



The future of chemistry

Chemistry is a very old discipline, with references to chemical transformations and debate about the nature of matter dating back to the times of the ancient Egyptians and Greeks. Modern chemistry began to emerge from alchemy in the seventeenth and eighteenth centuries, thanks to scholars such as Boyle and Lavoisier, leading to rapid advances in the following two centuries. In this feature, eight leading chemists with a broad spectrum of interests look to the future and share their vision for how their own fields may develop in the coming years. Even though research is increasingly interdisciplinary, the articles are roughly divided into traditional areas of chemistry. It is interesting to note, however, the key themes that occur in more than one article, including energy and sustainable chemistry. The chemical tools used to investigate biology — and the analytical tools chemists themselves use — are discussed, as well as the synergy between experiment and theory. Structure and bonding are at the core of the discipline, especially inorganic chemistry, whereas using weaker intermolecular forces to assemble supermolecules is a field with much still to explore. To begin, the central place of synthesis in chemistry is emphasized and extended to chemistry's place in science.

Synthesizing our future

Chemistry has a central role in science, and synthesis has a central role in chemistry. **Ryoji Noyori** from Nagoya University considers where synthetic chemists should focus their efforts.

Chemistry attempts both to understand the structures and characteristics of substances in minute details at the atomic and molecular levels, and to create new compounds with desirable properties and functions. One clear direction, both now and in the future, of this core science is to merge with other fields to produce more interdisciplinary science. In view of its significance, chemistry demands the highest level of scientific creativity and insight to explore its limitless possibilities.

With the characteristics described above, chemistry has rapidly expanded into the field of life sciences, as prophesized by James Watson (the 1962 Nobel Laureate for Physiology or Medicine) when he said “Life is simply a matter of chemistry.” When DNA was found to have a double-helical structure in 1953, chemistry really began to enter the core region of life sciences. The decoding of the human genome in 2003 led to a new world of chemical science. Thanks to advanced technologies and the diligent work of scientists in many fields, we are now able to elucidate the precise atomic-level structures of large

biomolecules such as DNA, RNA, proteins and polysaccharides.

Consequently, the focus of much chemical research has been moving from structure to function. As dynamic interactions between large biopolymers and small organic molecules often control the processes in living organisms, it seems certain that scientists will soon be able to elucidate the chemical mechanisms of cell functions and perhaps even of human thought and memory. We still have few solutions to the problem of creating peaceful human existence, but furthering our understanding of precise biological mechanisms through chemical biology and chemical genomics aided by advanced biomolecular imaging technologies will lead to the discovery of rational and more effective drugs in the post-genome era.

Although the properties of molecules and their assemblies remain unpredictable solely from their constituent elements, the possibilities for atomic and molecular manipulation are unlimited. Chemical synthesis provides a logical basis for the biosciences and materials sciences, and

their technological applications. Synthetic chemistry enables the flexible manipulations of elements — we can create value-added substances from abundant natural resources such as oil, coal and biomass. In principle, we can create molecules that have all kinds of properties at will. In view of the very nature of chemistry, its integration with other research fields will have enormous scientific and technological impacts.

Chemical synthesis has now reached an extraordinary level of sophistication, but there is vast room for improvement.

Looking at the course of human history, we see that man-made substances and materials have played a significant part in determining the quality of life. Although chemical synthesis has now reached an extraordinary level of sophistication, there is still vast room for improvement. Chemical



synthesis must pursue ‘practical elegance’¹ — that is, it must be logically elegant but must at the same time lead to practical applications. Many of the stoichiometric reactions used at present, although useful, can and should be replaced by more efficient catalytic processes.

Catalysis has been, and will remain, one of the most important research subjects, because this is the only rational means of producing useful compounds in an economical, energy-saving and environmentally benign way. According to a promotional brochure from the renowned German chemical company BASF, more than 80% of globally produced chemicals are made using catalytic processes. The importance of efficient heterogeneous, homogeneous and biological catalysts² is continually increasing. Practical catalysts must enable reactions that are rapid, capable of being scaled up, and selective in the products formed. Molecular catalysts displaying chiral efficiency that rivals or exceeds that of enzymes are highly desirable^{3–5}.

At the same time, industry demands the development of thermally stable, salt-, poison- and acid/base-resistant synthetic enzymes, because naturally existing enzymes are not robust. Catalysis is thus critical to the production of commodity chemicals and also new substances in research laboratories. In providing a path of

lower activation energy, however, it does not improve the ability to conduct endothermic processes, which require the investment of extra energy or the use of special product-separation technology to shift chemical equilibria to favour the formation of a desired product.

There are many reactions that do not work under thermal conditions. To enhance the power of synthetic chemistry, photosynthetic catalysis enabling otherwise energetically forbidden transformations needs to be explored in greater depth. Similarly, current step-by-step organic syntheses must be a combination of all thermodynamically downhill reactions, limiting the overall efficacy. Therefore, cascade syntheses⁶, or those that combine multiple components in a single step⁷, are particularly appealing. An intricately designed device that can integrate multiple catalysts along with suitable cofactors to achieve this without the necessity of human intervention is a worthy goal.

Ideally, we should aim at synthesizing target compounds with a 100% yield and 100% selectivity and avoid the production of waste. This process must be economical, safe, resource-efficient, energy-efficient and environmentally benign. In this regard, the atom economy⁸ and the E-factor⁹ should be taken into account. The 3Rs (reduction, recycling and reuse) of resources are particularly important.

Such ‘green chemistry’¹⁰ is creative and brings about prosperity, and at the same time takes responsibility for society at large. Any efficient chemical processes must also be socially acceptable. Green chemistry is not a mere catchphrase. It is an indispensable principle of chemical research that will sustain our civilized society in the twenty-first century and further into the future. Green chemistry must therefore be promoted and supported by the scientific community as well as by governments, industry, and all other sectors of society.

Science is destined to be more closely involved with society in this century. It should be no surprise that ‘Chemistry: the key to our future’ is the slogan of the 2010 Chemistry Olympiad, to be held in Tokyo. In contrast, uncontrolled, excessive economic activity based on science and technology has brought with it a range of global issues. Scientists’ efforts should be directed towards solving a range of existing or predicted social and global issues associated with energy, materials, the environment, natural disasters, water, food and health. Chemists have an immense responsibility to tackle these problems; however, the prevalent over-specialization in science tends to make it difficult to find solutions because there are usually multiple causes. To remedy this situation, we need a more broadly based science education, which will better equip future chemists to tackle the issues outlined above.

Science is, in principle, objective. But it is human intelligence and endeavour that discover and create scientific knowledge. The scientific world should be borderless; scientists from both advanced and emerging nations — with different backgrounds and values — must cooperate for the survival of our species within the confines of our planet. This is the greatest challenge facing chemists in conducting their research. □

*Ryoji Noyori is in the Department of Chemistry and Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan, and is President of RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.
e-mail: noyori@riken.jp*

References

1. Noyori, R. *Chem. Commun.* 1807–1811 (2005).
2. Schmid, A. *et al. Nature* **409**, 258–268 (2001).
3. Knowles, W. S. *Angew. Chem. Int. Ed.* **41**, 1998–2007 (2002).
4. Noyori, R. *Angew. Chem. Int. Ed.* **41**, 2008–2022 (2002).
5. Sharpless, K. B. *Angew. Chem. Int. Ed.*, **41**, 2024–2032 (2002).
6. Nicolau, K. C., Edmonds, D. J. & Bulger, P. G. *Angew. Chem. Int. Ed.* **45**, 7134–7186 (2006).
7. Dömling, A. & Ugi, I. *Angew. Chem. Int. Ed.* **39**, 3168–3210 (2000).
8. Trost, B. M. *Science* **254**, 1471–1477 (1991).
9. Sheldon, R. A. *Green Chem.* **9**, 1273–1283 (2007).
10. Anastas, P. & Warner, J. *Green Chemistry: Theory and Practice* (Oxford Univ. Press, 1998).

