyd/linseed oil compound but this was not confirmed. However, alkyd and linseed oil were components of a contemporary standard formula used in an automotive nitrocellulose primer,[18] as were talc, carbon black and titanium dioxide.

Raman spectra of the cross section of another fragment confirmed the carbon black and the white pigment as the rutile form of TiO_2, respectively (Fig. 2).

Understanding deterioration

In 1956 the Auckland Art Gallery acquired the painting *Still Life: Anemones and Hyacinths* by Frances Hodgkins c1925 (Fig. 3). The painting had severe flaking but it was hoped that it could be treated in future. It wasn't until years later that the 2015 Marylyn Mayo intern, Genevieve Silvester, identified that the damage was caused by a complex layering of incompatible paint media.[2] Although the main painting was done in oil, it was possible to classify the upper red brown layer as gouache through the identification of gum arabic and calcium carbonate by FTIR. Another upper pinkish layer was found to possibly contain shellac (a varnish) and possibly proteins. Samples of the pinkish paint were also sent to Auckland Science Analytical Services where they were analysed using LCMS/MS. Analysis positively identified the presence of bovine proteins derived from milk or a casein medium.[2]

Informing treatment

A monumental task for the Auckland Art Gallery paper conservators, Ute Larsen and Camilla Baskcomb, was the conservation of a large multi-part engraving *The Mocking of Christ* by François Langot (1641 – 1679*).* Acquired in 2010, the print was in an extremely deteriorated condition. It is one of only six copies known to have been made by Langot, after the original oil painting by Anthony van Dyck (1599-1641) was believed to have been destroyed in World War II.[5] This print made its way to Auckland in 1995 from a convent in Ecuador where it sustained extensive damage from an earthquake and subsequent flood-

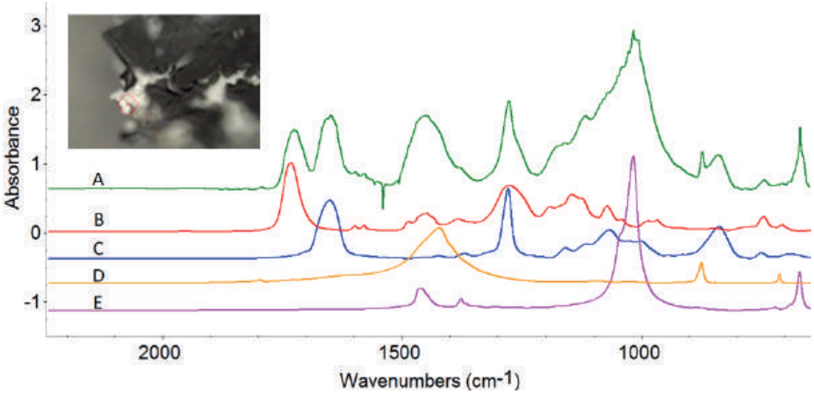

Fig. 1. (A) FTIR microscope transmission spectrum of a 50μm x 50 μm area of the white media in the paint fragment from a *Black Painting* (inset photograph). Reference FTIR spectra of (B) nitrocellulose component, (C) alkyd resin, and (D) calcium carbonate and (E) talc fillers.

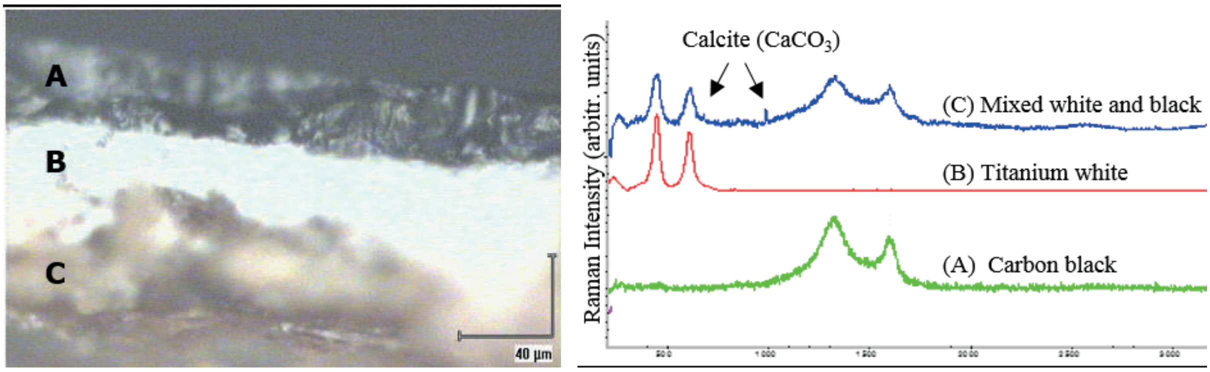

Fig. 2. Raman spectra of selected areas of a cross section from another fragment of a *Black Painting* identified the black pigment (A) as a carbon black and the white pigment (B) as the rutile form of TiO_2. The brown area (C) contains both pigments with some $CaCO_3$, with two small sharp bands indicated by arrows.

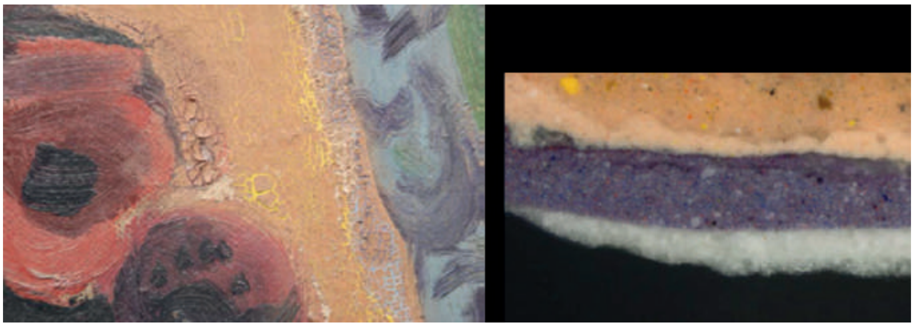

Fig. 3. Detail of flaking and cross-section from *Still Life: Anemones and Hyacinths* c.1925 by Frances Hodgkins, Auckland Art Gallery Toi o Tāmaki. Reproduced with permission.

ing (Fig. 4). The fine dust covering the work was identified by X-ray powder diffraction to contain anorthite and/or andesite which are found only in igneous environments of volcanic activity.[5] The ink was identified by Raman spectroscopy as carbon black (Fig. 5), and of poor quality. FTIR spectroscopy identified the adhesive between the cotton lining and paper on the back of the print as starch, also confirmed by the iodine/potassium iodide test. Restoration of the nine panels involved dissembling the nine sheets, removing the adhesive, washing out discolouration, repairing and retouching the damaged areas, reassembling all nine plates. The artwork after restoration is shown in Fig. 4b.

Identification of forgeries

While carrying out research for the Auckland Art Gallery exhibition *Gottfried Lindauer's New Zealand: The Māori Portraits,* a painting which had been known as a portrait *Hamiora Maioha* by Gottfried Lindauer from the Alexander Turnbull Library Collection was found to exhibit some uncharacteristic features which raised questions about its authenticity. The painting was examined in detail by conservators from the Auckland Art Gallery and the Museum of New Zealand Te Papa Tongarewa and samples were analysed.[3] Although Lindauer was painting more than a century ago, it is difficult to conclusively prove that a painting is a forgery because many of the materials

Fig. 4. François Langot after Anthony van Dyck, *The Mocking of Christ* c.1699, Auckland Art Gallery Toi o Tāmaki. Left: damaged print. Right: print after restoration. Reproduced with permission. Restoration sponsored by the Auckland Decorative and Fine Arts Society.

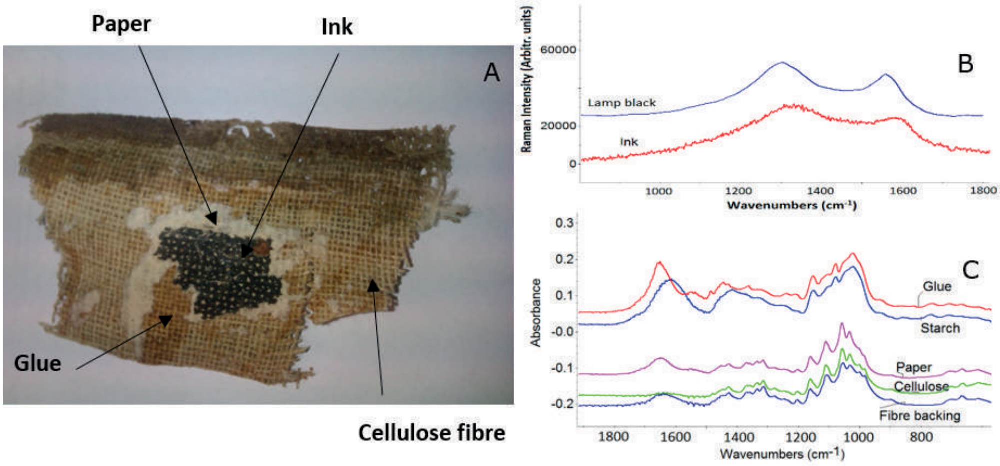

Fig. 5. Further analysis carried out on *The Mocking of Christ*: (A) Section of damaged fibre backing with glue, paper and ink, (B) Raman spectra of ink and lamp black pigment reference[17] and (C) ATR FTIR spectra of the glue, paper and fibre backing shown in (A), and starch and cellulose reference powders.

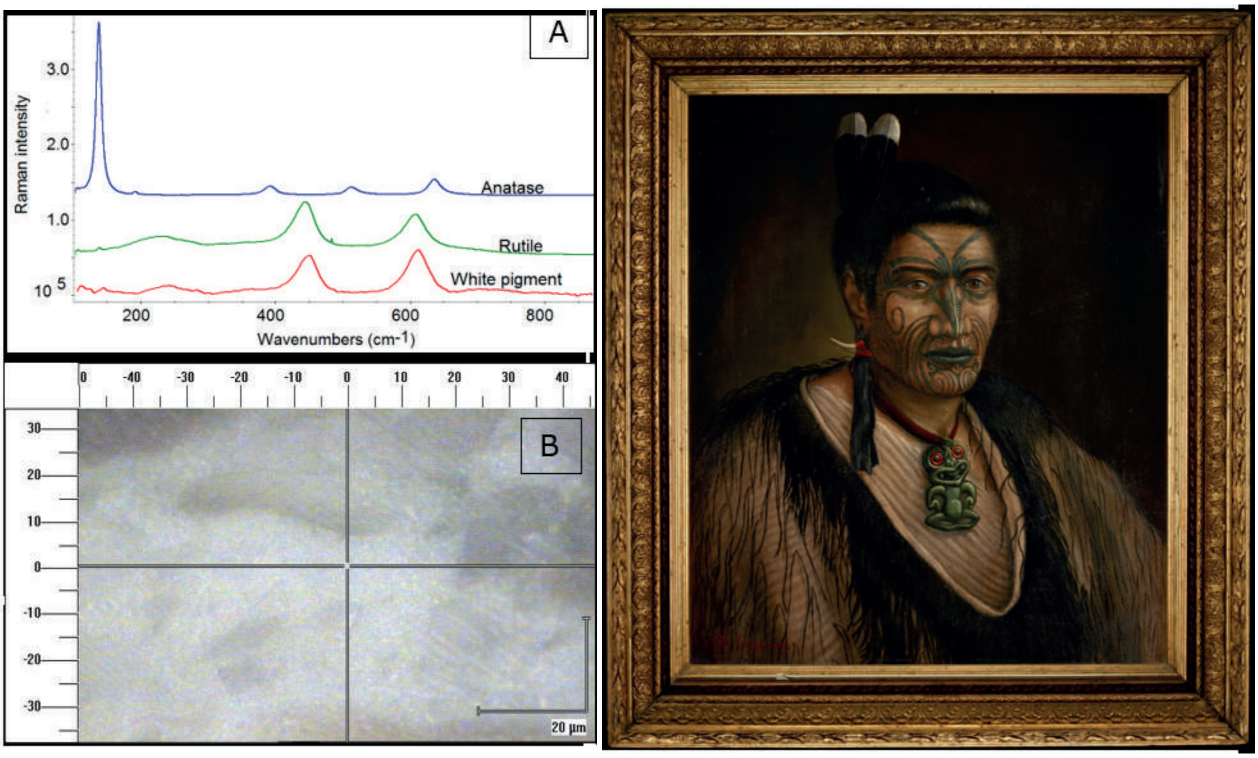

Fig. 6. A & B: Comparison of a Raman spectrum of the white pigment from the Lindauer forgery with the two TiO_2 polymorphs confirms the pigment as the rutile.[3] Image on the right: Portrait of an unidentified male Maori subject, oil on canvas, G-479, Alexander Turnbull Library, Wellington. Reproduced with permission.

are still available today. However, in this case, identification of titanium in the ground or preparatory layer by EDS at the Research Centre for Surface and Materials Science was of concern. Further analysis by Raman spectroscopy (Fig. 6) produced peaks that are characteristic of the rutile polymorph of TiO_2 This form of titanium dioxide was not available as an artist pigment until after 1941, long after Lindauer ceased painting between 1918-1920.[3]

Probing photodegradation in real time

Raman and FTIR can provide invaluable information about the products of degradation. Time-resolved spectroscopy informs about the mechanism and time-scale of that destruction. Photoexcitation of a molecule with ultraviolet or visible light – important components of natural and commercial lighting – places it into an excited state. Considerable energy has been put into the molecule, and it must go somewhere. For art pigments, this is a particular concern – their very vibrancy derives from strong interactions with light through this excitation process. However, that same interaction leads to their destruction. A photoexcited molecule can undergo bond-breaking, bond-forming, conformational changes, electron or proton transfer, or other sorts of degradation processes. The longer the excitation energy stays in the molecule or material, the more likely the system is to head down a path to irreversible photodestruction. Studying the first picoseconds (10^{-12} seconds) of a pigment's response to photoexcitation can thus tell us about its degradation on the 500-year timescale. We have used this approach to probe the anthroquinone chromophores in the Red Lake pigments, and demonstrated a clear correlation between the rapid 10^{-12} – 10^{-9} second timescale de-activation of the excited pigment and its photostability in works of art.[13,14] The next step is to determine how the details of this very fast response to light can then be used to inform us how to light art so that we can enjoy it without contributing to its photodestruction.

Summary

The examples described here show the valuable contribution of Raman and infrared spectroscopies to conservation of art in New Zealand. Characterisation of the pigments and paint media of artworks has enabled conservators to be better informed about the objects in their care. Not only does it mean that they have more information about the approaches taken by local and international artists, but the information can contribute to ensuring that the works are cared for and treated appropriately. The application of time-resolved methods can give us real-time insight into the methods we can use to prevent photodegradation. The breadth of information that can be revealed by these non-invasive and rapid techniques lend themselves to wider application in New Zealand's cultural heritage.

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Sharing and caring about intellectual property – preserving your IP rights in collaborations

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In the 18th Century painting by Joseph Wright of Derby, *The Alchemist Discovering Phosphorus* (see image) an alchemist kneels in front of a flask exuding a brilliant white luminescence, his eyes raised upwards to the heavens as he contemplates his discovery with religious reverence. Two apprentices work in the background (apparently extracting lead), but the sight of the discovery is obscured from their view by a heavy shroud.

If this was the first discovery of phosphorus or a method of obtaining it (its discovery is attributed to Hennig Brand in 1669), even a 21st Century scientist – or patent attorney – would be impressed to see that confidentiality was front of mind for this awe-struck alchemist. Even in the thrill of a technical breakthrough, this alchemist had one eye on the preservation of his intellectual property rights.

The popular imagining of a lone scientist conducting experiments in solitude bears little similarity to the real world today. Collaborations between research groups are incredibly common. Research and development is costly, so taking advantage of the experience of other teams can be more efficient than going it alone. Collaborations also enhance relationships between organisations, allow the customisation of a project team so that the researchers' skills match the subject matter, and enable the sharing of knowledge to everyone's mutual advantage. Collaborations also open avenues of funding that may not otherwise be available.

