

Computerised chemicals

Quantum chemist **Professor Michelle Coote** explains the unique opportunities offered by her field of science, describing her own work towards developing efficient computer models for investigating chemical reactions of industrial relevance



Can you explain the particular appeal of quantum chemistry, and what first drew you to work in this field?

The attraction of computational quantum chemistry is the ability it gives you to study any individual reaction within a complicated process directly, and effectively watch how the atoms and electron density rearrange as the reaction takes place. This is unthinkable experimentally, where it is normally only possible to study the macroscopic outcome of the process as a whole. I started my research career using experiments to study radical polymerisation kinetics but became frustrated with these limitations. Therefore, I made the switch to quantum chemistry to study this process more deeply and directly.

What are the key areas of research you are currently focusing on? How do your present investigations align with your overall research ambitions?

At present we are trying to design reagents for controlling the stereochemistry in free-radical polymerisation, polymers with improved resistance to degradation, thermally-reversible self-healing polymers that undergo debonding in a target

temperature range, and pH-switchable radical protecting groups that can release carbon-centred radicals at room temperature. At a more fundamental level, we are looking to understand the origin of enzyme catalysis, and the effects of electric fields on chemical reactions. The underlying universal aim of these projects is to better understand chemical reactivity so that we can design ways of manipulating and controlling it in practical applications.

How has quantum chemistry addressed the principal hurdles relating to free-radical polymerisation?

To derive a kinetic model you need to decide what reactions and side reactions are occurring in your process, and to what extent they depend on the chemical structure and chain length of the species involved. These are exactly the sorts of questions that quantum chemistry can answer – all we have to do is calculate the rate coefficients of the various reactions and from these we can assess which reactions are significant and need to be included, and which ones can or should be omitted. To implement a kinetic model, you also need to provide rate coefficients for these reactions and using quantum chemistry we can predict them from first principles, thereby reducing the need for model fitting. At a deeper level we have also used theory to study the relationships between chemical structure and reactivity for critical reactions, and in this way identify guidelines for selecting optimal control agents or even designing novel ones.

Can you explain the importance of the Schrödinger equation to our understanding of quantum chemistry?

The Schrödinger equation is the cornerstone of quantum chemistry – if you can solve it for an arrangement of atoms (ie. the chemical structure or geometry of a molecule) you can predict their energy and wavefunction,

the latter relating to the electron density distribution within the molecule. By solving this equation as a function of geometry it is possible to identify the preferred minimum energy geometries of molecules, map out their reaction pathways and study how they move. In principle, solving this equation gives you everything you need to know to predict the mechanisms, rates and energetics of chemical reactions. It can also be used to predict various absorption, emission and vibrational spectra, chemical shifts in nuclear magnetic and electron paramagnetic resonance, dipole moments, and various aspects of their electronic structure.

Computer-guided reagent design has not only proven successful in polymer chemistry, but also in a variety of other areas – can you elaborate?

We recently designed an improved nitroxide redox mediator for dye-sensitised solar cells. To this end, we used theory to determine how to change the chemical structure of a nitroxide radical in order to alter its oxidation potential – so as to target an optimal value to match the dye – while also making it resistant to side reactions that would otherwise compromise its efficiency. One of our computational designs was subsequently tested by an independent team of experimental researchers and shown to double the efficiency, compared with the original cell.

Do you foresee big changes in your field of science in the near future?

Despite all the advances in methodology and computer power, the biggest challenge faced by computational chemistry is still the question of how best to balance accuracy and efficiency. Moore's Law advances in computer power – and possibly the development of quantum computing – will help extend the range of accurate quantum chemistry.

Radical discoveries

Chemical reaction modellers at the **Australian National University** are developing computer simulation methods to change the way that industry approaches radical polymerisation

HOW CAN SCIENTISTS observe the actual dynamics of a chemical reaction? The short answer is they cannot. In the future it may be possible to develop femtosecond lasers and other technologies to the point where a chemical reaction could be made visible, but currently the most detailed insights to be gained are through using quantum mechanics to model chemical behaviour computationally. Using such methods, it is possible to secure an understanding of chemical reactions on a mechanistic level, to explore the relationship between molecular structure and reactivity, and ultimately begin optimising chemical processes to maximise yields and product qualities.

One area in which quantum chemical modelling is particularly useful is free-radical polymerisation – the complex chemical process of creating polymers from small unsaturated monomers using free-radicals (species with unpaired electrons that make them likely to bond with others). The high reactivity of these radicals can be an advantage, with free-radical polymerisation having a broad scope and generally occurring rapidly under mild conditions. As such it is attractive industrially, and indeed around half of all polymers fabricated worldwide are generated through some variant of this process.

Free-radical polymerisation involves a complicated multi-step mechanism in which radicals are formed from precursors called initiators, which then successively add to the monomer forming a growing polymer radical. This can in turn add further monomer or undergo a range of side reactions including termination processes that irreversibly end the chain growth. Each step of this intricate and extremely useful chemical reaction has a hand in governing the final polymer product created.

QUANTUM INQUISITION

Developing accurate models for predicting the outcome of the process in terms of the concentrations and chemical structures of the starting materials is a very complex task, particularly as the various individual reactions cannot be studied directly. If the process itself could be modelled and optimised using quantum chemical approaches instead, then the value could be huge for global industry. The main obstacle to achieving this goal is the current limitation of computer processing power; modelling a reaction as complex as free-radical polymerisation, which involves many large molecules, is too much for current systems. As such, one of the challenges facing scientists working in the emerging field of computer-aided chemical modelling and design is to find ways of maximising the accuracy of their simulations without exceeding the capacity of current technology.