Powering the planet with solar fuel

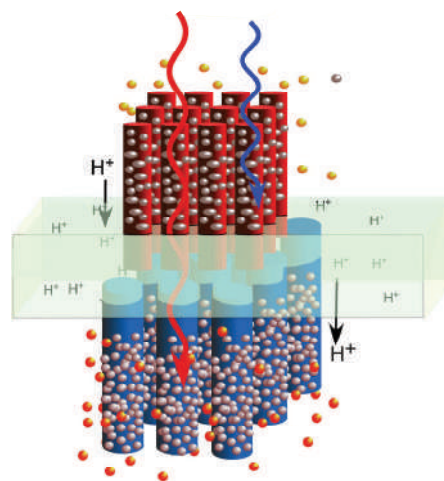
With energy swiftly rising to the top of the world's agenda, **Harry B. Gray** at the California Institute of Technology looks at how chemistry can help to harness the power of the Sun to meet the world's energy needs.

One of the grand challenges of twenty-first century chemistry is to convert abundant energy-poor molecules to energy-rich molecules using sunlight as the energy source. We need to replace fossil fuels with solar fuels such as hydrogen from water, or methanol from water and carbon dioxide. Solar fuels could be used round the clock, as the chemical energy stored during the day can be converted to mechanical or electrical power both day and night.

Viable renewable energy systems will require chemical catalysts that are far superior to any we have now. We must have catalysts made from dirt-cheap, Earth-abundant materials. When we say dirt-cheap, we mean that quite literally. Platinum is a wonderful and versatile catalyst, but there isn't enough of it on the planet to meet our energy needs (and we must save some for jewellery and best-selling albums!). Our catalysts must not only be cheap, but they must also last for years. That is a very tall order.

Long ago, nature figured out how to use abundant metallic elements in combination with proteins to activate small molecules. However, the organic frameworks of these biological molecules are readily degraded by oxidative and other chemical processes, greatly limiting their lifetimes. Nature copes with limited lifetimes — a living system can rebuild the key components it needs — but we must find other ways to deal with the problem. We and many other investigators have attempted to construct functional mimics of enzyme active sites, but one lesson we have learnt after much hard work is that these special metalcentres perform well only when they are embedded in their folded protein cages¹. The good news is that there is much activity in the field at present; indeed, we have every reason to believe that biological inorganic chemists will soon be able to design and construct bioinspired materials that will efficiently catalyse water oxidation and reduction.

What about pure inorganic materials? Rust and fool's gold could be an ideal catalyst pair were it not for lattice defects that cause photoinduced electrons and holes to recombine before they can be used productively. But any system that might be workable on the scale we need will probably use a robust metal



A solar fuel cell. The blue portion of sunlight is absorbed by the metal oxide anode (red), where it oxidizes water to release protons. The red portion passes through to be absorbed by the silicon nanorod cathode (blue), which combines these protons with electrons to make hydrogen for fuel. The membrane (light blue) must be permeable to the generated protons and conduct electrons between the two electrodes. The spheres in the region of the anode represent oxygen molecules; spheres in the region of the cathode represent hydrogen molecules. The hydrogen to oxygen ratio is 2:1.

oxide — literally a rock — to oxidize water to oxygen²; and any of a number of closely related materials, including metal sulfides³, to reduce water to hydrogen.

Our Solar Fuel Center for Chemical Innovation (CCISolar)⁴ involves many experimentalists and theorists in an interdisciplinary effort with the goal of building an assembly of nanorod catalysts to split water. The device that we envisage features nanorod anodes and cathodes of dissimilar materials embedded in a membrane to harvest sunlight (pictured). Blue light is absorbed on the anode side of the membrane, interacting with a catalyst to oxidize water and release protons. Red light is absorbed on the cathode side, where protons combine with electrons to make hydrogen. CCISolar researchers have made good progress in several areas, especially on the development of nanorod array photoelectrodes⁵, catalysts for water oxidation⁶ and reduction⁷, and bioinspired

photosystems⁸. However, we and other investigators worldwide have a long way to go before an efficient water splitter made from Earth-abundant materials is ready for deployment on a large scale.

We must solve many fundamental chemical problems before we can claim victory. But if we stay the course, we could have working solar-fuel plants before 2050. Facilities situated in coastal metropolitan areas could use sea water as the source of hydrogen and oxygen. The hydrogen produced from water splitting could then be run through adjoining fuel-cell electric power plants where the pure water by-product could go directly into the municipal water system. Imagine meeting local energy and clean water needs at the same time!

We have an even grander vision. Some time in the future we will be able to put three components of our atmosphere — carbon dioxide, nitrogen and oxygen — along with sea water into solar reactors to make not only fuels, electricity and pure water, but polymers, food and almost everything else we need. We have been taking from nature since the beginning of time, consuming the oil, gas and coal given to us by thousands of millions of years of photosynthesis. This is the century in human history when we will start paying back with the capital generated through fundamental research in chemistry. □

Harry B. Gray is in the Division of Chemistry and Chemical Engineering at the California Institute of Technology, Pasadena, California 91125, USA. e-mail: hbgray@caltech.edu

Acknowledgements

I would like to thank my colleagues Jay R. Winkler, Bruce S. Brunschwig and Douglas L. Smith for their contributions to this article.

References

- Gray, H. B., Malmstrom, B. G. & Williams, R. J. P. *J. Biol. Inorg. Chem.* **5**, 551–559 (2000).
- Harriman, A., Pickering, I. J., Thomas, J. M. & Christensen, P. A. *J. Chem. Soc., Faraday Trans. I* **84**, 2795–2806 (1988).
- Jaramillo, T. F. *et al. Science* **317**, 100–102 (2007).
- <http://www.ccisolar.caltech.edu>
- Spurgeon, J. M., Atwater, H. A. & Lewis, N. S. *J. Phys. Chem. C* **112**, 6186–6193 (2008).
- Kanan, M. W. & Nocera, D. G. *Science* **321**, 1072–1075 (2008).
- Hu, X. L., Brunschwig, B. S. & Peters, J. C. *J. Am. Chem. Soc.* **129**, 8988–8998 (2007).
- Shih, C. *et al. Science* **320**, 1760–1762 (2008).

Experiment and theory in harmony

Mark A. Johnson at Yale University discusses how the two sides of physical chemistry have necessarily developed together, and looks at how their synergy dictates the direction of contemporary research.

Physical chemists seek to anchor the empirical rules of chemistry to the laws of physics, and thus provide secure concepts to explain the trends seen in reactivity and molecular structure. This activity began, in earnest, over a hundred years ago with the development of chemical thermodynamics by pioneers such as J. Willard Gibbs and Ludwig Boltzmann. They revealed the nature of equilibrium and the factors that control the direction of spontaneous change. With the discovery of quantum mechanics, Paul Dirac announced¹ that the underlying laws of chemistry were completely known, the only hitch being that the resulting equations were too difficult to solve. Almost a century later, even with the powerful computers and sophisticated analytical methods now at our disposal, empiricism retains its place today as the skill most valued by practising chemists.