Unfortunately, the intellectual property system in many countries (including New Zealand) is a natural enemy to collaborations because sharing information can imperil future patent protection and the ability to rely on the law of confidence. Measures need to be put in place before

The Alchymist, In Search of the Philosopher's Stone, Discovers Phosphorus, and prays for the successful Conclusion of his operation, as was the custom of the Ancient Chymical Astrologers by Joseph Wright of Derby. Source: https://commons.wikimedia.org/wiki/Joseph_Wright_of_Derby#/media/File:Joseph_Wright_of_Derby_The_Alchemist.jpg an R&D relationship begins to neutralise these risks and protect future IP rights.

A research collaboration should be governed by a written agreement executed at the very beginning. The agreement should set out the terms by which the collaboration will operate, including a description of objectives, milestones and exit-points for each party. Important aspects of IP that should be covered include confidentiality, what happens to existing IP which is disclosed between the parties and what happens to IP that is developed during the project.

Confidentiality

Novelty of subject matter lies at the heart of patentability. For something to be patentable, it must be new in light of anything that is known or used before the date on which the patent application is filed. Novelty can be destroyed by publications, prior uses, offers for sale, and even by discussions with a small group of people. A collaboration agreement should prevent disclosure of information to the public by requiring discussions between teams, and the results of the collaboration, to be kept confidential. This assists in protecting team-to-team correspondence from being considered by courts or patent offices to be publicly disclosed, and thus preserves the patentability of the subject matter. The agreement may also include an embargo period for publishing project details (e.g. in theses or journal articles) to allow patent applications to be filed.

Existing IP

Each party will be bringing their own knowledge and skills from their organisations to a collaboration. Some knowledge may be sensitive and/or proprietary, so how this is treated in a collaboration needs to be addressed (for example, it may be prudent to specifically identify the applicable IP as falling within the scope of the confidentiality provision). Parties need to appreciate how much of their existing IP is flowing into the project, and to consider whether it is a concern that collaborators are gaining more than just the results of the project. A standard term in agreements is that the parties retain all rights in relation to the IP they brought to the table. There may be a need to grant the other parties continued rights to use some or all of a party's existing IP following termination of the collaboration (and this may include payment of an ongoing royalty or other compensation). However, this will usually depend on the extent to which the existing IP is either embedded within, or required to enjoy the benefit of, the results of the project.

New IP

The collaboration agreement should set out how new IP that is developed during the collaboration will be owned or controlled. It should describe which parties reap which benefits of the project, who has the option to take the research further by using results which were jointly discovered, and who has the rights to commercialise the IP.

There are several models. The default position (in the absence of an agreement) in New Zealand is that new IP is jointly owned by the collaborators. Unfortunately, this position is legally complicated, as the rules on what a co-owner can do without consent from other co-owners varies from country to country. If joint ownership is desired, it is often advisable to vest the IP in a company, and divide the company shares amongst the collaborators such that joint ownership is achieved.

An alternative but common model is where one party will wholly own the new IP, and the other parties will retain a licence to the IP. The extent of the licence will depend on the commercial strategies of each collaborator. In a research collaboration between a university and a private company, in which the company provides the majority of funding and the research is mainly carried out by university researchers, it may be acceptable for the IP resulting from the project to be owned by the company (who will have the rights to file patent applications), with a perpetual royalty-free licence to the university to be used for teaching and academic purposes. Such an agreement allows, for example, the publication of theses or journal articles (after, say, a twelve-month embargo period) and for further research to be carried out by the university, whilst still providing the commercial incentives for the private company to invest in the research.

Compared to collaborations, things are relatively simple for sole inventors. All the alchemist had to do to protect his IP was either to keep the information as a trade secret or file for a patent (admittedly, a bit of a gamble in the 1600s). There would be no complications as to the identity of the inventor or owner. Collaborations increase complexity from an IP point of view, but risks can be easily managed if arrangements are put in place at the beginning.

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Are antitumor polysaccharides more effective when digested? A theoretical study

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Keywords: *mushroom polysaccharides, metabolic enzymes, digestion, lead-like chemical space, drug-like chemical space, Known Drug Space (KDS), molecular descriptors, drug discovery*

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Dr Reynisson FRSC began his academic career at the University of Iceland where he read chemistry (BSc/MSc). His PhD was obtained from the University of Copenhagen in 2000; the research work was carried out at the Risø national laboratory. He spent two years in Germany as a postdoc at the Max-Planck-Institut für Strahlenchemie. He worked for five years at the Institute of Cancer Research in London as a molecular modeller/computational chemist developing anticancer drug candidates. Before he left the UK he was a lecturer in chemistry at the Nottingham Trent University. He has spent six months at Worcester Polytechnic Institute (MA, USA), Georgia Institute of Technology (GA, USA) and the University of Leipzig (Germany). He is currently a senior lecturer in computational chemistry and molecular modelling at the School of Chemical Sciences, University of Auckland.

Dr Lu Ren was born in Guizhou Province, China. He received his PhD degree from the University of Auckland in 2014, specialising in anticancer properties of mushroom polysaccharides. From 2015 to 2017, he was a postdoctoral researcher in the Department of Physiology at the University of Louisville, School of Medicine (KY, USA). His work involved macrophage mediated inflammation in hypertension, epigenetic regulation and mitochondrial damage in aged kidneys, effects of exercise in diabetes, and fibronectin signaling of mesangial cells. He is currently a postdoctoral researcher in the Department of Pathology and Laboratory Medicine at Indiana University School of Medicine (IN, USA). His studies focus on the function of epidermal PPARγ in skin cancer anti-tumour immune responses and the role of skin senescence cells in UVB-induced premalignant filed formation and tumourigenesis.

Yacine Hemar has a background in physics and fluid mechanics and obtained a PhD from the University of Strasbourg in France. He is an Associate Professor in Food Science at the School of Chemical Sciences, University of Auckland, and an Associate Investigator at the Riddet Institute. His research deals with the physical and chemical properties of polysaccharides and proteins in solution, emulsions or gels states, with an emphasis on their structure-function relationship as probed by rheology and scattering (light, neuron and x-ray) techniques. He has published more than 140 refereed papers in international journals. He is currently a member of the editorial boards of *Food hydrocolloids*, *bioactive carbohydrates and dietary fibre*, and *Starch/Staerke*.

Abstract

The effect of human digestion on the physicochemical parameters of fungal anticancer polysaccharides was investigated. 58 sugars were used and 18 (31%) of those can be theoretically cleaved by human digestive enzymes. The resulting fragments from the digestive reaction are obviously smaller than their parent polysaccharides resulting in a 47 – 56% shift towards smaller values for the whole collection for mainstream molecular descriptors. Since these polysaccharides originate from edible mushrooms this reduction is size can shed light on their mode of action.

Introduction

Many polysaccharides have been isolated from mushrooms, fungi, yeasts, algae, lichens and plants, and their biological activities have attracted considerable attention due to their medicinal properties.[1] The therapeutic effects of mushroom polysaccharide extracts are found for various indications, such as anticancer, antibacterial, antiviral, and antifungal. [2] Compared with many antitumor drugs, the polysaccharides derived from mushrooms are non-toxic and these mushrooms have been consumed since antiquity for their beneficial effects.[3] These medicinal properties have led to the marketing of fungal polysaccharides as anticancer pharmaceutical agents in Japan, e.g., lentinan from *Lentinus edodes*, schizophyllan from *Schizophyllum commune* and krestin from *Coriolus versicolor*, especially for stomach, prostate and lung cancers.[4, 5]

As examples of antitumor polysaccharides from mushrooms, lentinan extracted from *Lentinus edodes* has a backbone of (1-3)-β-glucan containing five (1-3)-β-glucose residues in a linear linkage and two (1-6)-β-glucopyranoside branches in side chains (Fig. 1A). Schizophyllan derived from *Schizophyllum commune* is also a (1-3)-β-glucan containing a β-glucopyranoside unit joined by a β-(1-6) linkage to every third or fourth residue of the backbone (Fig. 1B).

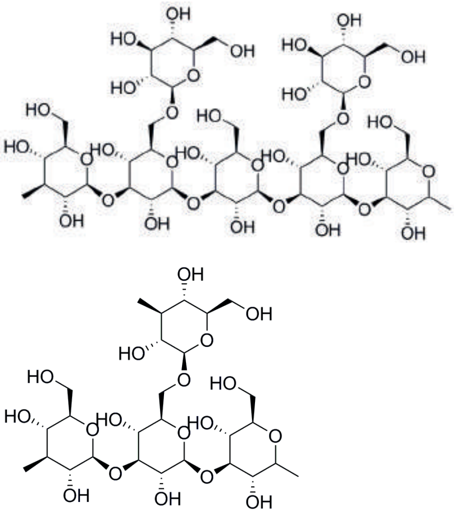

Fig. 1. Structure of repeating units of polysaccharides showing antitumor activity: (Top) lentinan from *Lentinus edodes* and (Bottom) schizophyllan from *Schizophyllum commune*

Currently, calculating physicochemical parameters of drug candidates using molecular descriptors are used to predict their Absorption, Distribution, Metabolism, Excretion and Toxicity profiles (ADMET).[6] The Lipinski's rule of five is the most widely used to define drug-like chemical space, which indicates oral absorption of the complying compounds.[7, 8] Also the concepts of lead-like[9] chemical space and known drug space (KDS)[10] are used to define useful regions of chemical space. These parameters are given in Table 1.

Recently, a host of fungal polysaccharides with reported anticancer properties were investigated for their physicochemical properties as calculated with commonly used molecular descriptors.[11] It was found that a unique region of chemical space is occupied by the polysaccharides (MW: $1.0 \times 10^5 – 2.5 \times 10^5$ g mol^{-1}; Log P: $-3.0 \times 10^3 – -1.0 \times 10^3$; HD: $1.0 \times 10^3 – 5.0 \times 10^3$; HA: $5.0 \times 10^3 – 1.0 \times 10^4$; PSA: $5.0 \times 10^4 – 1.0 \times 10^5$ and RB: $5.0 \times 10^3 – 1.0 \times 10^4$). Unsurprisingly, the parameters found were much larger than those of small molecules since the polysaccharides are macromolecules. The mechanism of action is still not clear for the sugars. Therefore, having the statistical distribution of the physicochemical parameters helps in elucidating their biological effect.

The source of the fungal sugars is often from edible species of mushrooms and their effect has been discovered through the means of ethnopharmaceutical investigations where certain populations are less prone to develop cancer.[12] This means that the anticancer efficacy of the sugars is either rendered in the digestive tract or the sugars are absorbed into the blood stream. The question therefore emerges whether digestive enzymes can cleave the fungal polysaccharides under investigation. The structures of the sugars are known as is the specificity of the human digestive enzymes. This will allow us to predict the impact of the human digestion enzymes on the physicochemical parameters of the sugars, which constitutes the main aim of the present paper. To the best of our knowledge, this is the first study on the effect of theoretical digestion on anticancer polysaccharides based on their physicochemical properties.

Methodology

Statistical analysis of the sugars was carried out based on the six molecular descriptors shown in Table 1. A total of 58 polysaccharides exhibiting antitumor ability were selected from Ren *et al*.[11] Forty polysaccharides were from mushrooms and eighteen were from other natural sources. Enzymes involved in digestion of carbohydrates in the human digestive system were found in the literature.[13-14] Fragments were obtained by a complete theoretical reaction between the enzymes and polysaccharides. The fragment structures were drawn in ChemBioDraw Office 12.0[15] and were optimised using the MM2[16] force field with Scigress (Project Leader).[17] The QikProp 3.2 software package[18] was used for calculating the molecular descriptors. The reliability of QikProp is established for the molecular descriptors used in this study.[19]

Results and discussion

Absorption of polysaccharides in human digestive system and enzymes involved in sugar digestion

In the digestive tract, dietary polysaccharides and disaccharides are converted to monosacharaides by glycosidase enzymes that hydrolyse the glycosidic bonds

Table 1. Criteria of lead-like, drug-like and known drug space (KDS) in terms of molecular descriptors

	Lead-like Space	**Drug-like Space**	**Known Drug Space**
Molecular weight (MW, g mol^{-1})	300	500	800
Lipophilicity (Log P)	3	5	6.5
Hydrogen bond donors (HD)	3	5	7
Hydrogen bond acceptors (HA)	3	10	15
Polar surface area (PSA, $Å^2$)	60	140	180
Rotatable bonds (RB)	3	10	17

between the sugars. The catabolism of oligo- and polysaccharides also involves glycosyltransferases. During the process, glycosidases transfer a glycosyl group to a water molecule, while glycosyltransferases transfer this group to a different acceptor.[20] All of these enzymes exhibit some specificity for the sugar, i.e., the glycosidic bond (α or β), and the number of saccharide units in the chain. The monosaccharides formed by glycosidases are transported across the intestinal mucosal cells by active transport into the interstitial fluid and subsequently enter the bloodstream. Undigested carbohydrates enter the colon, where they can be digested by bacteria. Enzymes involved in sugar digestions in the human digestive tract mainly include salivary and pancreatic α-amylase, α-glucamylase, sucrase-isomaltase, β-glycosidase and trehalase. The catalytic sites and principal activities of these enzymes are summarised in Table 2.[13-14]

Ren *et al*.[11] investigated and summarised the structural attributes of antitumor polysaccharides. It was found that seven monosaccharide residues including α-D-Glc*p*, β-D-Glc*p*, α-D-Gal*p*, β-D-Gal*p*, α -Man*p*, β-Man*p*and α-L-Fuc*p* are the building blocks for the backbone of the fungal polysaccharides and those components are connected by four types of linkages, namely 1→2, 1→3, 1→4, and 1→6. In the current study, those polysaccharides under theoretical enzymes digestion were further investigated to determine the physicochemical properties of their derivative fragments.

Based on the enzyme activities and polysaccharide structures, there are two enzymes in the human digestive system that are capable of cleaving the fungal polysaccharides. Theoretically, digestion of the anticancer polysaccharides can affect the structure of 18 polysaccharides out of the 58 investigated.

The theoretical fragments produced, their parental digestible polysaccharides and their original species are listed in Table 3. Interestingly, three identical fragments can be produced by several different parental polysaccharides as marked in the similarity column. To study the characteristics of fragments in chemical space, the fragments with the same structures from different polysaccharides were grouped as one type and only different fragments were used to calculate chemical descriptors. Thirteen polysaccharides have the α-1,4-D-Glup units, which can be theoretically cleaved by α-amylase. These polysaccharides are SEP from *Strongylocentrotus nudus*; glucan from *Calocybe indica*; APS-1d from *Angelica sinensis*; PS1A1 from *Mycobacterium bovis*; AAFRC from *Auricularia polytricha*; ASLP from *Arca subcrenata Lischke*; AIPS from *Cordyceps sinensis*; HPS-1 from *Hedysarum polybotrys*; WIPS from *C. sinensis*; HPS-1B23 from *Dendrobium huoshanense*; Yhps-1 from *Cordalis yanhusuo*; APS from *Astagalus membranaceus*; and PS from hybrid mushroom of *Pleurotus florida* and *Calocybe indica*. Theoretically, complete reaction between the enzyme α-amylase and the thirteen polysaccharides produced nine different fragments, which included monosaccharide, disaccharide, and oligosaccharide fragments. By contrast, another five polysaccharides with β-glycosidic linkages between glucose and galactose can react with glucosyl-ceramidase. Complete reaction between these polysaccharides and the enzyme produced nine different fragments. These five polysaccharides are POPS-1 from *Pleurotus ostreatus*; PS from the hybrid mushroom of *Pleurotus florida* and *Calocybe indica*; PS from *Lentinus squarrosulus*; PS-I from the hybrid mushroom of *Pleurotus florida* and *Lentinus squarrosulus*; GFPS1b from *Grifola frondosa*. The other enzymes found in the human digestive system (Table 2) are not predicted to cleave the polysaccharides under investigation due to active site incompatibility.