Professor Michelle Coote is Head of the Computer Aided Chemical Design research group at the Australian National University in Canberra. A member of the Australian Research Council's (ARC)'s Centre of Excellence for Electromaterials Science and Fellow of the Australian Academy of Science, Coote has already been universally recognised for her outstanding work in this field. Now her attentions are focused on getting more out of quantum chemical calculations, and applying their high-powered calculations to the pressing issues faced by industry. Working alongside both industrial partners and experimental collaborators, her team is dedicated to theory, but they are also making distinct practical impacts.

MOLECULAR MINIMALISM

In order to deal more effectively with large chemical reactions involving big molecules, the Canberra scientists create small models, involving only a few atoms that have the mechanistic and kinetic profile of the target reaction. This may sound like an overly reductive way to try and achieve accurate results, but as Coote explains: "Usually, the functional groups within molecules only influence chemical reactivity over a relatively short range". Therefore, beyond a certain radius from the reaction, the atoms present in the structure cease to have an impact – and can effectively be discarded from the simulation.

The Australian researchers are capable of making accurate predictions of the kinetic and thermodynamic properties of a wide range of chemical processes

One focus of Coote's work has been to find exactly how large that radius is. Her studies suggest that modelling functional groups within six to eight bonds of the reaction centre is often sufficient – but in some instances, where reaction entropy and electrostatic effects contribute to the reaction over longer ranges, these effects too must be taken into account. Relying on this minimalist approach, Coote and her collaborators can reduce a system composed of many thousands of atoms to only the 50 or so directly involved. Further calculation is saved by

INTELLIGENCE

COMPUTER-AIDED CHEMICAL DESIGN

OBJECTIVES

To use theory to clarify the mechanisms of chemical processes and design novel reagents for manipulating their outcome. Design targets include stereocontrol agents for free-radical polymerisation, pH-switchable radical protecting groups for polymerisation and synthesis, self-healing polymers with tuned debonding properties and polymers with improved thermal and photostability

KEY COLLABORATORS

Professor Christopher Barner-Kowollik, Karlsruhe Institute of Technology, Germany

Professor Stephen Blanksby, Queensland University of Technology, Australia

Professor Krzysztof Matyjaszewski, Carnegie-Mellon University, USA

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MICHELLE COOTE is a graduate of the University of New South Wales, where she studied industrial chemistry, followed by a PhD in polymer chemistry (2000). After her postdoctoral work in polymer physics at the University of Durham, UK, she joined the Research School of Chemistry, Australian National University (ANU) in 2001 and specialised in computational chemistry. Coote established the Computer Aided Chemical Design group in 2004, and became the first female Professor of Chemistry at ANU in 2011.

combining high- and low-level calculations on successively larger portions of the reaction.

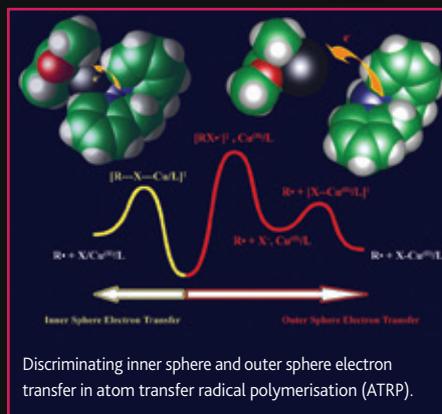
POLYMERIC PROGRESS

Using these strategies and with the help of collaborators, the Australian researchers are now capable of making accurate predictions of the kinetic and thermodynamic properties of a wide range of chemical processes, even succeeding in simulating controlled radical polymerisation from first principles. Designing novel reagents to help control the crucial qualities of free-radical polymer products is a goal that Coote describes as a holy grail in this field, but this quantum modelling can be turned to many purposes, since it offers a window into the characteristics of diverse reactions.

The Canberra group has used its computer-guided approach to investigate many forms of radical polymerisation. Using theory, they distinguished between inner- and outer-sphere electron transfer mechanisms in atom transfer radical polymerisation (ATRP), one of the most industrially successful methods for controlling radical polymerisation. In nitroxide-mediated polymerisation (NMP), they identified exactly which side reactions accompanied the process, and their studies on reversible addition fragmentation chain transfer polymerisation (RAFT), have uncovered the reasons behind reduced reaction rates. Furthermore, the team has also been active in designing new chemicals in order to significantly improve them.

THE NEXT STEP

The industrial implications of Coote's latest project, however, could be even greater. The chemists are currently searching for potential industry collaborators to help them develop new control agents designed for free-radical polymerisation that allow radicals to be switched on and off using pH. Although NMP, RAFT and ATRP are fairly effective, they each suffer disadvantages; ATRP reactions require transition metal catalysts, and RAFT involves control agents that cause colour and odour problems in the product. NMP does not suffer from these problems but instead requires high temperatures that add to its cost and limits its scope. The new pH-switching



technology developed by Coote would not only enable this temperature to be lowered, but would allow the process to be switched on and off at will, suggesting the possibility of sequence control and wider applications in natural product synthesis and self-healing materials.

By introducing negatively-charged functional groups into a chemical reaction, the scientists found that free-radicals could be made so stable that they violated the Aufbau configuration of electrons; their unpaired electron retreated from the outer shell to an inner, lower-energy orbit. This makes the previously reactive radical less so; removing the negatively-charged group caused the radical to revert to its original state, demonstrating that the process is reversible. Using pH and electrical field changes, which can alter the molecule in question and reverse the effect, the Australian researchers can direct these crucial chemical reactions – and they are now hoping to develop this into various synthetic applications.

INDUSTRIAL EFFICIENCY

This novel discovery could revolutionise the industrial radical polymerisation process, greatly reducing the need for costly catalysts and temperature conditions. What is more, it will allow for the fine control of polymer product qualities that is currently lacking in the production process. One way or another, the work being performed by Coote and her team is sure to generate a reaction.



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