Achieving Dirac's 'bottom-up' understanding of chemistry has become a celebration as well as an institutionalization of the interplay between theory and experiment at the core of physical chemistry. Experimentalists create new types of instrument that, with each generation, have given increasingly precise observations of chemical processes — culminating in the ability to observe individual molecules² and to make measurements on the timescales of molecular vibration³. Extracting molecular-level information from these measurements requires new theories, forcing theorists to 'push the envelope' of computation and simulation. Equally, new concepts empower experimentalists to form strategies for measuring properties that were once thought beyond our reach. A recurrent theme in contemporary physical chemistry is a convergence of experimental and theoretical methods towards sufficiently complex model systems. By this I mean systems that not only reproduce 'real' chemical processes but also do so in a fashion that reveals molecular-level, quantum-mechanically consistent pictures that are not greatly obscured by either thermal or ensemble averaging.

Much of this activity involves applying discoveries made in atomic physics, condensed-matter physics and interfacial physics as general tools with which to explore the complex (and messy!) chemical environment. It is important to acknowledge that the timescale required for



Equations such as Schrödinger's famous contribution to quantum mechanics underpin much of physical chemistry.

such endeavours often matches the scope of the challenge. For example, decades of work were needed to integrate many-body quantum mechanics and spectroscopy to allow a general and predictive understanding of both the covalent chemical bond and more subtle intermolecular forces.

In light of the long list of recent Nobel prizes recognizing achievements in this discipline, it is natural to ponder what 'grand challenges' or major unanswered questions dictate contemporary work in the field. This raises a fascinating and important aspect of physical chemistry's tradition, perhaps best articulated by G. N. Lewis's statement that its main concern is "anything interesting"⁴. On an abstract level, a new class of conceptual tools is needed to understand how intermolecular interactions underlie the assembly of molecules into larger objects with designed shapes and functions. Can this be achieved by chemically altering the microscopic building blocks and growth conditions? Can this be done with complex, interacting subsystems that provide feedback and error checking? How do we theoretically treat the transient excited states that are crucial to the performance of electronic devices constructed on molecular dimensions?

Rather than further engage the risky proposition of predicting future developments, I think it is useful to share some observations on how the nature of our enterprise changes as the tools we develop deliver increasingly clear microscopic pictures of chemical processes. By necessity, I will focus on the evolution of spectroscopy and kinetics, with which I am most familiar, in the hope that this experience reflects at least some aspects that span the many subfields within this diverse discipline. Thus, this is not intended to be a defining statement but rather an effort to convey a sense of trajectory — speaking directly to the notion of a 'grand challenge'. In a sense, making good on Dirac's prediction is our challenge.

Fledgling attempts spanning the 1930s and 1940s established that neither the experimental nor the theoretical tools available were remotely capable of handling even the simplest of chemical processes — such as a gas-phase reaction between two diatomic molecules. Improvements occurred over the period from the 1960s to the 1990s, during which laser spectroscopy was combined with molecular beam methods to essentially eliminate averaging⁵. This activity initially suffered from the severe limitation that the chemistry amenable to study with the developing experimental tools (for example, metal atom oxidation) was most challenging for theory, whereas the small systems (for example, H + H₂) that could be handled were too difficult to measure with linear spectroscopic methods of analysis. As a result, many physical chemists seemed obsessed with model problems that were only remotely connected to solving a practical problem.

Gradually, more general tools were refined that were capable of performing quantum-state-resolved measurements not only on small molecules⁶ but also on clusters that surrounded a reactive intermediate with a precisely determined number of solvent molecules⁷. Improved theoretical treatments then emerged that took advantage of the parallel advances in computational methods for electronic structure^{8,9}. Almost 50 years after the first crossed molecular beam experiment, we can easily envisage generating replicas

of highly complex, solvent-mediated reactive encounters — that can be photochemically or thermally triggered — and spectroscopically observing the ensuing reaction sequence in exquisite detail.

The ‘bottom-up’ approach is becoming sufficiently mature to be applied increasingly to specific, ongoing research in synthetic, biological and materials chemistry needed to meet the overarching scientific challenge of achieving sustainability and developing alternative sources of energy. With the overall perspective of contributing accurate, experimentally vetted, molecular-level

pictures of reactive pathways and relevant structures, physical chemists are in an excellent position to engage chemistry in all of its complexity. Looking ahead, the only thing one can guarantee is that this interdisciplinary effort will be at the foundation of the molecular sciences, even as traditional dividing lines inevitably and correctly become obscured or obsolete. □

Mark A. Johnson is in the Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107, USA.
e-mail: mark.johnson@yale.edu

References

1. Dirac, P. A. M. *Proc. R. Soc. A* **123**, 714–733 (1929).
2. Moerner, W. E. & Orrit, M. *Science* **283**, 1670–1676 (1999).
3. Gruebele, M. & Zewail, A. H. *Phys. Today* **43**, 24–33 (1990).
4. Lewis, E. S. *A Biography of Distinguished Scientist Gilbert Newton Lewis* (Edward Mellen Press, 1998).
5. Smalley, R. E., Wharton, L. & Levy, D. H. *Acc. Chem. Res.* **10**, 139–145 (1977).
6. Kitsopoulos, T. N., Buntine, M. A., Baldwin, D. P., Zare, R. N. & Chandler, D. W. *Science* **260**, 1605–1610 (1993).
7. Castleman, A. W. Jr & Jena, P. *Proc. Natl Acad. Sci. USA* **103**, 10552–10553 (2006).
8. Hehre, W. J., Stewart, R. F. & Pople, J. A. *J. Chem. Phys.* **51**, 2657–2664 (1969).
9. Kohn, W. & Sham, L. J. *Phys. Rev.* **140**, 1133–1138 (1965).

Interrogating biology with a chemical lexicon

Understanding the mysteries of life has always been a driving force in scientific research; **Barbara Imperiali** from the Massachusetts Institute of Technology reflects on the infinite opportunities for chemists at the biology interface.

The details of innumerable complex and interwoven biochemical pathways from living systems are being deciphered and described at an exceptional level through a host of biological, biochemical and physical approaches. Such studies provide rich information concerning the high specificity of cellular processes and the dynamic interactions that define them. For example, using molecular biology approaches, genes can be manipulated or controlled to interrogate function. Meanwhile, specific cellular components can be monitored and tracked in fixed or live cells by using antibody-based methods or by imaging targets that are tagged with natively fluorescent proteins. Alternatively, functional systems may be reconstituted *in vitro*, thereby providing simpler and more tractable systems for detailed investigations.