Molecular weight (MW)

Based on the three defined chemical spaces (Table 1), the frequency of occurrence of repeating units of the 18 digestible polysaccharides selected were assessed (Table

Table 2. The catalytic sites and principal activities of sugar enzymes in the human digestive tract

Complex	Catalytic sites	Principal Activities
α-Amylase	α-glucosyl units	Hydrolyse internal α-1,4 bonds between glucosyl residues at random intervals in polysaccharide chains
α -Glucamylase	α-Glucosidase	Split α-1,4 glycosidic bonds between glucosyl units, beginning sequentially with the residue at the tail end (non-reducing end) of the chain. Substrates include amylase, amylopectin, glycogen, maltose
	α-Glucosidase	Same as above but with slightly different specificity and affinities for substrates
Sucrase-isomaltase	Sucrase-maltase Isomaltase-maltase	Splits sucrose, maltose and maltotriose Splits α-1,6 bonds in a number of limited dextrins and the α-1,4 bonds in maltose and maltotriose
β-Glycosidase	Glucosyl-ceramidase	Splits β-glycosidic bonds between glucose or galactose and hydrophobic residues, such as the glycolipids glucosylceramide and galactosylceramide
	Lactase	Splits the β-1,4 bond between glucose and galactose. To a lesser extent also splits the β-1,4 bond between some cellulose disaccharides
Trehalase	Trehalase	Splits bond in trehalose, which is 2 glucosyl units linked α-1,1 through anomeric carbons

3). Using the above criteria, none of the repeating units of the polysaccharides are in the lead-like space, while one (5.6%) of these repeating units is in the drug-like space, and two (11.2%) of them are in the Known Drug Space. After the hypothetical digestion of the polysaccharides, 18 new fragments were generated. One (5.6%) of the digested fragments is in lead-like space, four (22.2%) of them are in drug-like space, and twelve (66.7%) in the Known Drug Space. Overall, 12 (66.7%) of these fragments fall into the three defined chemical spaces, while only 11.2% of the repeating units of the digestible polysaccharides are in the range of the three chemical spaces based on their molecular weight. The MW distribution is shown in Fig. 2.

Table 3. The predicted physicochemical properties of the sugar fragments formed by theoretical digestion as calculated using molecular descriptors

Source	Original species	Digestible polysaccharide	Theoretical fragment	WM (g/mol)	Log P	HD	HA	RB	PSA (Å²)	Similarity[a]
Fungus	*Auricularia polytricha*	AAFRC	**F1**-AAFRC	664.6	-6.2	13	34	23	287.7	
	Cordyceps sinensis	AIPS	**F1**-AIPS	180.2	-2.2	5	10	6	114.8	b
	Grifola frondosa	GFPS1b	**F1**-GFPS1b	796.7	-7.5	15	41	27	336.3	
			F2-GFPS1b	342.3	-3.3	8	19	12	165.7	
			F3-GFPS1b	*958.9*	-8.9	18	49	33	367.7	
	Calocybe indica	Glucan	**F1**-Glucan	664.6	-6.8	13	34	23	301.7	
	Pleurotus ostreatus	POPS-1	**F1**-POPS-1	1473.3	-16.6	27	75	52	639.4	
			F2-POPS-1	342.3	-3.6	8	19	12	176.2	
	Calocybe indica	PS	**F1**-PS-*CI*	824.8	-7.7	15	41	28	338.2	
	Hybrid of *Pleurotus florida* & *Calocybe indica*	PS	**F1**-PS-*PFCI*	824.8	-7.8	15	41	28	358	c
	Lentinus squarrosulus	PS	**F1**-PS-*LS*	664.6	-6.8	13	34	23	312.9	
			F2-PS-*LS*	502.5	-4.6	10	26	17	227.4	
	Hybrid of *Pleurotus florida* & *Lentinus squarrosulus*	PS-I	**F1**-PS-I	500.5	-3.6	9	24	16	222.8	
	Cordyceps sinensis	WIPS	**F1**-WIPS	342.3	-3.6	8	19	12	189	a
			F2-WIPS	180.2	-2.2	5	10	6	114.8	b
Non-fungus	*Astragalus membranaceus*	APS	**F1**-APS	342.3	-3.6	8	19	12	189	a
			F2-APS	180.2	-2.2	5	10	6	114.8	b
	Angelica sinensis	APS-1d	**F1**-APS-1d	960.8	-10.4	19	51	34	429.6	
	Arca subcrenata Lischke	ASLP	**F1**-ASLP	666.6	-7	14	36	24	315.6	
	Hedysarum polybotrys	HPS-1	**F1**-HPS-1	342.3	-3.6	8	19	12	189	a
			F2-HPS-1	180.2	-2.2	5	10	6	114.8	b
	Dendrobium huoshanense	HPS-1B23	**F1**-HPS-1b23	1679.5	-17.5	30	85	59	668.5	
	Mycobacterium bovis	PS1A1	**F1**-PS1A1	342.3	-3.6	8	19	12	189	a
			F2-PS1A1	824.8	-7.8	15	41	28	358	c
	Strongylocentrotus nudus	SEP	**F1**-SEP	342.3	-3.6	8	19	12	189	a
			F2-SEP	180.2	-2.2	5	10	6	114.8	b
	Cordalis yanhusuo	YhPS-1	**F1**-YhPS-1	502.5	-4.3	10	26	17	216.9	
		Mean (all)		585.4	-5.9	11.7	30.4	20.2	268.2	
		Standard deviation (all)		380.5	4.0	6.4	18.9	13.4	144.1	
		Mean (fungi)		617.5	-6.1	12.1	31.7	21.2	276.8	
		Standard deviation (fungi)		339.1	3.6	5.7	16.8	11.9	131.9	
		Mean (non-fungi)		545.3	-5.7	11.3	28.8	19.0	257.4	
		Standard deviation (non-fungi)		438.8	4.5	7.4	22.0	15.5	163.4	

[a] The same letters in the *Similarity* column represent the same structures of the fragments from theoretical digestion

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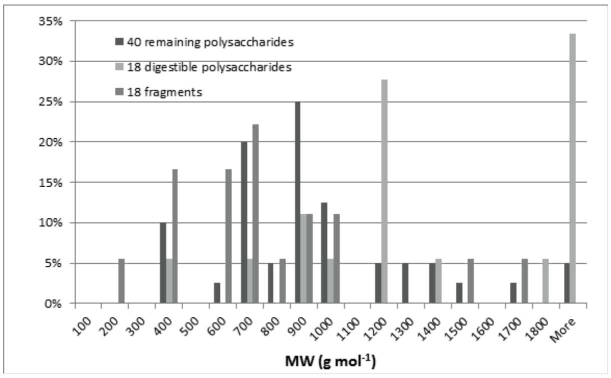

Fig. 2. Distribution of MW of 40 indigestible polysaccharides repeating units, 18 digestible polysaccharides and their 18 derivatives

Lipophilicity (Log P)

Log P is often regarded as the most important molecular descriptor related to toxicity issues and failure in clinical trials.[21, 22] The Log P values for all the polysaccharides are less than -1, suggesting that they are quite hydrophilic and therefore they are in lead-like space (Table 3 and Fig. 3).[23] The Log P values of the 18 digestible polysaccharides are located in a broad range from -50 to 0. However, after digestion, the values of the18 fragments obtained are in a reduced range from -20 to 0.

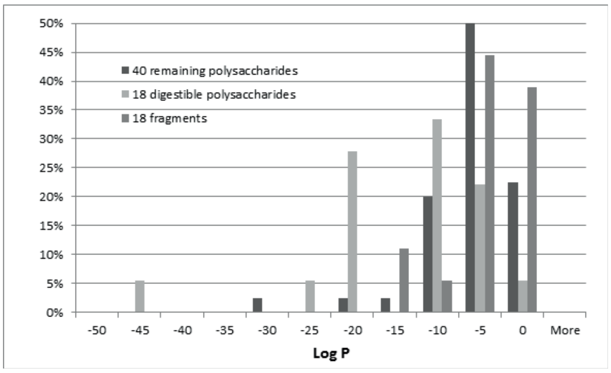

Fig. 3. Distribution of Log P of the 40 indigestible polysaccharides repeating units, 18 digestible polysaccharides and their 18 derivatives

Hydrogen bond donors (HD) and acceptors (HA)

According to the definition given in Table 1, no fragments are included in the lead-like space and with only one (5.6%) in both drug-like space and Known Drug Space for hydrogen bond donors. By applying the criteria of hydrogen bond acceptors, again only one of the fragments falls into the Known Drug Space. The incompatibility of the carbohydrates with the defined chemical spaces for hydrogen bond donors and hydrogen bond acceptors can be easily understood by the nature of sugars with their numerous hydroxyl groups. The imitative digestion makes the values of both hydrogen bond donors and acceptors shift to the field of low values. In particular, the values of hydrogen bond donors of fragments concentrate in area from 5 to 15, while their values of hydrogen bond acceptors are dominantly found between 10 and 50. The statistical distributions are given in Figs. 4 and 5.

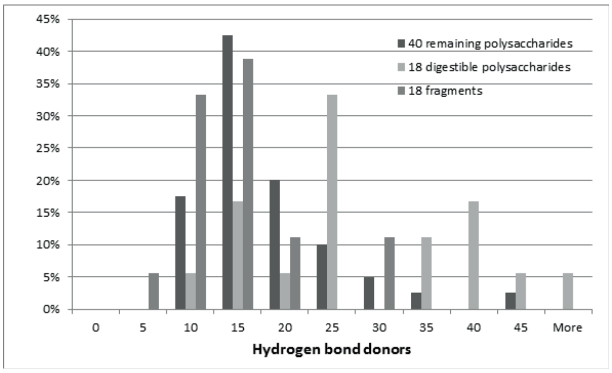

Fig. 4. Distribution of hydrogen bond donors (HD) of the 40 indigestible polysaccharides repeating units, 18 digestible polysaccharides and their 18 derivatives

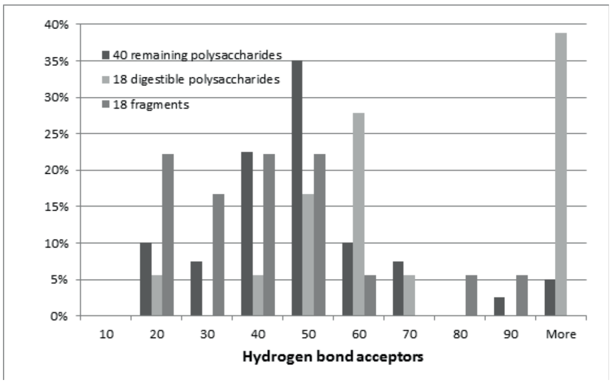

Fig. 5. Distribution of hydrogen bond acceptors (HA) of the 40 indigestible polysaccharides repeating units, 18 digestible polysaccharides and their 18 derivatives

Rotatable bonds (RB)

Based on the boundaries of RB in chemical space (Table 1), all are too big for lead-like space as shown in Fig. 6. One fragment is in drug-like chemical space and seven (38.9%) are in Known Drug Space. The values of rotatable bonds of 18 digestion derivatives fall into a much smaller region, mainly ranging from 0 to 60, compared with those of their original 18 polysaccharides.

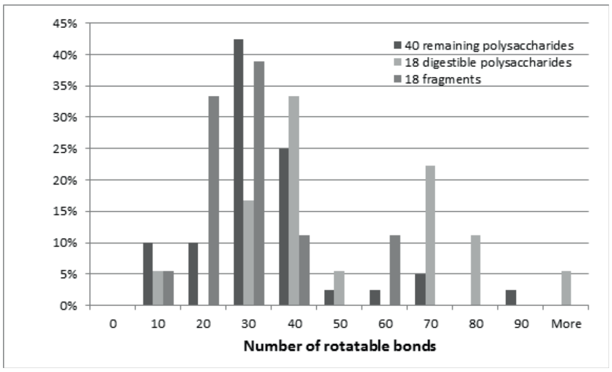

Fig. 6. Distribution of RB of the 40 indigestible polysaccharides repeating units, 18 digestible polysaccharides and their 18 derivatives

Polar surface area (PSA)

The distribution of PSA is given in Fig. 7. One fragment (5.6%) is in drug-like space and three fragments (16.7%) are in Known Drug Space but none exist in lead-like space. Again the plethora of hydroxyl moieties leads to relative incompatibility with the criteria given in Table 1. The 18 digestible polysaccharides and the remaining indigestible polysaccharides span the same range. Nonetheless, the fragments produced by digestion are in a smaller region, predominantly in the 100 - 400 Å^2 range.

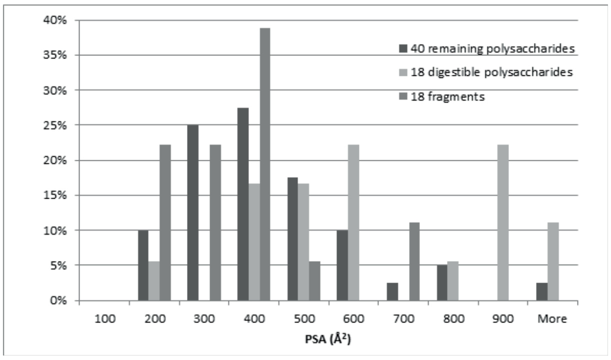

Fig. 7. Distribution of polar surface area (PSA) of the 40 indigestible polysaccharides repeating units, 18 digestible polysaccharides and their 18 derivatives

Effect of digestion

The mean for the 18 polysaccharides was compared to the mean generated after digestion for the six molecular descriptors and the results are shown in Table 4. All the molecular descriptor values of polysaccharide repeating units were shifted to lower values after hypothetical digestion and were in the range 47.5 – 56.4%.

The *in vitro* studies are usually carried out by dosing fungal polysaccharide solutions to cultured human cancer cells, such as human cervix carcinoma HeLa cells and human lung carcinoma A549 cells. This means that the effect of digestion is not captured by the experiments *in vitro*. However, the *in vivo* studies are mostly performed by implanting tumour cells into mice followed by administration of fungal polysaccharides solution intraperitoneally.[24] In fact, the effect of oral administration on the anticancer activity of mushroom polysaccharides has not been extensively studied. Only a few studies reported the anticancer properties of polysaccharides under the principle of oral digestion. For instance, polysaccharides isolated from the mushroom *Lentinus edodes*, such as LEM[25] and KS-2,[26] exhibited antitumor effects after oral administration. Nonetheless, the relevant mechanisms still remain unclear.

The different types of primary structures of polysaccharides that lead to secondary and tertiary structures provide differing types of properties, such as water solubility, aggregation, viscosity, gellation, digestibility, and biological recognition. In particular, biological recognition is found to be involved in infection and immunity, cell-cell interaction and receptor binding and response.[27] Multicellular organisms possess receptors called pattern recognition receptors (PRRs) which are able to detect innately foreign structures such as pathogen-associated molecular patterns (PAMPs). Some polysaccharides that are not synthesised by humans are considered as PAMPs, which can be recognised by appropriate cell surface receptors to stimulate an immune response.[28] Those polysaccharides are known to induce an immune response by directly activating B-lymphocytes.[29] In the current study, enzymatic digestion affects the structures and physicochemical properties of 18 digestible anticancer polysaccharides. The mean molecular weight of the 18 digestible polysaccharides is 385461.1 ± 570940.2 g mol^{-1}, which is about 538 times that of the 18 fragments investigated (716.2 ± 383.9 g mol^{-1}). However, the effect of the reduction in molecular weight after digestion on their anticancer ability is hard to elucidate since several mechanisms, such as apoptosis, cell cycle arrest, necrosis and anti-angiogenesis could be involved. Under those different anticancer working principles, some polysaccharides with either high or low molecular weight could both have opportunities to show anticancer ability.[11] Hypothetically, the resulting fragments produced could be recognised by those receptors to inhibit the proliferation of cancer cells or trigger the death of cancer cells by other anticancer mechanisms, which might also occur simultaneously. The modelling results confirmed that the fragments from digestion possessed more physicochemical similarity to the sugar based drugs[11] than the repeating units of digestible polysaccharides. Theoretically, the predicted fragments might offer a promising opportunity to study the interactions between the cell surface receptors and polysaccharides with relatively low molecular weight, which are possibly easier and more practical to clarify the proposed antitumor mechanisms.

Comparatively, the 40 indigestible polysaccharides collected from the literature also demonstrated potent anticancer activities based on the working principles mentioned above. Furthermore, their antineoplastic function can also be compared to those reported for dietary fibres (DFs). Firstly, it has been suggested that increasing DFs in the diet leads to an increase in faecal weight and a decrease in transit time which decreases the probability of carcinogen interaction with the colonic mucosa.[30] Secondly, it has been suggested that DFs are able to absorb carcinogens.[31-32] Thirdly, DF can be fermented by bacteria to produce short chain fatty acids (SCFA) in the colon. The concomitant decrease in faecal pH may reduce solubility

Table 4. The values of the six molecular descriptors for the repeating units of the 18 digestible polysaccharides before and after digestion

Descriptors	Mean before	Mean after	SD before	SD after	Change of mean after digestion
MW (g mol^{-1})	1452.7	716.2	754.6	383.9	-50.7%
Log P	-16.4	-7.1	10.3	4.2	-56.4%
HA	73.6	36.8	39.5	19.3	-50.1%
HD	26.4	13.9	13.8	6.5	-47.5%
PSA (Å^2)	618.3	314.0	289.8	148.2	-49.1%
RB	51.0	24.8	27.7	13.6	-51.4%

of faecal bile acids and affect their conversion to secondary forms that are the most effective tumour promoters and inhibit bacterial degradation of faecal constituents to potential carcinogens.[33, 34] These hypotheses probably do not apply to fungal polysaccharides since they are found in minute amounts in their original sources.

Most of the 58 fungal polysaccharides displayed anticancer activities in *in vitro* studies which suggests that they possess more structural and physicochemical properties showing anticancer ability than DFs. Furthermore, the indigestible polysaccharides could be tentatively classified into a different group compared to those capable of producing fragments by enzymatic digestion. Those indigestible polysaccharides and the enzyme-derived fragments might have different paths to exhibit anticancer activities based on distinct mechanisms since the former have higher molecular weight and conformational properties such as branches and helix structures. Hence, in order to reveal those mechanisms, further studies need to be carried out to understand the relationship between biochemical interactions and their physicochemical properties.

Conclusions

It was found that 18 out of the 58 (31%) fungal polysaccharides in this study are susceptible to human digestive enzymes. 18 hypothetical fragments were produced with considerably smaller physicochemical parameters than their parent structures. The digestive processes led to ~50% size reduction of MW, Log P, HA, HB, PSA and RB for the total collection. The previous *in vitro* and *in vivo* experimental setups designed to gauge anticancer properties of the fungal polysaccharides did not include any digestive effect. This is of interest since these sugars are often discovered by researching beneficial effects of edible fungi, i.e., the polysaccharides are consumed and have their effect *via* the digestion tract. The predicted fragments present an interesting research topic to further elucidate their mechanism of action.

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Characterisation and control of water drops on structured hydrophobic surfaces

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Abstract

This article reviews and demonstrates recent research into wetting of structured hydrophobic surfaces. Here, ‘structured’ refers to features smaller than a typical water drop: sub-millimetric, microscopic, and nanoscale. Characterisation of wetting properties, including superhydrophobicity, is important for such surfaces, and drop impact has emerged as a near-standardised testing method for dynamic wetting. Wetting can be strongly influenced by designed structural elements with length scales comparable to a drop. Examples include ridges, fields of micropillar arrays, and surfaces designed to capture condensation. Fabrication of structured hydrophobic surfaces, especially superhydrophobics, is of broad interest for applications involving passive control of water drops.

Introduction

Superhydrophobic surfaces (SHSs), which are extremely water-repellent, hold intrigue due to the high mobility of water drops upon them. Drops ‘bead up’ to form very high contact angles, will readily roll off a SHS at a small angular incline, and can even bounce cleanly from the surface (Fig. 1a). The study of SHSs is largely biomimetic,[1] and superhydrophobicity is also known as the *lotus effect*, named for the self-cleaning leaves of the lotus (*Nelumbo nucifera*).[2,3] Another commonly-cited natural example is a dew-harvesting beetle of the Namib Desert (*Physosterna cribripes*).[4,5] Interest in such SHSs has increased over the past two decades, driven by prospective applications, improvements in high-speed photography, and the increasing sophistication of fabrication and characterisation techniques.

In terms of applications, the promise of SHSs (and similar surfaces) for harvesting of atmospheric water is increasingly being recognised.[4] SHSs are also well-known for their potential to reduce or prevent adhesion of ice, particularly on aeroplanes. Among several investigations into the design and performance of ice-repellent surfaces,[6] there have also been less optimistic views regarding their potential in this area.[7] Among many other applications, SHSs could be useful for self-cleaning surfaces,[8] drag reduction,[9] anti-fouling in marine environments,[10] and green engineering and energy applications.[11,12]

Water drops on SHSs adopt the Cassie state (Fig. 1b), so that much of the drop’s underside is actually in contact with air. For this state to be stable (or metastable), the surface must have properties of (i) chemical hydrophobicity, and (ii) microstructural roughness or texture.[2] For example, leaves such as the lotus form SHSs from epicuticular wax nodules (Fig. 1c), which show evidence of hierarchical structure – that is, features are observed over a range of length scales. High water repellence can be achieved through any number of material combinations, and an enormous range of surfaces which are superhydrophobic (or nearly so) have been reported, with a matching breadth of fabrication methods. Numerous reviews are available,[1,12-14] including those which focus on the characteristic phenomena and physics of SHSs,[2,15] fabrication methods,[13,16] electrospun[17] and polymer-based SHSs,[18] and durability,[19] for example.

Many fabrication techniques can produce structured hydrophobic surfaces that achieve very high standards of water repellence, if not always superhydrophobicity. In the next section of this article, characterisation of the performance of such surfaces is discussed, and the importance of dynamic wetting experiments such as drop impact is introduced. In recent times, control over *imperfect* hydrophobicity has become of interest. For example, the size of surface structural elements can become comparable to the length scale of a liquid drop, influencing wettability. This idea is reviewed and demonstrated later

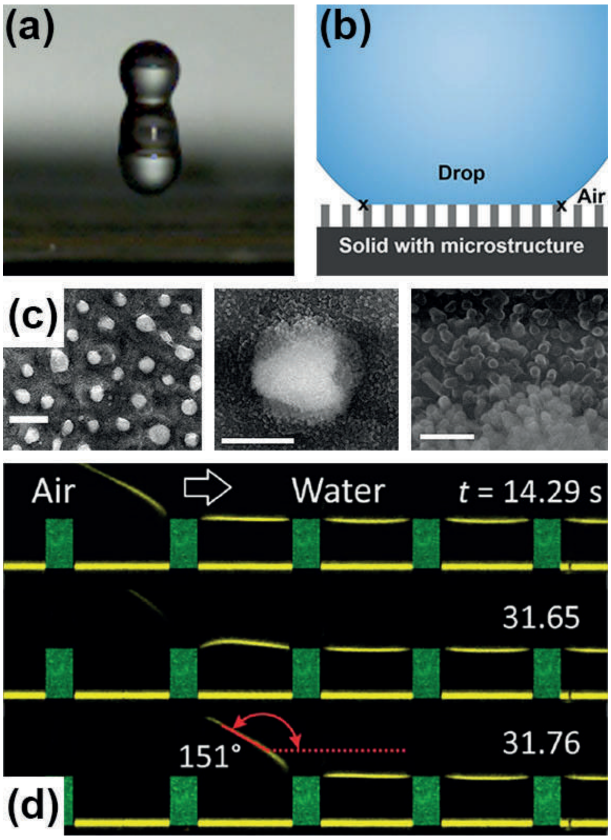

Fig. 1. (a) Still image from a high-speed video showing a water drop bouncing following impact on a thiolated Cu/Ag SHS. (b) Schematic of the Cassie state, in which the contact line between solid, liquid drop, and air is pinned atop microstructural elements (at the crosses). (c) Scanning electron microscopy of a lotus leaf. Scale bars (left to right) are 20 μm, 5 μm, and 1 μm. (d) Laser scanning confocal microscopy time series showing the receding contact line for a water drop moving over a micropillar array (post diameter 10 μm, height 16 μm). Adapted with permission from Ref. 25. Copyrighted by the American Physical Society.

in this article, with reference to ridges, micropillar arrays, and condensation applications. The concluding section discusses the potential for specialisation of structured hydrophobic surfaces in particular applications.

Characterising structured hydrophobic surfaces

Contact angles and superhydrophobicity

Contact angles are measured as a drop is gently placed or slowly moves over a surface, so that the contact line is either advancing or receding during (or prior to) measurement. Typical definitions of superhydrophobicity found in the literature require a high advancing contact angle (> 150-160°), with low contact angle hysteresis (< 5-10°)[2,20-22] which is the difference between advancing and receding contact angles. These values are somewhat arbitrary, not least because of difficulties in obtaining consistent and reproducible measurements. The advancing rate of the three-phase line, gravity, and data acquisition and analysis can all affect the outcome of a contact angle measurement.[23] Regardless, the qualitative description of an SHS has been consistent: contact angles as high as 150° are only achieved for drops on a textured hydrophobic surface, and low hysteresis is necessary for the drop to bounce and roll on a SHS, rather than being pinned at a receding contact line.

For water drops on SHSs to achieve this high mobility, they must adopt the Cassie state (Fig. 1b), so that a large fraction of the macroscopic boundary between the drop and the surface is composed of a high energy water-air interface. The alternative (Wenzel) state, formed when the water wets the entire solid surface, can also increase the contact angle of an inherently hydrophobic surface.[24] However in the Wenzel state, drop dynamics are inconsistent with SHS definitions: the receding contact line is strongly pinned to posts, preventing rolling and bouncing, and producing high contact angle hysteresis. In the Cassie state, hysteresis is also determined by the degree to which the receding contact line is pinned. Recently, it has been proposed that the definition for SHSs should require only a large receding contact angle, suggesting that water drop mobility is the key qualitative feature of SHSs. This proposal was linked to a laser scanning confocal microscopy study which analysed the work required to break individual capillary bridges at the receding contact line (Fig. 1d).[25]

Dynamic wetting and drop impact

The advancing and receding angles observed in contact angle measurements are sometimes referred to as dynamic. However, in many applications drops impact, roll, and slide on surfaces, rather than being gently placed. Further characterisation of dynamic behaviour at high strain rates is therefore important. In particular, drop impact is emerging as a possible standard method for characterisation of dynamic wetting. Impact of liquid drops on to smooth liquid and solid surfaces has been studied for over a century, and is reasonably well understood.[26] However, most real solid surfaces are not ideally smooth, and research into impacts on rough and complex surfaces is ongoing.[21,27]

In a drop impact experiment, the drop size, velocity and angle of impact can be readily controlled and varied. Description of impact conditions is typically simplified by using the Weber and Reynolds numbers,

$$\mathrm{We} = \frac{\rho l v^2}{\gamma}, \text{ and } \quad \mathrm{Re} = \frac{\rho l v}{\eta},$$

where ρ, γ, and η are respectively the density, surface tension and viscosity of the drop, *l* is a length scale (both drop radius and diameter are used in the literature[28]), and *v* is a velocity scale (impact velocity). We and Re are dimensionless numbers representing the importance of inertial forces relative to surface tension and viscous forces (respectively) during drop impact.

With increasing accessibility of high-speed photography (HSP), a wide range of measurable quantities relating to drop impact has emerged, including the maximum spreading diameter,[21,27] or the contact time for bouncing.[29-31] A water drop landing on a SHS can bounce (i.e. rebound intact), and indeed one proposed definition of SHSs involves counting the number of drop bounces following impact.[32,33] Other measurements on structured surfaces can produce more complex, interesting results. These include the onset of splashing,[26,34-36] and thresholds for penetration of a superhydrophobic microstructure to produce the Wenzel state.[22,28,37-39] Controlled generation of asymmetric outcomes following drop impact has become a topic of particular interest, as explained in the next section.

Challenges for researchers wishing to execute standardied drop impact experiments often relate to the assumption that the impacting drop is spherical. If the drop diameter is smaller than the capillary number (~2.7 mm for water in air), gravity does not significantly affect the drop. However, it is near-impossible to avoid non-sphericity introduced by the drop pinching off (i.e. detaching) at its point of release, and air resistance. For some measurements, image analysis protocols should also be carefully considered.

Air, as the third phase in a typical liquid-solid drop impact experiment, has influence beyond shaping the drop in flight. At the moment of impact, the gas beneath an impacting drop is significantly compressed. Gas pressure influences splashing[34,40] and entrapped air explains the formation of small bubbles formed directly on the axis of impact within a spreading lamella.[27] Researchers are currently striving to clearly resolve and understand air flow under impacting drops, for example using interferometry to measure air layer thickness,[41] or in theoretical work.[42]

Thorough analysis of drop impacts is also linked to our developing understanding of fundamental aspects of wetting dynamics. For example, various models have been developed to describe dependence of the contact angle on the velocity of the three-phase contact line, driven by inertia.[43] Also, non-zero slip occurs when water flows over hydrophobic surfaces,[44] and structured SHSs generate greater effective slip.[45] Slip is of especial interest near moving contact lines, where classical theories predict a singularity if there is no slip.[46]

Water drop impact on structured hydrophobic surfaces

Surface fabrication

Drop impact outcomes on water-repellent surfaces can be passively controlled by patterning the surface microstructure. Here, we firstly introduce some of the most widely-used and interesting microstructural designs, along with their associated fabrication methods. For example, photolithography can be used to produce regular arrays of pillars[2,47] (Fig. 2) or ridges (Fig. 3a).[29,48] Silicon pillars can be rendered superhydrophobic by applying long-chain halogenated silanes[2] using either vapour[29] or solution[31] phase methods. Pillar arrays can also be produced in polymers via soft lithography, typically using polydimethylsiloxane (PDMS) cast from a hydrophobised silicon[28] or SU8[39] master (Fig. 2b). Soft lithography is somewhat easier to employ than silicon fabrication, but provides less spatial resolution, especially for pillars < 10 µm and with height:width aspect ratios greater than 1. Also, PDMS is not as strongly hydrophobic as surfaces coated with fluoropolymers or long-chain silanes.

For structural features at length scales closer to 100 µm, there is a greater variety of ways to easily and accurately fabricate samples. Examples include ridges that have been laser-ablated in silicon,[29] milled in aluminium oxide or Cu plate,[29] or produced using thin (25-250 µm radius) Ni wires stretched out over a polished Al surface.[30] ~1 mm ridges can simply be machined into polished Al,[49] while square lattices of posts with 1:8 aspect ratio have been produced in Cu plate using a wire-cutting method.[31] However, well-performed SHSs require additional, chemically hydrophobic structure on smaller scales. To achieve this, surfaces with large features are often etched to produce additional structure on scales < 10 µm prior to the application of silane. Strategies have included etching electropolished, anodised aluminium oxide in a mixture of chromic and phosphoric acids to produce a pitted microstructure,[29] or etching Cu with NaOH to produce spiky nanostructures[29] or flower-like structures on graduated posts.[31] An alternative way to produce superhydrophobicity on top of a larger-scale structure is to apply a commercial coating such as Ultra Ever Dry (UltraTech International), which generates SHSs using hydrophobic nanoparticles dispersed in a solvent (acetone) that evaporates following spray-on application.[30,49]

Ridges

Experiments have recently been reported in which drops bouncing from SHSs were in contact with the surface for record low times – shorter than a theoretical limit defined by a spherical drop's period of oscillation.[29] This was achieved using macroscopic ridges (a few hundred µm in size) to break the spreading symmetry of the drops (Fig. 3a).[29,30] A similar outcome was achieved by creating pancake-shaped drops using a post array microstructure (see also the next section).[31] These results have implications

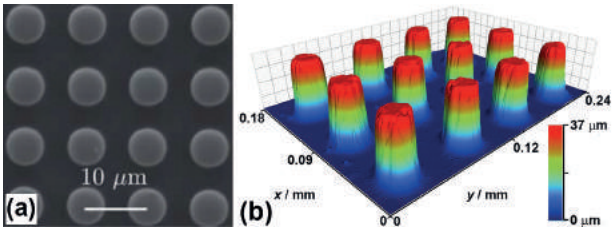

Fig. 2. Examples of polymer micropillar arrays. (a) Top-down scanning electron microscopy view of pillars molded from a silicon wafer master. Reproduced in part from Ref. 28 with permission of The Royal Society of Chemistry. (b) Optical profilometry of PDMS pillars produced using soft lithography. Reproduced from Ref. 39 with permission from The Royal Society of Chemistry.