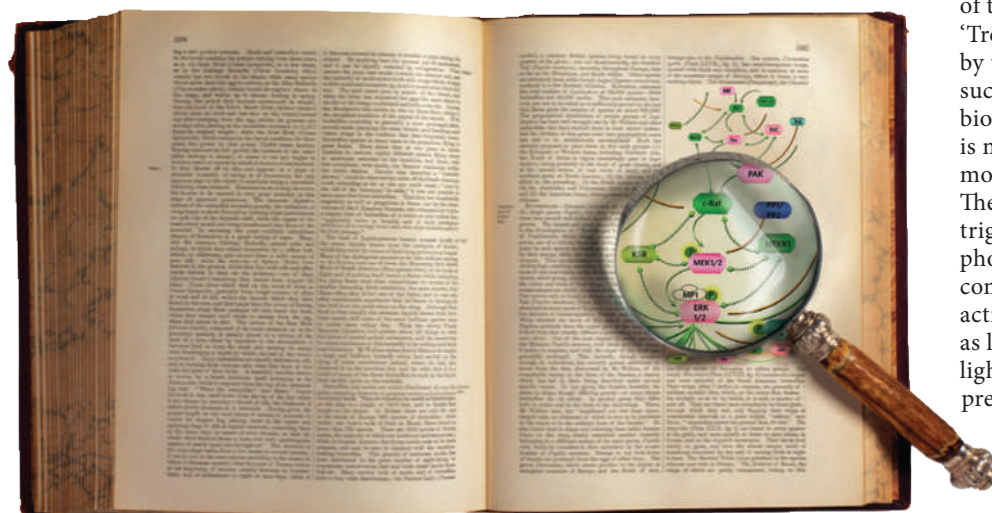
Against this astounding backdrop of knowledge, the prevailing question is: “What can chemically driven strategies do to help navigate through this complex universe and provide new and complementary insight into the fundamental processes of life?” Major challenges to understanding the molecular basis of how living systems function, and the related chemical processes, centre on temporal dynamics, spatial resolution and pleiotropic effects — for example, when a single signal triggers multiple events.

Living systems are highly compartmentalized and in constant flux. A single cell is not a single vessel representing a static homogeneous solution of macromolecules and metabolites; similarly, a multicellular organism does not comprise a set of identical cells. Biochemical processes are spatially defined and segregated by membranes

and through macromolecular interactions. Many of the biological methods for studying cellular processes, although incredibly powerful, have limitations when it comes to temporal resolution. Monitoring the molecular changes in cells that occur on timescales of minutes is not attainable with approaches that require a longer time for the build-up of a protein, the generation of a small-molecule messenger or the removal of existing regulators.

Chemically inspired approaches, including the application of light-activated uncaging or switching, afford a valuable dimension in temporal and spatial control. They can be used to enable the introduction of masked and inert analogues of bioactive species that can be liberated at will through the application of the appropriate light energy. This ‘Trojan horse’ strategy has been applied by using a variety of bioactive species such as metal ions, small molecules and bioactive peptides and proteins^{1,2}. There is much for the chemist to do to assemble molecules that exploit light activation. The development of new caging and triggering groups that have advantageous photophysical properties, and that are compatible with living systems, is an active area with expanding opportunities as laser-based methods for delivering light with high spatial resolution and precise energies become more accessible.

In addition, new methods for the incorporation of caged amino acids into native proteins, for example through protein semisynthesis³ and



engineered translation machinery⁴, greatly expand the potential for their application in exciting biological studies.

Living systems are highly dynamic and by necessity are exquisitely synchronized and synergized. A vital area of current activity is the development of fluorescence-based sensors for quantifying enzyme activities and analyte concentrations in living systems in real time. In this context, strategies that enable the continuous monitoring of specific targets are being developed broadly in the

What can we do to help navigate the complex biological universe?

community and are finding widespread use⁵. However, there is a need for a variety of complementary strategies; for example, particular analyses may benefit from the use of genetically encoded sensors that are based on fluorescent proteins⁶, but others may necessitate the more robust signals of chemically tailored synthetic fluorophores. In addition to sensing, fluorescent approaches are also essential for investigating the dynamics of protein trafficking and protein–protein interactions. Once again, chemical approaches with cleverly orchestrated bio-orthogonal

(non-native, non-perturbing) labelling strategies enable the application of synthetic fluorophores⁷.

Many of the molecular and macromolecular participants in living systems are pleiotropic. A single signal can trigger multiple events, and a single catalyst may act on more than one substrate and in more than one pathway. The prototypical example of this phenomenon is in the protein kinase field, in which a single kinase may phosphorylate numerous target sites using adenosine triphosphate (ATP) as the common phosphoryl transfer agent. A powerful, and uniquely chemical, strategy for unravelling the specific actions of single kinases has been conceived and broadly implemented by Shokat⁸. It involves a two-pronged approach comprising the mutation of a single kinase such that it can accept only an alternative ATP analogue as co-substrate and be uniquely sensitive to chemically tailored inhibitors. This approach provides the added ability to chemically knock out genes that would be otherwise impossible to study with molecular biology techniques, due to *in utero* lethality. The uniquely reactive kinases and their cognate inhibitors are being used to derive important new insight into signalling pathways and their roles in normal cellular function and disease.

Ultimately the chemical tools that are developed must work robustly ‘in the field’

and be useful for providing new knowledge. Indeed, the taste that researchers have acquired for pre-packaged kits with bullet-proof ‘how to’ instructions cannot have escaped any of us. However, most good things take time and we must remind the community that chemistry, like a fine wine, may take many years to mature. Indeed, the solid-phase chemical synthesis of a peptide was first disclosed in 1963, in an article⁹ that described a single hydrophobic tetrapeptide with no known biological activity; now, all we have to do is pick up the phone and order the sequence we need! □

Barbara Imperiali is in the Department of Chemistry and the Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA. e-mail: imper@mit.edu

References

- Lawrence, D. S. *Curr. Opin. Chem. Biol.* **9**, 570–575 (2005).
- Rothman, D. M., Shults, M. D. & Imperiali, B. *Trends Cell Biol.* **15**, 502–510 (2005).
- Pellois, J.-P. & Muir, T. W. *Curr. Opin. Chem. Biol.* **10**, 487–491 (2006).
- Xie, J. & Schultz, P. G. *Curr. Opin. Chem. Biol.* **9**, 548–554 (2005).
- Lavis, L. D. & Raines, R. T. *ACS Chem. Biol.* **3**, 142–155 (2008).
- Giepmans, B. N. G., Adama, S. R., Ellisman, M. H. & Tsien, R. Y. *Science* **312**, 217–224 (2006).
- Baskin, J. M. & Bertozzi, C. R. *QSAR Comb. Sci.* **26**, 1211–1219 (2007).
- Shogren-Knaak, M. A., Alaimo, P. J. & Shokat, K. M. *Annu. Rev. Cell Dev. Biol.* **17**, 405–433 (2001).
- Merrifield, R. B. *J. Am. Chem. Soc.* **85**, 2149–2154 (1963).

Weighing up the future of scientific tools

The foundations of science are built on the ability to make sensitive, precise measurements. Gary M. Hieftje from Indiana University, Bloomington, considers how analytical instruments and methods are being developed to meet tomorrow's needs.

The nineteenth-century chemist Sir Humphry Davy once said, “Nothing begets good science like the development of a good instrument.” If that statement was true in Davy’s day, it is all the more so now. Modern science, indeed much of the future, will be driven and enabled by the scientific instruments that are just now emerging. Although many of these innovations will be derived from other areas of science and engineering, in the field of chemistry it is analytical chemistry that focuses most strongly on the development of instruments and techniques.

In this brief overview, several current and projected innovations that seem likely to influence the pursuit of chemistry and other areas of science are outlined. Admittedly, as one would expect, the selections are influenced by personal bias, and a much

larger initial compilation has been pared down brutally; other individuals might have chosen differently. The selected topics fall into several broad categories, most not surprisingly related to two areas of rapid scientific growth — bioscience and nanoscience. Others are related to the analysis of ‘things as they are’, or to enhancing sensitivity, precision, accuracy, simplicity or cost.