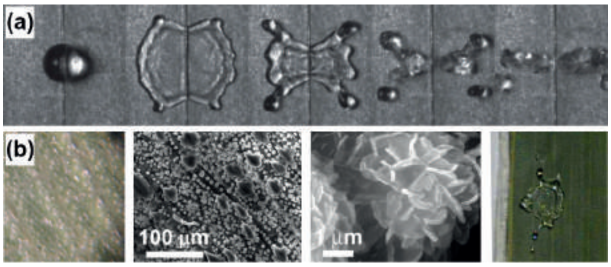

Fig. 3. (a) A water drop (diameter ~2 mm, We = 30) lands on a fluorinated aluminium oxide SHS. The spreading symmetry is split by a ridge, and the total contact time is < 10 ms. Reprinted by permission from Macmillan Publishers Ltd: Nature (Ref. 29), copyright (2013). (b) Drop impact on a fountain bamboo (*Sinarundinaria nitida*) leaf. From left to right: optical microscopy image showing ridges over a ~10 mm field of view, SEM of the epicuticle wax microstructure and nanostructure, and asymmetric spreading of a water drop following impact (diameter ~2 mm, We = 81).

for applications involving heat transfer, such as prevention of ice adhesion. When considering applications, it is important to note that the contact time is not so greatly reduced when the drop strikes the ridge off-centre,[29] nor when ridges are closely packed together,[49] and that the distribution and trajectories of drops after lifting from the surface have not been reported. These studies pose a more basic question for ongoing research: under what conditions do dynamically spreading drops lift off from a surface following interaction with a ridge?

Ridges are also important for water drops landing on leaves. As mentioned above, leaf surfaces have hierarchical structure, and this extends to the millimetric length scale of vascular bundles (veins). In a study of superhydrophobic New Zealand leaves, it was found that drops striking such ridges spread laterally, in similar ways to drops landing on synthetic ridge surfaces (Fig. 3b).[20] Directional wetting is also observed for drops sliding on rice leaves.[50] Any attribution of these dynamics to evolutionary pressures is speculative. However, passive control of drop dynamics could be advantageous for efficient removal of water from the leaf, or perhaps for directing drops towards water collection points. It is also interesting that the waxy microstructures of New Zealand leaves are consistent with those from overseas, despite geographical isolation.[20]

Micropillar arrays

A surface structure may consist of microscopic elements which are patterned over the macroscopic length scale of an impacting drop. The most commonly-studied examples are ordered arrays of micropillars, typically fabricated using photolithography. In these arrays, posts of fixed geometry (height, and width or diameter) are positioned at regular intervals over a surface, creating a 2D lattice (Fig. 2).

Drop impacts on micropillar arrays are particularly interesting for two reasons. Firstly, surface structure can be systematically varied in a controlled manner from sample to sample, allowing dynamic wetting outcomes to be understood. In this way, researchers have developed an understanding of the conditions under which the inertial pressure under an impacting drop is sufficient to induce microstructure penetration.[22,28,37,38] When considering this transition, there is an important critical pillar height, below which the transition is triggered by the water-air interface touching the surface between posts, and above which the three-phase contact line becomes dislodged from the top of a post.[37] The influence of variations in regular microstructure on spreading and splashing after impact has been further studied elsewhere.[36,51]

The second reason to study micropillar array surfaces is that they can generate asymmetric impact outcomes that are consistent with the underlying patterns (Fig. 4a). HSP observations of such impact outcomes have been reported over the past decade. Sivakumar et al.[52] observed rhombus-like drop spreading patterns, extended in the principal directions of a square micropost array, for large (~300 µm) hydrophilic posts with 1:1 aspect ratio. Xu[53] also worked with non-SHSs: 60 µm wide, 18 µm tall posts fabricated in the photoresist SU8 - and observed prompt splash fragments at 45° to the principal array axes. Reyssat and co-workers had earlier observed polygonal penetrated areas of microstructure beneath water drop impacts, working with SHSs composed of fluorinated cylindrical silicon pillars with dimensions < 10 µm.[54] The same team then reported that an array with graduated pillar density (i.e. changing pillar spacing) can generate net horizontal momentum for a drop bouncing following a vertical impact,[47] and that for a square post array,[22] the drop outline can take octagonal or square-like shapes (especially while receding). Tsai et al.,[28] using PDMS pillars with dimensions < 10 µm, demonstrated polygonal rim outlines on square arrays, and hexagonal rim shapes on a hexagonal array with the drop receding near its maximum spread. Interestingly, jetting at the edge of drops landing on square pillar arrays has been observed to occur both predominantly on-axis,[22] and predominantly at 45° to the array.[28,53] Pearson *et al.*[48] used a superhydrophobic array of microscopic ribs with dimensions < 50 µm (which may be seen as an extension to smaller scales of the ridge structures from the previous section) and observed two-pronged jets aligned with the ridge direction.

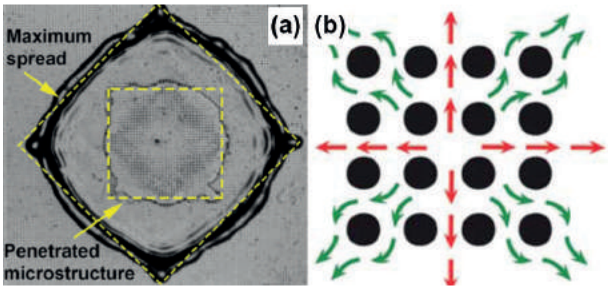

Fig. 4. (a) Bottom-up HSP image following impact of a 2.5 mm diameter water drop on a PDMS micropillar array, with typical trends in asymmetry denoted by dashed lines. Reproduced from Ref. 39 with permission from The Royal Society of Chemistry. (b) Schematic top-down view showing possible pathways for gas flowing from underneath a drop impacting on a micropillar array. Reproduced from Ref. 28 with permission of The Royal Society of Chemistry.

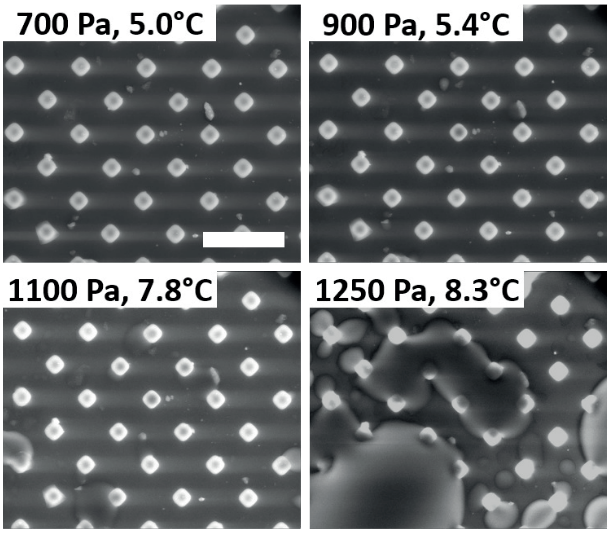

Fig. 5. ESEM images showing gradual nucleation of water drops on a PDMS pillar array with rising pressure at > 90% humidity. Scale bar = 100 µm.

How are these asymmetries generated? One proposed mechanism involves the gas under the impacting drop, which should preferentially flow along paths of least resistance through the microstructure (Fig. 4b), affecting the motion of the adjacent fluid, thereby producing jets and fingers at the edge of a drop.[28,52] We have been studying water drops landing on PDMS micropillar arrays, with systematic variations in the array geometry.[39] Asymmetries have been observed in many aspects of the impact process, including the regions of penetrated microstructure and of the drop's maximum spreading diameter (Fig. 4a), but also in horizontal jets emitted immediately following impact, in the emergence of fingers at the edge of the drop, and in patterns of microbubbles within the spreading lamella. The micropillars (height 5 – 75 µm, diameter/width 5 – 40 µm) were arranged in square lattices (spacing 20 – 190 µm), and the asymmetries usually involved differences between the directions parallel to the principal axes of the array ('on-axis') compared with directions at 45° to these axes.

At least two different mechanisms were found to be at work in these experiments. Typically, the external spread of the drop was more extended on-axis (diamond-like), while the penetrated region of the microstructure was least extended on-axis (square-like, Fig. 4a). For the maximum spread, it appears that the preferred directions of fluid flow were indeed determined by the maximum projected 2D area for fluid moving through the microstructure. For a square lattice, this projected 'corridor' area can be quantified as the pillar height multiplied by the horizontal gap between pillars, and asymmetric outcomes were strongly dependent on this quantity.[39]

In contrast, the geometry of the penetrated microstructure area (square, with rounded corners) arises from competition between surface energies. When considering individual neighbouring pillars, surface energy is minimised by a straight water-air contact line. However, when considering the entire area of the penetrated microstructure, surface energy is minimised by a circular region if the penetrated area is held constant. This patterning of wetting has some parallels with contact line positioning relative to pillar arrays, whether studied at the level of detatchment from individual pillars,[25] or larger scale wetting line geometries.[18,55]

The formation of microbubbles in micropillar arrays within the spreading lamella is largely still to be explored. Such microbubbles are probably generated by air trapped behind pillars,[52] and their spatial distribution is patterned relative to the array.[39] These patterns suggest that the bubbles might be used to infer air flow through the microstructure as the drop lands. Bubbles are observed at the impact point after a drop falls on any solid surface, and often on micropillar arrays there are equivalent, large microbubbles attached to a small number of pillars at the impact point.

Condensation

When a water drop has recently nucleated via condensation, it may be comparable in size to individual microstructural elements on a surface. Understanding the nucleation and growth of water drops on structured surfaces is becoming increasingly important for technologies involving water capture from the atmosphere, which hope to address critical global water scarcity issues.[4] In particular, many synthetic materials are now exploring sub-millimetre scale architectures involving hydrophilic patches on a hydrophobic background. Such approaches mimic surfaces on the body of the Namib Desert beetle,[4,5] which harvests atmospheric dew that blows over the crest of sand dunes. Water drops nucleate and grow on hydrophilic patches; once a drop is large enough, it will detach and roll over the predominantly hydrophobic surface, eventually being collected for consumption. Other biological examples of materials which enable passive water capture include spider silk[56] and cactus thorns.[57]

Development of environmental SEM (ESEM) has provided an important tool for studying drop nucleation and growth on structured surfaces. ESEM enables visualisation of water drops at relatively low vacuums by maintaining a differential pressure between the electron gun and a sample. Figure 5 shows an experimental example in which drops form on a polymer micropillar array. In this case, drops nucleate on debris on the substrate, before growing to engulf spaces between posts. The atmospheric conditions during such an experiment are usually not consistent with realistic dew points in applications. However, the spatial resolution can be considerably better than conventional microscopy, and ESEM imaging is a relatively efficient process. As a result, the technique is increasingly being used to observe and characterise the condensation performance of surfaces.[33]

Horses for courses

The examples presented above, united by the theme of designed surface structure, provide a snapshot of an emerging range of functions for water-repellent surfaces. The challenge of linking specific functions to surface design will continue to stimulate research. For example, different sizes and shapes of posts in pillar arrays can be tested to determine impact conditions producing particular forms of spreading, splashing, and bouncing drops. Hierarchical structures could prove particularly useful, such as surfaces which use intricate post designs (inspired by the leaves of the *Salvinia molesta* plant) to support air-water layers of much greater thickness than usual.[9] Superomniphobic lubricant-infused surfaces (inspired by carnivorous *Nepenthes* pitcher plants[58]) have also attracted considerable recent interest.[59,60] On these surfaces, microstructures including post arrays are infused with a lubricant such as a perfluorinated oil,[59] and the influence of the structural geometry may be important for applications.

For each of the many applications typically envisaged for SHSs, a particular property of a fabricated surface may (or may not) be appropriate. For example, the fabrication costs of ice-repellent surfaces must be considered when they are applied to large surface areas on aircraft and ship hulls. However, surfaces which prevent icing on small scale instruments provide higher value, and so surfaces could be more specialised. For water capture, the local environment is critical – for example, the strategy employed by the Namib Desert beetle (and also relevant to fog-capture nets) relies on a regular, localised flow of air with sufficient humidity to provide condensation.

Supply of fresh water for agriculture, industry, and human consumption is a global issue entwined with climate change and population growth. New Zealand has an opportunity to become a centre for development of water-related technologies that have global impact. This opportunity is provided by the variety of socio-economic and environmental conditions found here. Water in New Zealand is generally plentiful, but shortages do occur in rural, regional, and urban areas, where populations have both high and low disposable incomes to fund solutions. At the present time, there is a particular interest in reducing agricultural pollution of fresh water sources.[61] If surfaces with capabilities for passive water control can be proven under specific local conditions, they may be exported to similar areas throughout the world.

Acknowledgements

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The 2017 Nobel Prize in Chemistry

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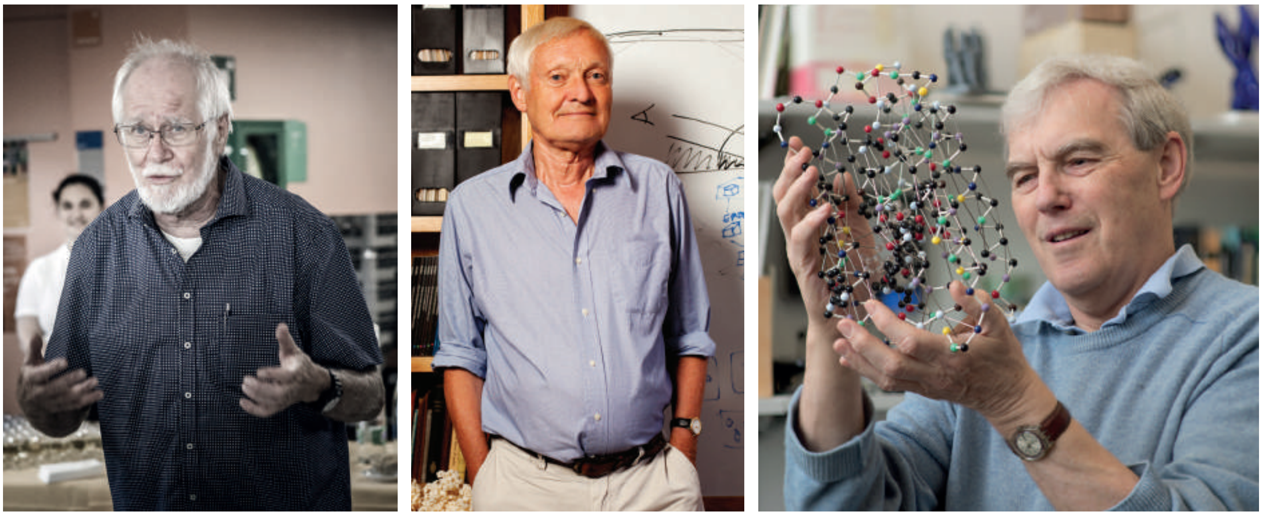
The Royal Swedish Academy of Sciences awarded the 2017 Nobel Prize in Chemistry jointly to **Jacques Dubochet (**University of Lausanne, Switzerland), **Joachim Frank (**Columbia University, New York) and **Richard Henderson (**MRC Laboratory of Molecular Biology, Cambridge, UK) *for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution.*



L-R: Jaques Dubochet (© Willy Blanchard, EMF, Université de Lausanne, Switzerland), Joachim Frank (courtesy Jorg Meyer, Columbia University Medical Center, New York), Richard Henderson (courtesy MRC Laboratory of Molecular Biology, Cambridge, UK).

The 2017 Chemistry Nobel Prize was awarded to **Swiss Jacques Dubochet**, Honorary Professor of Biophysics at the University of Lausanne, German born US citizen **Joachim Frank**, Professor of Biochemistry, and Molecular and of Biological Sciences at Columbia University, New York, and Scotsman **Richard Henderson**, Programme Leader at the MRC Laboratory of Molecular Biology, Cambridge, UK. They were jointly awarded the Prize for the development of cryo-electron microscopy (cryo-EM), instrumentation that both simplifies and improves the imaging of biomolecules.

Alan Burdick, writing on the 2017 announcement in the New Yorker on October 4 last year had the following to say:[1]

Chemistry sits halfway between physics and biology; it's the middle child in the scientific family, as dependable as it is overshadowed. On Monday, the Nobel Prize in Physiology or Medicine was awarded to three researchers who helped elucidate the mechanics of circadian rhythms, the gene-based clocks within our cells (using cryo-electron microscopy); *on Tuesday, the physics prize honoured the discovery, finally confirmed in 2016, of gravitational* *waves. By the time chemistry rolled around, on Wednesday, the siesta of weekdays, it felt in some ways like just another item on the list. For many people, the remaining store of Nobel anticipation had already shifted to the Peace Prize, which will be announced on Friday…. The fact that it's chemistry doesn't help—it's fiddly and subvisible, architecture for microscopists. Occasionally, the Nobel committee recognizes an achievement with obvious appeal; last year, the chemistry prize went to a trio of scientists who built the first molecular-scale motors and machinery. More commonly, though, the prize recognizes developments that, although unquestionably essential, at first glance defy the English language.*

Cryo-EM (or electron cryomicroscopy) is a form of transmission electron microscopy that has moved biochemistry into a new era because the awardees developed a new way to assemble precise three-dimensional images of biological molecules such as proteins, DNA and RNA. As a result of the work of the laureates, researchers can now freeze biomolecules mid-movement and visualise processes never previously seen, decisive for both the basic understanding of life's chemistry and for the development of pharmaceuticals. Scientists can now follow previously invisible processes within cells and gain better understanding of viruses such as the Zika virus that had caused an epidemic of brain-damaged newborns in Brazil. For the future, this work could offer roadmaps in the development of drugs to treat disease.

The work that led to the 2017 award began in Cambridge with Richard Henderson, a PhD X-ray crystallographer from that institution, failing to crystallise a protein that was naturally embedded in the membrane surrounding the cell, which rendered the use of NMR spectroscopy and X-ray crystallography ineffective.[2] The only alternative was EM but many regarded the electron microscope as suitable only for imaging dead matter because the power of the electron beam destroys biological material. However, in 1990, Henderson succeeded in using an electron microscope to generate a three-dimensional image of a protein at atomic resolution.[3] This served to illustrate the technology's potential. Joachim Frank had evolved a theoretical strategy where the apparently minimal information found in the electron microscope's two-dimensional images could be merged to generate a high-resolution, three-dimensional whole.[4] This advance came from Frank's work in the decade from the mid-1970s developing an image processor that took the fuzzy two dimensional images from the electron microscope and merged them to give a sharp three-dimensional one.[4-6] Jacques Dubochet's contribution involved him incorporating water into EM studies in the early 1980s. His success came from recognising that cooling would solve many of the problems in the use of EM in structural biology. He felt that problems associated with crystalline ice surrounding the biological sample would go if the water was vitrified, viz. transformed into a glass [non-crystalline amorphous (*vitreous*) ice distinguished by a lack of long-range order in its molecular arrangement]. It is generated by rapid cooling of liquid water (so the molecules do not have adequate time to form a crystal lattice). Freezing water so rapidly that it solidified around a biological sample while allowing the biomolecule to retain its natural shape has allowed the apparently minimal information found in the electron microscope's two-dimensional images to be merged to generate a high-resolution, three-dimensional one, even in the vacuum involved.[7] This is done by transferring the sample in water to a mesh where it forms a micro-film. This is rapidly shot into liquid ethane in a container surrounded by liquid nitrogen.[8] At that temperature in the electron microscope the biological sample is enveloped in a glass of vitrified water and unharmed by the low electron power now employed. This technique allows the preparation of sufficiently thin unsupported water layers to permit rapid vitrification, yet thin enough to accommodate a single layer of randomly oriented molecules or complexes in their natural state. Dubochet and his co-workers showed the method to be generally applicable and it is now in worldwide use in the cryo-EM field. The image of the Semliki virus (first isolated from mosquitoes in the Semliki Forest, Uganda by the Uganda Virus Research Institute in 1942; Fig. 1) is taken from Dubochet's seminal 1984 paper,[7] while an example of the method and the improved sensitivity over the five year period from 2011 is given in Fig. 2.[9,10]

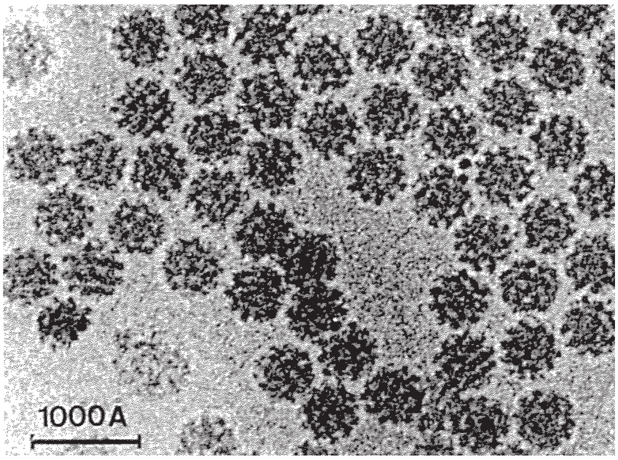


Fig. 1. Image of a Semliki Forest virus suspension from Ref. 7 (with permission)

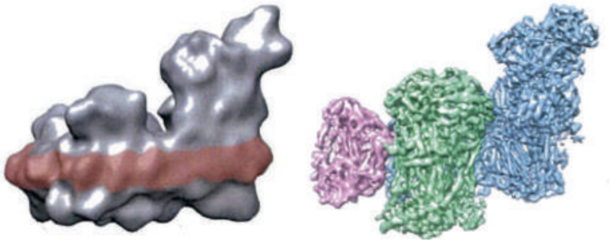


Fig. 2. Left: Models of electron-transport chain components in a mitochondrial super complex $I_1III_2IV_1$ determined in 2011 taken from Fig. 4 of Ref. 9 at a resolution of ca.2 nm, and right as determined in 2016 from Fig. 1 of Ref. 10 at a resolution ~0.6 nm, respectively (with permission). On the left, the coloured shape indicates the position of amphipols used for solubilisation. On the right, complexes I, III and IV are shown in blue, green and pink, respectively.

It was in 1990 that Henderson and colleagues provided the first high-resolution structure of a biomolecule using cryo-EM,[3] that of bacteriorhodopsin (Fig. 3). The results were obtained from use of several electron microscopes in various countries so as to optimise the data quality based on the analysis of millions of protein molecules in a 2D crystal; the electron dose on the individual particles is minimised.[3] By 1995, Henderson had sufficient data and experience to outline the scope and limits of cryo-EM,[11] with the Dengue virus (11,200 kDa) at 0.36 nm, ribosome (2,300 kDa) at 0.29 nm, β-galactosidase (465 kDa) at 0.22 nm, LDH (145 kDa) at 0.28, and GDH (334 kDa) at 0.18 nm[12] (data from Refs. 2 and 12). Subsequent developments have come not from the experimental procedures rather than the advances made in electron microscopy, and it was only in 2013 that desired atomic resolution was reached. Specifically, new, more sensitive detectors have entered the market and dramatically increased the signal-to-noise ratio and the spatial resolution.[2a] The electron source field emission gun, stable cold stages, the Volta phase plate and the automation of data collection are significant to the more recent developments. Examples of recent studies and cryo-EM images can be found in reference 12.

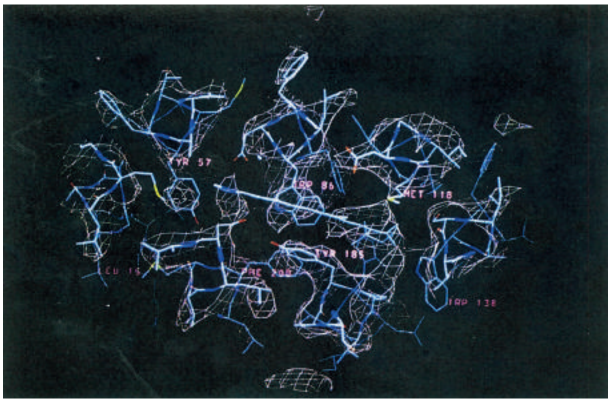


Fig. 3. Model for the structure of bacteriorhodopsin based on high-resolution electron cryo-EM from: Ref. 3.

It is worthy of mention that the technique of cryo-EM was used to elucidate the structure of proteins involved with circadian rhythms, advances that were recognised with the 2017 Physiology or Medicine Nobel Prize. Biochemistry's future seems set for an explosive development and is all set for an exciting future.

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Some Unremembered Chemists

A series of articles that explores the lives and work of selected chemists who have made a significant contribution to the advancement of the discipline, the profession and well-being of mankind, yet who are little remembered.

Aleksandr Mikhailovich Butlerov (1828-1886) and the Cradle of Russian Organic Chemistry

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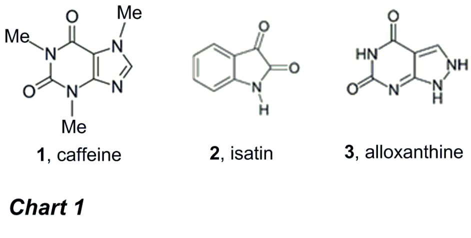
Aleksandr (Alexander) Mikhailovich Butlerov was born on September 15, 1828, in Chistopol near Kazan in the Tartar region of Russia.[1] The town, now named Tatarskaya, is located some 830 kilometers east of Moscow and lies between the Volga River and its tributary the Kama.

Alexander's father, Mikhail Vasilievich Butlerov was a retired lieutenant colonel and a landowner of the district, while his mother, Sofia Alexandrovna, died shortly after he was born.[2-4] The boy spent his childhood at the home of his maternal grandparents, the Strelkovs in the small village of Podlesnaya Shantala near Butlerovka but was brought up by his aunts with his father having significant input to his upbringing. Mikhail's financial situation allowed him to have his son educated in the well-known Topornin private school in Kazan. It was housed in a gloomy barracks-like building on Fedorovskaya St., with a huge sign on the wall that read: *Alexander Semeonovich Topornin Boarding School for Noble Youths*.[5] After arrival at the school aged eight,[3] Butlerov was subjected to the usual inauguration procedures being tormented by his fellow boarders but, according to Nazariev,[5] he remained always good natured, pleasant and polite. Butlerov was active and filled his time to the full. Initially, this mani-

fested itself in painting but after a while he turned to *vials, jars and bowls*,[5] which one of the staff, a former army drummer nicknamed *Furious Roland*, took delight in taking away, putting the boy in a corner and/or depriving him of dinner. Butlerov persisted with his experiments while retaining his good nature and with the backing of the physics teacher. Unfortunately, on one spring evening there was a deafening explosion in the boarding school kitchen (it has been suggested this was an attempt to make gumpowder[3,6]) and Furious Roland dragged Butlerov out by his hair with his eyebrow singed; he was followed by the older tutor accomplice who had supplied the materials for the experiments. Butlerov's crime was extreme in the view of the school board and a new punishment was required. Thus: *The criminal was taken from his dark punishment cell two or three times into the common dining hall, with a black board hanging on his chest on which* great chemist *was written in large white letters*.[5] The irony of this cannot be ignored! However, Topornin, who was also the boarding school director, and a number of teachers generally treated the students well.



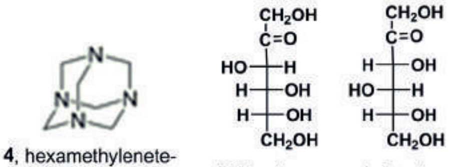
1, caffeine **2**, isatin **3**, alloxanthine

Chart 1

Following his time at the Topornin School, Alexander attended the Gymnasium in Kazan, and in 1844, at age 16, he entered the department of physics and mathematics of Kazan University. The university, founded in 1804 and the easternmost outpost of Russian higher education, had by the mid-19th century the pre-eminent school of Russian organic chemistry despite its location and status. Butlerov studied there until 1849, initially showing interest in botany and zoology, but then followed his earlier interest in chemistry, deciding to devote his life to the science.[7] After enrolling, he worked under Professor Klaus (Claus) on the preparation of antimony but was soon attracted to Professor Zinin's organic chemistry and became an ardent pupil even conducting experiments in his lodgings, much to the dismay of the fellow occupants. Thus, he prepared caffeine (**1**), isatin (**2**), alloxanthine (**3**) and other materials (Chart 1) and took them to the university laboratory.[2] However, Professor Zinin, a mathematics graduate of Kazan who started teaching chemistry there in 1835, left Kazan for the chair at St. Petersburg Medical-Surgical Academy in 1847. Butlerov's Kazan graduation was in 1849 (a degree in natural sciences) and followed submission of his thesis, not in chemistry but in entomology and entitled: *Diurnal butterflies of the Volga-Ural fauna*. He had collected the material for this during his excursions around Kazan and during a trip to the steppes on the east bank of the Volga River and near the Caspian Sea in the spring and summer of 1846. Butlerov's interest in entomology continued throughout his life and he became the founder and first chief editor of the *Russian Apiculture Leaflet* in 1886.[1,8] Following graduation, the faculty at Kazan did not want to lose Butlerov as his abilities were well recognised; he was offered the only position available,[2] a lectureship in physics and physical geography that he accepted and occupied from 1849 to 1850 teaching chemistry part-time until he became Klaus' personal assistant.[1] During this period he was working on his master's thesis. The 1851 submission was entitled: *On the oxidation of organic compounds,*[1] and provided a critical review of all the known information, though it also included his first experimental work on the oxidising action of osmium tetroxide (osmic acid; OsO_4) on organic compounds. He also indicated his thoughts on molecular structure saying that it is the basis for isomerism and that changes in chemical characteristics are associated with structural changes, and this at a time when such ideas had not been previously enunciated.[1]

After Klaus left Kazan in 1852 for the professorship at Dorpat (the University of Tartu since Estonia became independent in 1918), Butlerov became the lecturer in chemistry and taught all of the chemistry courses and that year married Nadezhda Mikhailovna Glumilina, niece of the writer S.T. Aksakov.[1] His teaching ability immediately attracted the attention of both his students and his colleagues, although initially he taught by lecture only - work in the laboratory was not required of his students and he worked there only occasionally. Butlerov was working for his doctoral degree and had his thesis (*About essential oils*) completed in 1853. It concerned the ethereal oil of a Russian plant and the isolation of a camphor-like compound.[2] While the thesis was approved by the professors of chemistry and mineralogy, the professor of physics found it unsatisfactory. There was no mechanism in existence then for an independent assessment of the work and it was the decision of the Kazan Senate to allow Butlerov to submit his thesis to the University of Moscow where he defended it in 1854. He was granted the degree of Doctor of Chemistry and Physics by that university.[2] Following the oral, Butlerov travelled to St Petersburg to visit Zinin and found him to be a supporter of the unitary theory of Gerhardt and Laurant, which had Laurant believe that radicals could react and were not the elements of organic chemistry as was routinely thought. On Zinin's advice, Butlerov familiarised himself with the work of Laurent and Gerhardt and became one of their passionate supporters. He was appointed an extraordinary professor of chemistry at Kazan and in 1858 an ordinary professor. By then Kazan had assumed a pre-eminent position in Russian organic chemistry despite its provincial location and status.