It is becoming imperative to characterize the contents of individual biological cells or nanostructures; in particular, cells contain the biological machinery that dictates health or disease, normal or impaired development, and proper differentiation. Moreover, it is becoming clear that one cell, although nominally identical to another, has unique content that defines its fate. A number of new chemical imaging tools are being explored to meet these challenges. For example, near-

field or tip-enhanced laser ablation (or desorption) has been shown capable of removing material from 30-nm sections of a specimen, with the resulting material being used for analysis by any of a number of methods — as reported by R. E. Russo at the 2008 Annual Meeting of the Federation of Analytical Chemistry and Spectroscopy Studies¹. Similarly, tip-enhanced Raman spectrometry, exploiting both resonance and surface enhancement, can be used to extract, in a non-destructive manner, chemical information from nanometre-scale areas of a sample².

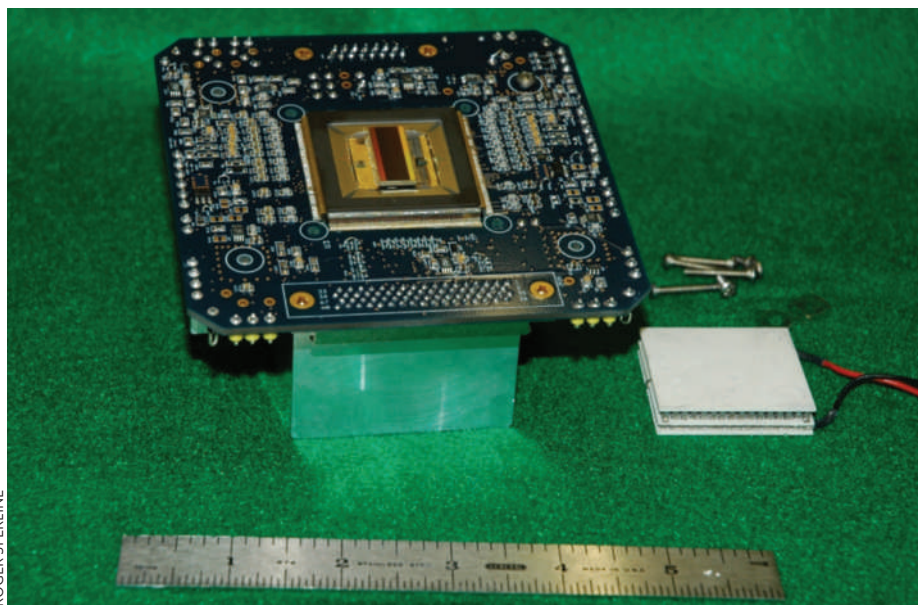
Moving down from the nanoscale into an even smaller world, it has been possible for some time to measure individual atoms or molecules. However, what was once an

analytical novelty is now becoming a tool for removing the ensemble-averaging effect of large collections of species. It is now clear that one enzyme molecule, for example, might not behave as another, and that the actions of a large group of molecules is only an approximation of what might be expected from an individual³. Similarly, the ability to measure single atoms in a solid, and to probe their interactions, promises insight into the behaviour of materials and could serve to guide the design of new ones.

The relatively new, and very active, field of metallomics considers the presence and function of metals and metalloids in biological systems and has provided a large impetus for the development of new analytical methods. Many new scientific tools are needed because of the unique challenges in this area⁴. For example, the concentrations of metals in living systems span a range as large as 14 orders of magnitude (10^{14}). Moreover, metals might be bound to proteins or other species, or they might be found free; indeed, as much as one-third of all proteins are known to contain, or be associated with, metals. In one new method, a two-dimensional gel electropherogram is used to produce a western blot (a surface image of the proteins in each spot), and the blot is analysed by means of elemental emission from a pulsed radiofrequency glow discharge. A monochromatic image of the emission pattern then reveals, simultaneously, which of the separated proteins contains a metal, which metals are there, and what the stoichiometry of the association is⁵.

It is becoming imperative to characterize the contents of individual biological cells or nanostructures.

New electronic, ion-optical and measurement developments are in the process of transforming traditional analytical tools such as high-performance mass spectrometry, NMR spectroscopy and X-ray methods. A class of truly simultaneous multichannel detectors is emerging for mass spectrometry that will offer the same advantages that multichannel detectors such as charge-coupled devices have imparted to optical measurements. In recent work presented at the 2009 European Winter Conference on Plasma Spectrochemistry⁶, we have shown that the largest of these detector arrays now has 1,696 channels and can integrate an incoming ion flux directly, provide a dynamic range of over 10^8 , be read either destructively or non-destructively, and measure fewer than 100 ions in each channel



ROGER SPERLINE

The new 1,696-channel ion detector for mass spectrometry or ion-mobility spectrometry, recently presented at the European Winter Conference on Plasma Spectrochemistry⁶ in Austria.

(pictured). The same devices might be useful in other areas of ion measurement, such as ion-mobility spectrometry.

Staying with mass analysis, the emerging area of ambient mass spectrometry seeks to determine constituents at or on the surface of a sample, in the open atmosphere, and without any sample preparation. There are several new ion sources that have been designed for this purpose, including DART (direct analysis in real time), DESI (desorption electrospray ionization), FAPA (flowing atmospheric-pressure afterglow), and a host of others⁷. All have individual strengths and weaknesses and seem to be best for certain kinds of samples. However, the capability they collectively offer is exciting and will no doubt find its way into a range of applications, from airport screening to forensics to clinical diagnosis.

In NMR spectroscopy, new solid-state methods are now being applied to ever-smaller sample regions, to assist in characterizing new materials. In X-ray spectrometry, both fluorescence and diffraction are benefiting from instrumental innovations. X-ray diffraction is being performed on ever-faster timescales ($\sim 10^{-6}$ s) and at a spatial level that approaches single atoms. X-ray fluorescence is being achieved with both synchrotron and conventional sources to yield information on sub-monolayer surface coverages, to give depth-resolved information and, in conjunction with tomographic reconstruction, to map the three-dimensional distribution of atoms within a solid.

Finally, droplets — which are fascinating in their own right — have recently enjoyed a renewed interest, especially for analysis. Individual droplets can contain nanolitre to femtolitre volumes of a sample solution, so they are attractive as sample vessels in fields as diverse as NMR spectroscopy and fluorimetry. They can also be used as extraction vessels to permit the pre-concentration of dissolved materials for later examination by other methods. Because of the high surface-to-volume ratio of tiny droplets, they can also provide information about interfacial effects.

Clearly, the foregoing account offers only a selective glimpse into a few new techniques and instruments that seem likely to influence future advances in chemistry. There are many others that may have significant roles and some could have an even greater impact than those discussed here. The author regrets any omissions that may seem particularly glaring and waits in anticipation to see what the future of analytical science brings. □

Gary M. Hieftje is in the Department of Chemistry, Indiana University, Bloomington, Indiana 47405, USA. e-mail: hieftje@indiana.edu

References

1. <<https://facss.org/contentmgr/showdetails.php/id/32995>>
2. Deckert-Gaudig, T., Bailo, E. & Deckert, V. *J. Biophotonics* **1**, 377–389 (2008).
3. Li, J. & Yeung, E. S. *Anal. Chem.* **80**, 8509–8513 (2008).
4. Koppenaal, D. W. & Hieftje, G. M. *J. Anal. Atomic Spectrom.* **22**, 855 (2007).
5. Gamez, G., Ray, S. J., Andrade, F. J., Webb, M. R. & Hieftje, G. M. *Anal. Chem.* **79**, 1317–1326 (2007).
6. <<http://www.winterplasmagraz.at>>
7. Shelley, J. T. et al. *J. Am. Soc. Mass Spectrom.* (in the press).