This appointment was after Butlerov made his first excursion to the science centres of Europe in 1857 together with his wife. His first stop was in Berlin at the laboratory of Mitscherlich where he saw and gained experience of coal gas in a laboratory; at Kazan only spirit lamps and furnaces were available. His travels through Germany encompassed most of the chemical centres including Heidelberg where he met Kekulé, at that time a privatdocent preparing his classic 1858 paper[9] in which he stated the carbon was *tetratomic* (valence of four) based on the simple compounds it formed with hydrogen, chlorine (in CCl_4 and CH_2Cl_2), etc.[10] The discussions and friendship that followed impacted markedly on Butlerov's subsequent research activities. By December 1857, Alexander was working in Wurtz's laboratory in Paris. There he conducted his first serious chemical researches and discovered a new way to obtain methylene iodide (from NaOEt and I_2) and studied many methylene derivatives and their reactions. As a result, he was the first to obtain hexamethylenetetramine (urotropine; **4**) and a polymer of formaldehyde which in the presence of limewater is transformed into what was described as a sacchariferous substance – a carbohydrate containing racemic fructose **5** (Chart 2) (as established by Fischer),[1] and the first complete synthesis of a carbohydrate. Whilst there he joined the Paris chemical society.[3]



4, hexamethylenetetramine or urotropine

D-Fructose L-Fructose

5, racemic fructose

Chart 2

While most of the early advances in organic chemistry were taking place in Germany and France, the Russians were also progressing both theoretical and experimental organic chemistry. The science, as practiced in Germany and France, was brought to Russia by Alexander Butlerov and his great service to Russian chemistry was the creation of the first sustained chemistry research school in Russia. It subsequently led to the transformation of the local chemical research of the 1850-1860s,even into the1870s, to international chemical concerns and the professionalisation of the science.[11] The changes he instigated initiated professional chemistry in Russia and were instrumental in making it the strongest scientific discipline there before 1917.

After his return from abroad in 1858, Alexander began to impart the improvements he had seen in Europe to his students and installed a gas generating plant. The storage tank needed a convenient home and, as the only available space was under the floor of the laboratory, that is where it was located much to the dismay of most of the students. The provision of gas, however, made the laboratory work much easier. He then required his students to complete practical work and his noted first graduates appeared. Of these, Markovnikov, Zaitsev and Popov occupied professional chairs in universities during Alexander's lifetime. His work on the methylene series ended in 1861, when he stated the basic ideas of his theory of chemical structure and directed his experimental investigations toward the verification and support of this new theory. Summing up his research, he arrived at the theory of chemical structure, which, according to Markovnikov, he began to expound in his lectures as early as 1860. However, the beginnings of his thoughts appeared in his address to the Paris Chemical Society in 1858 and his writings of 1859. This theory was embodied in his paper *On the Chemical Structure of Substances* read at the chemical section of the Congress of German Naturalists and Physicians in Speyer on September 19, 1861 while on his second visit to European centres. At the Speyer meeting Butlerov was disturbed by the lack of agreement on a theory to explain the facts of organic chemistry.[2] It was here that he defined the concept of chemical structure. This paper was published in *Zeitschrift fur Chemie und Pharmacie* in 1861 and published in the *Journal of Chemical Education* in 1971 following translation by Kluge and Larder.[12] In part, he said:

> *…. assuming that each* chemical *atom is characterised by a specific and limited quantity of chemical force [affinity], with which it participates in the formation of a substance, I would call this chemical bond or [this] capacity for the mutual union of atoms into a complex substance* chemical structure.[12]

From his definition the concept of chemical structure (a term used by Russian chemists before Butlerov, but in another sense) could only be brought forward after there had been a sufficiently clear definition of the concepts *atom*, *valence* and *interatomic bond*. These had been formulated in the 1858 works of Kekulé and Couper. Butlerov advanced the basic proposition of the classical theory of chemical structure by stating that *the chemical nature of a compound molecule is determined by the nature of its component parts, by their quantity, and by their chemical structure*.[1] On his return to Kazan his report to the university authorities said, in part:[2,13]

> *None of the ideas which I found in Western Europe seemed especially new to me. Laying aside here misplaced false*

modesty, I can say that these ideas and conclusions have been quite familiar in recent years in the Kazan laboratory, and they have not been considered especially original. They were developed in the general course of the work and were introduced in part into the lecture.

By the mid-1850s theoretical organic chemistry was at a crossroads. The theory of radicals was being dropped and the theory of types was taking its place making it possible to classify organic compounds and to indicate the types of reactions they would undergo by analogy with inorganics. The real purpose of Butlerov's 1861 paper was to try to move the chemical community from a halfway position, mixing older type and radical theories with the new theory of atomicity of elements, to the position of full structuralism.[13] His proposition, as is evident from its wording, broke with these traditional views and all the remaining proposals relating to the classical theory of chemical structure are directly or indirectly associated with that of Butlerov. The starting point of his thoughts was that for any given structural formula there existed only one compound, and for any individual compound only one formula could be written. He discarded the idea of Gerhardt who had said that the formula for a compound should vary according to its different methods of synthesis or reaction. Butlerov discarded the type theory altogether whilst Kekulé continued to use type formulae in his textbook for several years. In essence, Butlerov concluded that a structural formula should not be just an abstract image of a molecule rather than reflect its real structure. He was the first chemist to suggest that studying chemical properties of substances may lead to finding their chemical structures and *vice versa*;[6] he was the first to produce a model of tetrahedral carbon even thought it was irregular. Although his writings are more theoretical in nature than most of his contemporaries and his concepts those which match our accepted ideas, he went on to substantiate his theoretical views with experimental studies on aliphatic hydrocarbons and alcohols, unexpectedly obtaining *tert*-butanol as the first tertiary alcohol to be prepared. It was obtained by treating phosgene ($COCl_2$) with dimethylzinc, presumably via acetone reacting with excess of the zinc reagent. Alexander continued the study of tertiary alcohols by preparing many derivatives and improving the methods of preparation. He deserves credit for the prediction and proof of positional and skeletal isomerism, later proving, with the aid of his students, the existence of homologues. Thus, he predicted the existence of two butanes and three pentanes in 1864. Later, the expectation of isobutylene (2-methylpropene) led to the discovery of the isomeric butanes and butenes. He went on and predicted the number of isomers of the homologous hydrocarbons. He then wrote the first chemistry text to be based entirely on structural theory. It appeared in Russian in 1864 and in German in 1867, a little later than Kekulé's 1865 report on the structure of benzene.[13] By that time the proposals that Kekulé and Couper made simultaneously in 1858 on tetravalent carbon, and the latter's method for graphic representation, were well accepted even though they did not provide the detail that Butlerov clearly had in 1861.

By the mid-1860s, the number of chemists adopting the structural theory had increased and their way of depicting of structural formulae was that put forward by Butlerov.[10] Then, as now, the issue of priority was important and by 1867 Alexander Butlerov felt that he must stake his claim. In a footnote to his paper concerning the number of C_4H_{10} isomers[14] he pointed out that he had provided the theoretically possible number of isomers of C_5H_{12} before Friedel and Ladenburg, and went on to state that numerous chemists had made unjustifiable claims.[13] He stated:

> *… the mutual chemical method of binding elementary atoms in molecules (the principle of chemical structure) will more and more be the chief basis of most chemical speculations in the newer chemistry. … and I am now obliged to assert that to me belongs an important part of the priority for complete and consequential development of this principle. ….*

One of the chemists he named was Lothar Meyer (best known for his part in the periodic classification of the elements) who defended himself bitterly but missed the significance of Butlerov's contributions.[13] Both Meyer's defense and Butlerov's response appeared in the Annalen of 1868.[15] The latter acknowledged the major contributions of Kekulé to the theoretical and experimental branches of chemistry and this must have played its part in quietening the matter. What subsequently happened was that Butlerov's theory of chemical structure became so much a part of our science that the work of this early protagonist became and remains largely forgotten.

It was in 1868, while in Nice, that Alexander's reply to Lothar was penned and during that same trip he was advised that he had been appointed to the chair in St Petersburg. He was also awarded the Lomonosov prize that year. In fact, it was earlier in that decade that Butlerov looked to leave Kazan. One reason for this was his unsuccessful term as rector.[1] In March 1860 he had become the last rector of Kazan University to be appointed by the Imperial Government. However, his attempts to instigate liberal changes, as well as end student abuse of individual teachers, failed and he was allowed to leave the post in August 1861. In November the following year, he became the first elected Rector of the University, but this was against his wishes. There was a struggle between groups of professors and Butlerov clashed with a university trustee and that led to his second retirement from the position in July 1863. He was very unhappy with the experience especially as he had not wanted the position in the first place and he began to seek a post outside of Kazan. Only the insistence of his friends, and the birth of his only child, a son, Vladimir Aleksandrovich, in April 1864 stopped him from departing immediately.[1]

The legacy that Butlerov left to Kazan was the establishment of the first decisive school of organic chemistry and its recognition in Russia. Thus Kazan became the cradle of Russian organic chemistry with his students almost always successful as exemplified by the three most noted ones from there, Markovnikov, Popov, and Zaitsev. Each one of these went on to establish Russian organic chemistry at other centres (see below).

Butlerov's transfer to St. Petersburg University as professor of chemistry ran from 1868 until 1885, when he was required to retire on pension. Despite this he continued to give special lecture courses. Much of his time at St. Petersburg was spent defending and substantiating the theory of chemical structure from his university colleagues Menschutkin (his successor) and, to a lesser extent, Mendeleev.[1] Butlerov felt strongly that chemists not only had the right, but also the responsibility, to speak of molecules and atoms as though they existed and, in so doing, preserved the conviction that this belief would not become a baseless abstraction. Whether Butlerov is the father of chemical structural theory, as implied by many Russian authors, or whether he simply played a major role in its development and acceptance is debatable.[16] Nonetheless, a prominent group of Russian organic chemists worked with Butlerov at St Petersburg as in Kazan. Of these, A. E. Favorskii is the most noted (see below), though I. L. Kondakov deserves mention as he and his co-workers achieved remarkable success as he was the first to produce synthetic rubber in 1901 when Head of Chemistry at Tartu University (1894-1918). It should also be noted that Egor Egoroviè Vagner, a graduate of Markownikov, also worked in the Butlerov laboratory. Vagner (born in Kazan) subsequently gained a chair in Warsaw and published under the German translation of his name, Georg Wagner;[17] he discovered that α-pinene rearranged to bornyl chloride in 1899 and is the Wagner of the Wagner-Meerwein rearrangement.

Butlerov's outstanding characteristic as an instructor was that he taught by example and his students could always observe what he was doing and how he was doing it; he always answered questions and was never dismissive of his students.[1] He was a staunch advocate of higher education for women and from 1878 organised university lecture and laboratory courses in chemistry for them at St Petersburg. In addition, Butlerov delivered there, as he had earlier done in Kazan, a large number of public lectures, most of which had a chemical and/or technical basis. By the end of the 1870s, organic chemistry in Russia had reached the stature needed to make it unnecessary for a student to leave the country for advanced training in the discipline. By then there were vibrant schools of chemistry headed by Russian and Russian-trained professors. Thus, St. Petersburg was served by Zinin, Butlerov, Menshutkin and Borodin,[18] Moscow had Markovnikov, and Kazan, Zaitsev.

Although Butlerov did nothing to improve the ways and procedures for identifying or synthesising new compounds with particular structures, he experimented to prove his theory. He was able to formulate isomerism rules from the theory, and chemists were able to predict the existence of the four valeric acids ($C_4H_9CO_2H$), three of which were synthesised outside Russia in 1871, while the last isomer was synthesised in Butlerov's own laboratory in 1872 – verification not only by the proponents but also independently. At the very least, Butlerov must be accepted as *one of the main philosophers of the structural theory*.[3]

Butlerov also spent considerable time on practical agriculture, horticulture and beekeeping. He wrote a book on beekeeping in 1871 entitled: *Bee, its life and the main rules of sensible beekeeping*. It went to ten editions before the Russian Revolution and was the practical handbook of its time.[4] In his later life in the 1860s he grew tea in the Caucasus[6] where the tea plant flourished on the western lowlands of Transcaucasia (modern Georgia, Armenia, and Azerbaijan), notably at Soukhourn.[19]

In the spring of 1886 Butlerov's health deteriorated and, though not thought serious, he ended his work and returned to his estate in Butlerovka on the banks of the Kama River. He died there on August 17, aged 58. He was buried in the family chapel in the rural cemetery. A statue of him was erected in Kazan in 1978 and the successes of the Kazan chemists contributed to the organisation of a Research Chemical Institute named after him in 1929 at Kazan University. As a result of the reorganisation of Soviet Universities in 1933, the Department of Chemistry in Kazan University was reopened. Then, in 2003 the Alexander Butlerov Institute of Chemistry was established when the Research Chemical Institute and the Chemical Faculty of Kazan State University merged. The crater Butlerov on the moon is named after Alexander Butlerov.

(Top) The Butlerov Institute, Kazan University built in 1804 and in which Butlerov worked. (Bottom): The Butlerov Statue in Kazan (both courtesy of V. Vysotskii)

Brief commentaries on Butlerov’s noted students in the cradle of Russian organic chemistry:

A.M. Butlerov with members of the Kazan Department before leaving for St. Petersburg; Kazan 1868 (courtesy of Professor Gulnar Valitova and the *Museum*, *Kazan* School of *Chemistry*; *image enhanced for clarity). Butlerov is front row (centre) with Zinin (3rd from right). Markownikov and Zaitsev are likely 2nd and 3rd from left on back row) and 19 year old E.E. Vagner is likely front row right (caption courtesy Professor A. Vedernikov)*

Vladimir Vassil'evich Markovnikov (1838-1904)

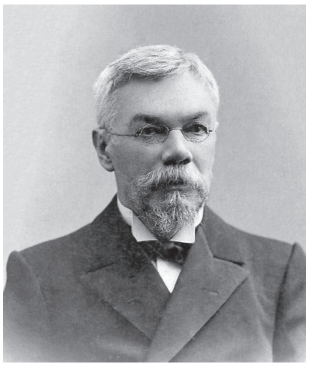
Vladimir Vassil'evich Markovnikov was born on December 22, 1838, in Nizhny Novgorod about 400 km east of Kazan. He studied under Butlerov in Kazan (1860 graduate) and St. Petersburg making his most noted contribution to organic chemistry in 1869, namely the Markovnikov Rule, which predicts the regiochemistry of addition reactions. He was a lecturer at Kazan in 1862, succeeded Butlerov in 1869, gained a chair in Odessa in 1871 then transferred to the chair in Moscow in 1873. His further contributions to the field of organic chemistry were his discovery of the naphthalenes in the early 1860s, the cyclobutanes in 1879 and the cycloheptanes in 1889. He died in Moscow on February 11, 1904. He was a founder of the Russian Chemical Society in 1868.

Alexandr Nikiforovich Popov (1840-1881)

Popov was born in about 1840 in Vitebsk in Belarus. He studied at Kazan under Butlerov graduating with his PhD in 1865. In 1869 he graduated with a DSc degree from Kazan and was appointed to Warsaw University on its inauguration that year where he remained until his untimely death on August 6, 1881. He was known for the Popova Rule which came from his study of the oxidation of organic compounds by a chromium mixture; the rule allows methods of determining the chemical structure of ketones, acids, alcohols, and hydrocarbons.

Aleksandr Mikhaylovich Zaitsev (1841-1910)

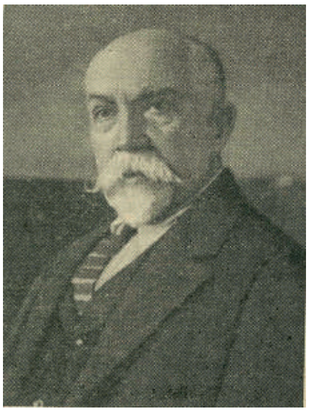
Zaitsev graduated with a degree in economic science in 1862 but had to study chemistry as well and was converted by Butlerov. At the time of his graduation he was no longer an economist, but a committed chemist. Not complying with Russian traditions, Zaitsev moved to Germany and then Paris where he studied under several of the noted chemists. His return to Kazan was not simple, but in 1869 he was appointed to the chair in Chemical Technology while Markownikov held the chair of chemistry; there was little love lost between the pair. Whilst at Kazan, Zaitsev enunciated his empirical rule for elimination, the Zaitsev (or *Saytzeff*) rule which states that the most substituted product will be the most stable, and therefore the most favoured. He remained at Kazan and had as students Egor Egorevich Vagner (Georg Wagner, 1849–1903) and Sergei Nikolaevich Reformatskii (1860–1934). Zaitsev died in Kazan on September 1, 1910.



Ivan Laverntievich Kondakov (1857-1931)

Kondakov was born on October 8, 1857 in Viluisk in the Yakutsk territory of Eastern Siberia. He studied at St Petersburg University under Butlerov then transferred to Warsaw University in 1886. In 1895 he moved to Tartu University in Estonia where he discovered the polymerisation of 2,3-dimethylbutadiene (1899). He synthesised synthetic rubber (methyl rubber) in 1901 and his procedure was used in Germany in 1916. He also studied the rearrangement(s) of 2-methylbut-2-ene seeking a diene product. He died in the village of Elva in Estonia in 1931.

Alexey Yevgrafovich Favorskii (1860-1945)



Favorskii was born in Pavlovo, Nizhny Novgorod on March 3, 1860. He studied chemistry at the University of St Petersburg from 1878 to 1882 under Butlerov, where he then stayed for several years. In 1891 he was appointed lecturer, gained his PhD in 1895 and became professor for technical chemistry. His discovery of the Favorskii rearrangement in 1894 (the rearrangement of an α–haloketone to a cyclopropanone and then a carboxylic acid) and the Favorskii reaction (the nucleophilic attack of an acetylide on a carbonyl group) between 1900 and 1905 are his most noted works. He was at the (new) inorganic department from 1897, and served as its director from 1934 to 1937. For his improvement of the production of synthetic rubber, Favorskii was awarded the Stalin Prize in 1941. He died on August 8, 1945 and is buried at the Volkovskoe Orthodox Cemetery in St Petersburg.

Acknowledgements

I am especially grateful to Professor Vladimir Vysotskii (shown centre in the Butlerov Institute photograph) for his invaluable comments and many helpful suggestions for this article. Professor Andrei Vedernikov (University of Maryland) has been of invaluable assistance in gaining permission to reproduce the image of Butlerov and his colleagues and providing a caption for it. Ms Natalia Primak was instrumental in facilitating these latter matters.

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Dates of Note

January

21 ***Felix Hoffmann,*** the German chemist who discovered aspirin while working for Bayer & Co. was born this day in 1868, 150 years ago.

Solomon Spiegelman, the American microbiologist and geneticist who discovered that only RNA carries the genetic information to produce new substances, died in 1983. In 1962 he developed nucleic acid hybridisation, credited for helping to lay the groundwork for current advances in recombinant DNA technology.

23 ***Charles Glen King***, the American biochemist who discovered vitamin C with its structure quickly determined and synthesised by, e.g. Haworth and Reichstein in 1933. He died in 1988.

John Davy, the brother of Humphry Davy and an English chemist and doctor who first prepared, named and characterised the gas phosgene, died in 1868, 150 year ago today.

25 ***Horace Wells***, the American dentist, who pioneered the use of surgical anaesthesia, died in 1848.

28 ***Victor Moritz Goldschmidt***, the Swiss-Norwegian geochemist, mineralogist and petrologist who established a theoretical background for geochemistry, was born in 1888.

Crystallographer Dame ***Kathleen Lonsdale*** was born in 1903.

31 ***Theodore William Richards***, the American analytical chemist who was awarded the 1914 Nobel Prize for Chemistry in recognition of his accurate determinations of atomic weights, was born 150 years ago today and died on Apr 2, 1928.

February

1 Sir ***George Gabriel Stokes***, the British physicist known for his spectroscopic work, died in 1903.

2 The first sale of anti-knock gasoline containing tetraethyl lead was in 1923.

7 ***Wilder Dwight Bancroft*** died in 1953. He was the American physical chemist who introduced a number of thermodynamic and colloidal concepts into American physicochemistry. His favourite demonstration proved something whichever way it went. Thus: a solution of iodine in water is shaken with charcoal, filtered and tested with starch paste. If the colourless solution does not turn the starch blue, the experiment shows how completely charcoal extracts iodine from aqueous solution. If the starch turns blue, the experiment shows that the solution, though apparently colourless, still contains iodine which can be detected by means of a sensitive starch test.

This day also marks the day in 1863 that ***John Newland*** announced his Law of Octaves where he organised the known elements in order by atomic weight. This was based on his observation that after each interval of eight elements, similar physical and chemical properties reappeared. The article '*On relations among the Equivalents*' (*Chem News,* **1863**, *7*, 70-72) was ridiculed by The Chemical Society to the extent that little significance was then attached to atomic weights. However, he was recognised, belatedly, in 1887 by the Royal Society with the award of the Davy Medal – but only after Mendeleev had more successfully introduced his table.

10 ***Victor Mordechai Goldschmidt***, the German mineralogist who made important studies of crystallography publishing the *Index der Kristallformen* in three volumes (1886-1891), was born in 1853.

Frederick Cossom (Fred) Hollows, the NZ-born Australian physician and a leader in the campaign to combat eye diseases (especially trachoma), died 25 years ago.

Wilhelm Röntgen died in 1923.

11 ***Robert W. Holley***, the US biochemist who shared the 1968 Nobel Prize for Physiology or Medicine (with Nirenberg and Khorana) for work that helped to decipher the genetic code chemically, died 25years ago today.

Anders Gustav Ekeberg, the Swedish chemist who discovered the element tantalum in 1802, died in 1813.

13 ***Alfred Wolf***, the American nuclear and organic chemist who made pioneering contributions in the field of organic radiochemistry, was born in 1923.

14 ***Julius Arthur Nieuwland***, the Belgian-born American organic chemist who studied reactions of acetylene and invented neoprene, was ordained as a priest before earning his PhD (1904); he was born in 1878.

Gottlieb Sigismund Kirchhof, the German-Russian chemist who applied the first controlled catalytic reaction to produce glucose, developed a method for refining vegetable oil, and experimented with brewing and fermentation, died in 1833.

17 ***Friedrich Konrad Beilstein***, the Russian chemist who compiled the *Handbuch der Organischen Chemie*, was born in 1838.

18 In 1913, English chemist ***Frederick Soddy*** introduced the term *isotope* to science and then received the 1921 Nobel Prize for Chemistry for investigating radioactive substances.

22 This is the day in 1828 that German biochemist ***Friedrich Wöhler*** informed Jakob Berzelius that he had synthesised urea, the first synthesis of an organic from inorganic precursors.

23 This day marks 125 years since ***Rudolf Diesel*** received a German patent for his diesel engine.

24 This is the day in 1938 that saw DuPont begin commercial production of nylon toothbrush bristles.

25 ***William Thomas Astbury***, the English physical biochemist and first to use X-ray diffraction to study the structure of nucleic acids in 1937, was born in 1898.

26 ***Giulio Natta***, the Italian chemist who contributed to the development of high polymers, was born in 1903.

In 1878 ***Émile Littré*** choose the word *microbe* (rather than *microbial*) for certain micro-organisms, even though it was coined from two Greek words that together would mean short-lived rather than small life.

27 ***David Keilin***, the Russian-British biochemist who discovered cytochromes as enzymes critical to the cell's use of oxygen, died in 1963.

George Herbert Hitchings was the American pharmacologist awarded a share of the 1988 Nobel Prize for Physiology or Medicine (with Elion and Black) for developing the drugs thioguanine, 6-mercaptopurine (for leukaemia), azathioprine (for rheumatoid arthritis and other autoimmune disorders) and allopurinol (for gout), died 20 years ago.

28 ***René-Just Haüy***, the French mineralogist and founder of the science of crystallography by his discovery of the geometrical law of crystallisation, was born in 1743.

Eilhard Mitscherlich, the German chemist who proffered the principle of isomorphism following his discovery of the similarity of crystalline forms of compounds, died in 1863.

This day marks 65 years since ***James Watson*** who, from early on what was a Saturday, spent his time at the Cavendish Laboratory in Cambridge, shuffling cardboard cut-out models of the molecules of the DNA bases: adenine (A), guanine (G), cytosine (C) and thymine (T). After a while he discovered their complementary pairing. Together with Francis Crick he submitted their first article on the structure of DNA to *Nature* on March 6, 1953. He was born on Apr 6, 1928.

29 In 1908, Dutch scientist ***Heike Kamerlingh Onnes*** told an academy meeting that the previous day he had produced solid helium.

March

1 On this day in 1813, ***Michael Faraday*** was appointed as Chemical Assistant to Humphry Davy at the Royal Institution.

3 ***Arthur Kornberg***, the US biochemist who shared the 1959 Nobel Prize for Physiology or Medicine (with Ochoa) for the discovery of the mechanisms in the biological synthesis of DNA and isolated the first DNA polymerising enzyme, was born 100 years ago today.

Albert Bruce Sabin, the Polish-American physician and microbiologist best known for developing the first oral polio vaccine in 1955, died 25 years ago.

On this day in 1863 the National Academy of Sciences was chartered with President Abraham Lincoln approving the Act of Congress which established it.

6 This day in 1913 saw ***Niels Bohr*** mail his first paper describing his new ideas on atomic structure to his mentor, Ernest Rutherford; it was the first of three historic papers on the subject.

7 ***David Baltimore***, the American biochemist and virologist who shared the 1975 Nobel Prize for Physiology or Medicine (with Temin and Dulbecco) for his independent discoveries of retroviruses - viruses with an RNA genome - has his 80th birthday today.

In 1883 ***Johann Kjeldahl*** reported to the Chemical Society of Copenhagen on his procedure, still used at the present time to enable the laboratory determination of the nitrogen content in organic compounds (the Kjeldahl method).

9 ***Walter Kohn***, the Austrian-American physicist who shared the 1998 Nobel Prize in Chemistry (with Pople) for his work on the development of the density-functional theory, was born in 1923.

Johannes Diederik van der Waals died in 1923.

In 1893, ***James Dewar*** advised a meeting of the Royal Society that he had succeeded in freezing air into a clear, transparent solid; he died on March 27, 1923.

10 ***Johann Rudolf Glauber*** of salt fame and regarded by many as the German father of chemistry, died this day in 1668, 350 years ago.

11 ***Henri-Étienne Sainte-Claire Deville***, the French geologist and chemist who invented the first industrial process for producing aluminium, was born this day 200 years ago.

12 ***Walter Norman Haworth*** of projection formulae fame was born in 1883.

Vladimir Ivanovich Vernadsky, the Russian geochemist and mineralogist who was a founder of the sciences of geochemistry and biogeochemistry, was born in 1863.

Sir ***William Perkin*** of aniline purple fame was born in 1838.

13 ***Joseph Priestly***, the English chemist who discovered oxygen, was born in 1733.

15 Sir ***Henry Bessemer***, the English industrialist, metallurgist, inventor and engineer who developed the first process for manufacturing steel inexpensively, died in 1898.

16 Sir ***Derek H.R. Barton***, the joint recipient of the 1969 Nobel Prize for Chemistry (with Hassel) for research that helped establish conformational analysis, died in 1998.

17 250 years ago, in 1768, ***William Cookworthy*** obtained a British patent for his process to take local china clay and manufacture fine white porcelain. This was significant because he could produce hard paste porcelain that competed in quality as finished goods imported from China.

19 ***Mario Molina***, the Mexican-American chemist who shared the 1995 Nobel Prize for Chemistry (with Crutzen and Rowland) for research on the ozone layer, has his 75th birthday today.

Sir ***Walter Norman Haworth***, the English chemist who shared the 1937 Nobel Prize for Chemistry (with Karrer) for work determining the chemical structures of various carbohydrates and the synthesis of vitamin C, was born in 1883.

22 ***Pierre-Joseph Pelletier***, the French chemist known for his work on vegetable bases and the resulting contributions of alkaloids in medicine, was born in 1788.

24 ***Adolf Friedrich Johann Butenandt***, was the German biochemist and co-winner (with Ruzicka) of the 1939 Nobel Prize for Chemistry for pioneering work on sex hormones, dominantly the isolation of estrone. He was forced to refuse the prize by the Nazi government, but was able to accept in 1949. He was born in 1903.

26 ***James B. Conant***, the chemist President of Harvard University and 1951 University of NZ honorary DSc, was born in 1893, 125 years ago.

Alexander Crum Brown, the Scottish chemist who developed of a system of representing chemical compounds in diagrammatic form, was born in 1838.

It is the day 65 years ago in 1953 that Dr ***Jonas Salk*** announced his vaccine to immunise people against polio.

27 ***Elijah McCoy*** (the real McCoy) was born -in 1843; he held many patents for the automatic lubrication of machinery.

Sir ***James Dewar***, the Scottish chemist and physicist who blurred the line between physics and chemistry and invented the Dewar vacuum flask in 1892, died in 1923.

This was the day in 1933 that polyethylene was discovered by ***Reginald Gibson*** and ***Eric William Fawcett***.

30 ***Auguste Bravais***, the French physicist and mineralogist best remembered for his work on the theory of crystals with Bravais lattices named after him, died in 1863.

April

2 ***Theodore William Richards***, the American analytical chemist awarded the 1914 Nobel Prize for Chemistry in recognition of his accurate determinations of the atomic weight of a large number of chemical elements, died in 1923.

6 ***James Watson*** of Watson and Crick DNA fame was born in 1928.

It is 65 years since *Nature* published the Watson and Crick paper describing the double helix structure for DNA.

This day in 1938 saw Du Pont researcher ***Roy J. Plunkett*** and his technician ***Jack Rebok*** accidentally discover polytetrafluoroethylene (PTFE; Teflon).

8 ***Martin Julian Buerger***, the American crystallographer who devised or improved many of the standard methods, techniques, and instruments of modern crystal structure analysis, was born in 1908.

August Wilhelm von Hofmann, the noted German heterocyclic chemist, was born 200 years ago today.

10 ***Paul-Louis-Toussaint Héroult***, the French metallurgist and chemist who invented the electric-arc furnace, was born on Apr 10, 150 years ago.

12 In 1888 a French newspaper mistakenly published an obituary for ***Albert Nobel***, inventor of dynamite, calling him "a merchant of death.” The mistake was that it was Albert's brother, Ludwig, who had died (aged 56; heart trouble). However, shocked by the newspaper's report, Albert began to seek a change in public opinion, which led to his decision to establish the Nobel Prizes.

13 ***Leopold Gmelin***, the German chemist who discovered potassium ferrocyanide (1822), devised his test for bile pigments and researched the chemistry of digestion, but is best known for his *Handbook of Chemistry*, died in 1853.

15 Insulin became generally available for use by diabetics in 1923.

16 ***Ernest Solvay***, the Belgian industrialist who invented the commercially viable ammonia-soda process – the Solvay Process – for producing sodium carbonate, was born in 1838.

Joseph Black, the Scottish chemist and physicist who experimented with carbon dioxide (fixed air), discovered bicarbonates and identified latent heat, was born in 1728.

Rosalind Franklin, the English X-ray crystallographer who contributed to the discovery of the molecular structure of DNA, died in 1948.

This is the day in 1943 when ***Albert Hofmann***, the first to synthesise LSD, accidentally adsorbed the drug through his finger tips and recorded its hallucinogenic effect. Three days later he deliberately ingested the drug and had his *trip* on a bicycle. April 19 is now known as *bicycle day*.

17 ***Friedrich Karl Johannes Thiele***, the German chemist who researched conjugated unsaturated organic molecules yielding new ideas for theories on the mechanisms of organic reactions, died 100 years ago today.

18 ***Justus von Liebig***, the German chemist who made important contributions to the early organisation of organic chemistry, died in 1873.

It is also the day French chemist ***Paul-Émile Lecoq de Boisbaudran*** was born in 1838. Although relatively unknown, he developed and improved the spectroscopic methods developed by Kirchhoff. In 1859, he scanned minerals for unknown spectral lines and discovered the elements gallium (1875), samarium (1880), and dysprosium (1886). He ranks with Bunsen, Kirchhoff and Crookes as one of the founders of the science of spectroscopy.