Chemistry goes green

Diminishing fossil fuel reserves, hazardous chemicals and wasteful processes have led to the emergence of 'green' technologies; James H. Clark at the University of York considers how metals, materials and organic compounds can be prepared by clean and sustainable routes.

Green chemistry emerged in the 1990s when research increasingly focused on the development of environmentally benign alternatives to hazardous chemical processes. This was prompted by a rising awareness of the costs of waste in industries, and the need for cleaner chemical manufacturing in governments. Through a combination of targeted research funding, tougher legislation and awards for best practice, the green chemistry movement quickly gained momentum and helped nurture what are now well-recognized clean technologies in process chemistry. Wasteful separations, for example, were addressed through the use of supercritical CO₂; atmospherically damaging volatile organic solvents were replaced by non-volatile ionic liquids; and heterogeneous reagents and catalysts were introduced to avoid the use of soluble reagents and other process additives that were hazardous or difficult to separate.

The importance of new metrics for measuring process greenness, championed by the pharmaceuticals industry, also became recognized. One of the earliest and most popular — the ratio of waste to product, or 'E factor' — highlights the wastefulness of many chemical processes. More recent assessments have also shown the need to consider a wider set of metrics across a product's life-cycle¹.

The legislative, economic and social drivers for change now influence all the stages of a chemical product's life-cycle.

Diminishing reserves and marked price fluctuations have been highlighted for oil — the main raw material for chemicals — but in reality the problem is much wider. Resource depletion of many key minerals and price increases for commodities affect almost all chemicals and jeopardize the survival of manufacturing in its present form. At the other end of the life-cycle, mounting pressure from the public as well as non-governmental organizations (NGOs) has led to an exponential growth in product-focused legislation (notably the European Registration, Evaluation, Authorization and Restriction of Chemical substances, or REACH) and a degree of consumer choice that is threatening the continued use of countless chemicals. These challenges can only be embraced with a combination of pure, discovery-oriented research and translational, application-focused research.

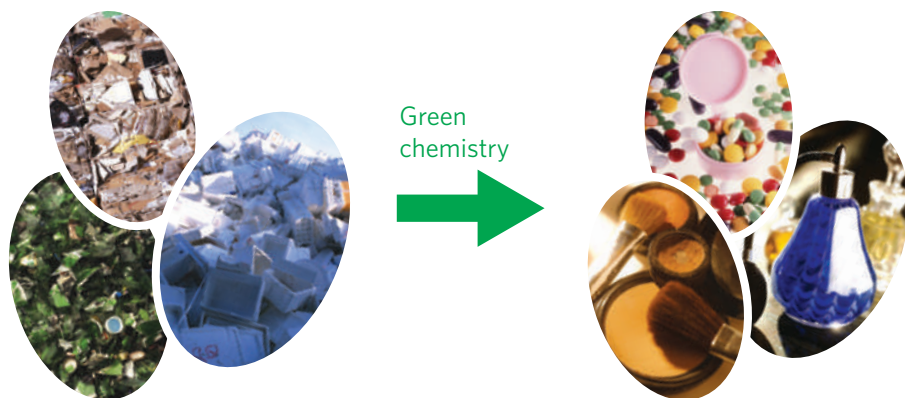
Today's waste will be tomorrow's resource.

Chemists working with biologists and engineers will learn how to make greater use of the only practical sustainable source of carbon: non-food biomass². This includes agricultural, food and forestry wastes, as well as the co-products from some large-scale processes such as biofuel manufacturing. Large volumes of consumer and industrial wastes, such as discarded electrical and electronic equipment, can

also be exploited by using the low-environmental-impact technologies developed in the 1990s. This will not only be a major step towards the creation of a new generation of green and sustainable chemicals, but will also help solve the escalating waste problems faced by modern society.

In particular, we can make more imaginative use of the extracts from biomass: cellulose, starches and chitin can act as a source of small molecules, but they could also become the building blocks of new macromolecular materials. Compounds such as ethanol, lactic acid, succinic acid and glycerol would then replace — or at least reduce our reliance on — fossil-based compounds such as ethene, propene, butadiene and benzene. The future green chemistry toolkit thus needs to be flexible and versatile as well as clean, safe and efficient.

Here the chemistry–biology and chemistry–(bio)chemical engineering interfaces are crucial: we need to develop synthetic pathways starting from the oxygenated and hydrophilic molecules produced through most current biomass conversions. That also means we cannot afford to include wasteful and costly steps before these synthetic transformations. A wider range of chemistry in water will help (and often make processes safer), as will the further development of other important synthetic strategies such as reducing processes through telescoped reactions, which combine several reactions into one process step³. At the chemistry–engineering interface⁴, catalytic membranes, intensive processing techniques and more energy-efficient reactors will also become more important. Fermentation technology will remain an important route for the decomposition of complex biomass to small molecules, but with better control of pyrolysis — through catalysis and alternative activation methods (such as microwaves) — we should also be able to develop parallel routes to different molecules, which would give us a much wider range of building blocks⁵. Finding new, sustainable and cost-effective routes to aromatics is proving to be especially difficult: we need better ways



Biomass, waste electronics and other consumer waste can be exploited as raw materials for the production of metals, materials and organic compounds through green chemistry techniques.

of opening up the structures of nature's aromatic stores, such as lignin and suberin.

The challenge for green chemistry is not just to replace undesirable chemicals such as chromates and polyhaloaromatics but also to make sure that, wherever possible, the substitutes and the chemistry used to manufacture them are green and sustainable. More research is currently needed to address the challenges that REACH and other product-focused legislation present — safer, more environmentally benign products are required in just about every commercial sector, with particular emphasis on flame retardants, plasticizers, adhesives and primers.

This new century will see a gradual transfer from a petroleum-based chemistry to a chemistry based on a wide diversity of feedstocks. Although virgin fossil-derived and mineral-derived resources will continue to be important for the foreseeable future, chemicals and materials derived from non-food biomass and from the increasing mountain of what we still refer to as 'waste' must take over: today's waste will be tomorrow's resource. Green chemistry can help in converting these feedstocks into resources through low-environmental-impact technologies, processes and methodologies. In this way we will be able to achieve the

essential goal for future generations of green and sustainable products. □

James H. Clark is at the Green Chemistry Centre, University of York, York YO10 5DD, UK.
e-mail: jhc1@york.ac.uk

References

1. Lapkin, A. & Constable, D. *Green Chemistry Metrics* (Wiley-Blackwell, 2008).
2. Clark J. H. & Deswarte, F. E. I. (eds). *Introduction to Chemicals from Biomass* (Wiley, 2008).
3. Taylor, R. J. K., Reid, M., Foot J. & Raw, S. A. *Acc. Chem. Res.* **38**, 851–869 (2005).
4. van Noorden, R. *Chemistry World* **5**, 8 (2008).
5. Bridgewater, A. V. *Chem. Eng. J.* **91**, 2–3 (2003).

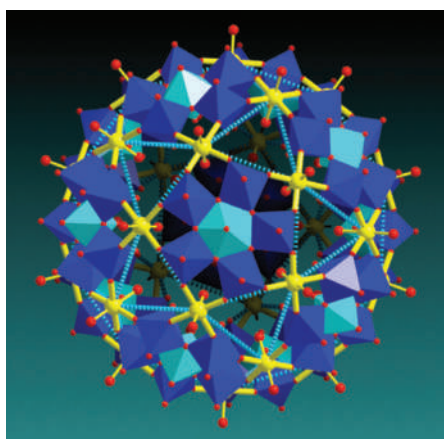
Predicting a structured future

If syntheses and structures can be more easily predicted, what will it mean for inorganic chemistry?

Achim Müller of the University of Bielefeld looks into his (quasi)crystal ball.

In a recently published essay¹, Jon McCleverty stated that “the developments in inorganic chemistry ... over the last 100 years have been awe-inspiring”. His article referred to examples such as the coordination chemistry of *s*-block elements based on macrocyclic polydentate ligands (initiating the development of supramolecular chemistry), bioinorganic chemistry (regarding the use of a variety of inorganic compounds in chemotherapy) and solid-state chemistry (leading to the discovery of high-temperature superconductivity). Most of these spectacular breakthroughs came from unexpected discoveries.

In the future, inorganic chemistry will continue to embrace materials, bioinorganic and environmental chemistry, as well as traditional areas such as catalysis. Furthermore, it will extend down to new length scales, controlling matter on the nanoscale. In my view the following three topics will be of central importance: (1) predictable syntheses in solid-state chemistry and — as the major point considered here — of nanosized multifunctional compounds/clusters, seeking to understand fully the relationship between structure and function (multifunctionality can only be realized by larger, nanosized, species²); (2) reactions under confined conditions, such as in nanopores/capsules, which is an area that might lead to fundamental discoveries, and (3) the realization of new aperiodic structures, as well as new bonding types and different reactivity paradigms. An underlying theme is in the prediction of inorganic structures. This is intrinsically difficult because of the extremely wide variety in



A missing link between the world of molecules and solids. This keplerate, $M'_{30}\{(Mo)Mo_5\}_{12}$ ($M' = Fe, Cr$) (ref. 4), is a spherical inorganic superfullerene. Its 12 $[(Mo)Mo_5O_{21}(H_2O)_6]^{6-}$ pentagonal ligands (blue polyhedra, O atoms red) are linked by 30 M' centres (yellow spheres), resulting in 20 corner-sharing M'_3 triangles like those in kagome lattices. The highlighted blue triangles form an Archimedean solid, an icosidodecahedron. Spherical periodicity is obtained because the linking of the 12 pentagons with five-fold symmetry — their centres span an icosahedron — cannot lead to translational periodicity, so the system itself resembles a quasicrystal.

structural motifs and geometries, which itself arises from the huge number of different chemical elements showing a range of bond properties and coordination numbers.

To illustrate the case of the predictable synthesis of multifunctional nanoparticles I shall consider soluble and stable spherical

metal-oxide-based nanocapsules². They have gateable pores, well-defined external surfaces and tunable internal ones; the latter can be of either an organic/hydrophobic or an inorganic/hydrophilic type and can influence the structure of encapsulated species². The capsules contain 12 metal-oxide-based pentagonal building blocks (pictured; comparable to the basic elements for spherical structures such as the C_{60} buckyball, icosahedral viruses or geodesic domes³). They can be linked by means of well-understood self-assembly processes: by either mononuclear spacers M' (such as Cr^{3+} and Fe^{3+}), leading to smaller capsules/pores⁴, or by dinuclear spacers ($Mo_2O_4^{2+}$), leading to larger ones³ (both with 120 equal metal–ligand bonds; pictured, yellow sticks). This is an example of real multifunctionality and recognizable structure–function relationships: the corner linking of the M'_3 triangles leads to magnetic frustration such as that found in kagome lattices (see ref. 4), whereas the presence of 20 gated pores with crown-ether function enables, for the larger capsules, the controlled take-up or release of alkali cations, mimicking biological transmembrane processes².

Molecules confined in nanopores react differently from those in homogeneous distributions. To study how a variety of encapsulated molecules react under the influence of different functional groups, appropriate inorganic capsules or 'nano-test-tubes' should be considered. Interestingly,

little is yet known about this, in contrast to organic chemistry, in which chemical transformations in (flexible) cages have been investigated⁵. Confined conditions can accelerate reactions — analogously to enzymes — or lead to new types of reactions altogether. A general challenge is to master energy and information on the nanoscale to create new technologies rivalling the complexity of living matter. This could be achieved, for example, through the discovery of different highly functionalized responsive species that can react specifically with their environment and self-assemble².

We now turn from discrete porous species to consider porous solids, such as metal–organic frameworks (MOFs): these materials are a promising new research area witnessing explosive growth and studied almost exclusively by inorganic chemists⁶. They have well-defined tunable cavities and surfaces, can be responsive to guests and can be orchestrated to trap, detect and even catalytically transform quite different species. Although until now MOFs have been studied mainly for storage (because of their large surface areas) and sieving, another role for them in the future could be their use as nanoreactors, allowing the production of a variety of interesting monodisperse nanoparticles⁶.

Solid-state syntheses have, until now, been assumed to be unpredictable, but even so they have led and will lead in the future to the discovery of materials with important properties and exotic phenomena. Future research in this field may initiate substantial technological advances, as well as breakthroughs in basic science. A new methodology for planning syntheses is on the way⁷, seeking to predict new targets

by computationally exploring the energy landscape above the configuration space of a given chemical system. This involves searching for global as well as local minima and ‘transferring’ the identified candidates to the thermodynamic space characterized by the respective hypersurfaces of free enthalpies; the procedure enables the successful candidate’s synthesis⁷. This could also include searching for links between structures of nanospecies and solids. For instance, the icosahedral quasicrystals mentioned in the next paragraph contain shells of atoms forming beautiful Platonic and (partly distorted) Archimedean solids⁸ such as the keplerates² (above; pictured).

One of the most exciting developments in solid-state inorganic chemistry has been the advent of aperiodic ordering, which caused a paradigmatic change. Experienced crystallographers — Linus Pauling included — argued vehemently against the proposed existence of quasicrystals. A weird and wonderful world of new phases and phenomena has since been reported. The best-studied class so far is that of the so-called Tsai-type phases⁸. These binary, stable, icosahedral quasicrystals are very interesting objects for future studies of structure–property relationships. In the wake of quasicrystals, a silent revolution has taken place regarding another class of aperiodic objects, namely incommensurately modulated phases. Some of these derive directly from the Tsai-type phases such as the modulated $\text{Ce}_{13}\text{Cd}_{58}$ (ref. 9). The extreme richness and complexity of the structural chemistry involved in these examples is astounding and unprecedented in the whole area of chemistry. We may be sure that new phenomena with possible applications

— especially related to complex surfaces — will be discovered in the field of aperiodic structures in the future.

I have discussed some classes of compounds in which interesting developments might be expected, such as solids with aperiodic ordering and confined chemistry in MOFs as well as multifunctional inorganic nanocapsules, with the potential for discovering new phenomena; I have also referred to the search for a rational design of syntheses and structures. However, chemists should always have their eyes open for interesting but unexpected phenomena that could open new avenues of research. It is also crucial to continue studying important technologies, such as the realization of artificial photosynthesis systems (particularly those for solar-driven water splitting to hydrogen), and working towards the discovery of compounds relevant for new pathways in catalysis using noble metals and oxygen (see ref. 10). □

Achim Müller is in the Faculty of Chemistry, University of Bielefeld, Universitätsstrasse 25, D-33615 Bielefeld, Germany.
e-mail: a.mueller@uni-bielefeld.de

References

1. McCleverty, J. A. *Annu. Rep. Prog. Chem. A* **100**, 3–13 (2004).
2. Proust, A., Thouvenot, R. & Gouzerh, P. *Chem. Commun.* 1837–1852 (2008).
3. Schäffer, C. et al. *Angew. Chem. Int. Ed.* **48**, 149–153 (2009).
4. Todea, A. M. et al. *Angew. Chem. Int. Ed.* **46**, 6106–6110 (2007).
5. Lützen, A. *Angew. Chem. Int. Ed.* **44**, 1000–1002 (2005).
6. Férey, G. *Chem. Soc. Rev.* **37**, 191–214 (2008).
7. Jansen, M. *Angew. Chem. Int. Ed.* **41**, 3746–3766 (2002).
8. Takakura H., Gómez, C. P., Yamamoto, A., De Boissieu, M. & Tsai, A. P. *Nature Mater.* **6**, 58–63 (2007).
9. Piao, S. Y., Palatinus, L. & Lidin, S. *Inorg. Chem.* **47**, 1079–1086 (2008).
10. Cao, R. et al. *J. Am. Chem. Soc.* **129**, 11118–11133 (2007).

Thither supramolecular chemistry?

The way forward for a field in its infancy is to focus on complexity and integrated systems that may lead to emergent phenomena, suggests **J. Fraser Stoddart** at Northwestern University.

If the atoms are the letters, if the molecules are the words, and if the supermolecules are the phrases, then the language¹ we call chemistry took less than half a century to make the revolutionary transition from molecules to supermolecules, on the back of having taken well over a century to make the painstaking journey from atoms to molecules. If we peg the growth of chemistry to the expected lifespan of someone living in a developed country, then we are looking at no more than a two-year-old child who is just starting to string a few words

together. The chemist has still to learn how to construct sentences that adhere to some grammatical rules — that is, to introduce meaningful and helpful complexity at the simplest of levels into chemistry — and then acquire the skill set required to bridge, in a logical fashion, from sentence to sentence and so produce coherent paragraphs that ultimately tell a story when they are merged together in the form of a complete work.

Often, the seedlings of change are already planted in former times, yet they remain dormant within a community. So it

was with what became known² as supramolecular chemistry. Many would agree that it witnessed its formal beginnings with the appearance of Charles Pedersen’s seminal paper³ in *Journal of the American Chemical Society* in 1967. It fell, nonetheless, to the joint talents and ingenuity of Donald Cram⁴ and Jean-Marie Lehn⁵ to alert the chemical community at large to the generality and fundamental significance of a chemistry beyond

the molecule that, ultimately, became branded² supramolecular chemistry.

If we want to reach even further back in time for an example of supramolecular phenomena, then where better to go than to the field of liquid crystals, which has preserved its independence, remaining aloof from supramolecular chemistry yet, ironically, providing the one compelling example so far of supramolecular phenomena that has been commercialized on a grand scale? It is little wonder that I am forever reminding my students that there are no firsts in science.

So where is supramolecular chemistry going to leave its mark in science and beyond in the next decade? In a formal sense, it has now had four decades to establish its credentials and to have its fundamentals explored by many talented chemists the world over. Arguably, it has captured the imaginations of some of the best (young) minds and laid claim to the intellectual frontiers in chemistry, revitalizing traditional areas such as analytical chemistry, coordination chemistry and physical organic chemistry, while also bringing a whole new perspective and dimension into the practice of chemical synthesis — a core activity that no longer begins and ends with the making and breaking of covalent bonds under kinetic control. It has also witnessed its relevance and

reputation rise on the back of the emergence of nanotechnology these past two decades. Indeed, its associated molecular recognition and self-assembly processes represent one of the best hopes we have yet for forging a 'bottom-up' approach to nanotechnology, a half-century after Feynman pointed out that "There's plenty of room at the bottom" without offering any blueprint to the chemist.

It is at this crossroad with nanotechnology that I recognize some of the most promising opportunities for us supramolecular chemists to carve out a creative future for ourselves and our science. First, we need to forsake simple systems for complex ones. The building blocks and supramolecular systems constructed from them need to become more intricate with respect to both structure and function. Dynamic chemical bonding needs to be harnessed across its entire energy spectrum from the tiniest of van der Waals forces to thermodynamically reversible covalent bonding interactions. Second, we need to forsake the solid and solution states for surfaces and interfaces. Supramolecular systems need to become bigger and to express multivalency and cooperativity with feedback.

In essence, we need to forsake embracing routine projects that we know will yield results and lead to answers that are largely expected, so as to face challenges that are function-oriented and applications-driven,

requiring the design of integrated systems whose complexity is such that (perhaps unexpected) emergent behaviour is likely to be the end result. The time has come to design and craft a systems chemistry in which processes, including chemical reactions, are compartmentalized in a highly interconnected and 'talkative' manner so that they can be orchestrated in tune in an orderly and rhythmic fashion by the hundreds and thousands in space and time.

It seems that most supramolecular chemists these days are biologically inspired by nature of the wet and squelchy kind. If we decide to be function-oriented, we should ask ourselves whether it is realistic to have our thinking rooted in classical biology. Take, for example, the function of flight — the birds and the bees and the bats have been flying around since time immemorial. Yet in the past century we have rather quickly and successfully engaged airplanes, helicopters and rockets in flight. Dare I venture to suggest that for the next ten years at least we might do well to wear our chemistry on our sleeve and ask ourselves how an architecture that is dry, yet highly porous and rigid, might be mimicked to create another 'biology' in the same way that airplanes, helicopters and rockets have exemplified another form of flight from the birds and the bees and the bats? This parable leads me to suggest that a marriage between supramolecular and reticular chemistry⁶ could prove to be a rewarding experience all round. It is at this architectural interface where I am going to place my money.

Let me close this tale where I began it and return to the human experience, this time as seen through the eyes of William Shakespeare in his soliloquy on the seven ages of man in *As You Like It*. Let us concede that we have passed the stage of the infant mewling and puking in its mother's arms and are about ready to assume the mantle of the whining schoolboy with so much to learn in the next ten years that it had better be structured, robust and resilient in tone, yet open-minded, adventuresome and ambitious in spirit. Thereafter comes the sighing lover with the wherewithal to be inspired by nature of the wet and squelchy kind. □

*J. Fraser Stoddart is in the Department of Chemistry, Northwestern University, 2145 Sheridan Road, Illinois 60208-3113, USA.
e-mail: stoddart@northwestern.edu*

References

1. Philp, D. & Stoddart, J. F. *Angew. Chem. Int. Ed. Engl.* **35**, 1155–1196 (1996).
2. Lehn, J.-M. *Science* **227**, 849–856 (1985).
3. Pedersen, C. J. *J. Am. Chem. Soc.* **89**, 7017–7036 (1967).
4. Cram, D. J. *Angew. Chem. Int. Ed. Engl.* **27**, 1009–1020 (1988).
5. Lehn, J.-M. *Angew. Chem. Int. Ed. Engl.* **27**, 89–112 (1988).
6. Yaghi, O. M. *et al. Nature* **433**, 705–714 (2003).



Two of my grandchildren — surrounded by a collage of supermolecules spanning the past 35 years — capture the state of supramolecular chemistry, present and future, as they leave their footsteps on the sand and prepare to step into that delightful interface we call the water's edge. The younger, at two going on three, is symbolic of where supramolecular chemistry finds itself today. The other, who is five, and a schoolboy-elect, represents where the field is heading during the next decade.