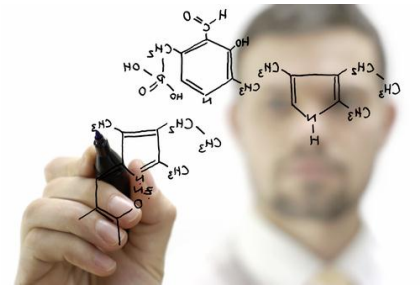
Dial-a-Molecule Newsletter

Welcome to November's edition of the Dial-a-Molecule newsletter. Highlights in this edition include the outcomes from the "*A Step Change in Synthesis*" and "*Selectivity, Sustainability, Predictability: Multi-Disciplinary Issues for 21st Century Catalysis*" meetings as well as a brief presentation of a project taken forward by Dial-a-Molecule member, Dr. G. Richard Stephenson. Also we are announcing one Dial-a-Molecule event which will take place at the end of this year.

A Step Change in Synthesis Meeting - Outcomes



The two-day workshop built on ideas captured and developed at the *Launch Meeting* in Birmingham, the *Next Steps* workshop at Imperial College and the *Industry Focus Meeting* at the SCI, London. These meetings identified two contrasting approaches to the problem of tackling the synthesis of any given molecule. The first, with the working title '*1000 Click Reactions – Stepwise Perfection*', is based the idea that with sufficient 'perfect reactions' (close to 100% yield, no waste, always work), we would be able to build even the most complex molecules in a stepwise fashion.

Challenges are legion. The goal of achieving stepwise perfection first requires the establishment of an inventory of reactions needed to tackle any synthetic challenge. Diversity is essential and implicit as it is clear that our current armoury is insufficient for the task. In parallel we need to establish criteria against which 'perfection' can be judged. These include chemical yield, solvent compatibility, by-product management, functional-group tolerance, selectivity (including chemo-, regio-, stereo-, enantio- and torquo-selectivity) *etc.* Thus, the meetings recommended the establishment of

- ✓ **A Think-Tank to Define 'Perfection' and Identify the Reactions Inventory** needed to address the Dial-a-Molecule Grand Challenge. The group will be tasked with establishing criteria against which perfection can be judged. In parallel they will identify the inventory of chemical reactions needed to tackle the Grand Challenge. The challenge to the community is then to raise the performance of known transformations to the 'perfection' level, and to invent new ones to complete the inventory.

The potential for automation and sequencing was recognised as a necessary guiding principle of the stepwise-perfection approach. Indeed, to achieve *a step-change in chemical synthesis* groups will need to work hand-in-hand with *lab of the future* technologists and those developing catalytic processes able to perform essential reactions with manageable or no waste stream. In addition to these themes, 'reagentless' transformations emerged as an area to develop as these have the potential to be the ultimate 'green reactions'.

- ✓ **'Reagentless Transformations Partnership'**. The working group recommends the promotion of a 'reagentless' transformations partnership to bring together researchers in photochemistry, thermochemistry, hypobaric chemistry, sonochemistry, synthetic electrochemistry and computer modelling. The group will seek to develop a full understanding of existing processes in order to make them utterly predictable in complex systems. In parallel they will seek to use *in silico* methods to predict new and useful chemical reactivity and develop these into perfect reactions in the laboratory. They will address issues of compatibility and complementarity of processes to enable sequencing with other perfect reactions in an automated fashion.

The second approach, entitled '*A Holistic Approach to Synthesis*', adopts a radically different philosophy. Here the aim is to identify the shortest possible synthesis from the outset, using approaches

Newsflash

The Dial-a-Molecule team is proud to announce that the Dial-a-Molecule roadmap, together with 18 month report and case for extension of the network were submitted to EPSRC on November 2nd.

We are grateful to all the Dial-a-Molecule members who contributed to the development of the roadmap through participation in meetings or feedback provided directly or through our discussion forum.

The Roadmap will be made available after consideration by EPSRC.

Richard Whitby, Steve Marsden, David Harrowven and Bogdan Ibanescu

leading to the rapid and predictable generation of complexity. It requires the development of new paradigms for the construction of organic molecules and the abandonment of traditional stepwise approaches. The straight-jacket imposed by petrochemical-derived starting materials; lack of integration with computational methods and biotechnology; poor understanding of fundamental parameters, compatibility issues and potential for sequencing were identified as current barriers to progress. This led to the recommendation for targeted research in

- ✓ **'Complexity Generation and Manipulation'**. The theme would focus synthetic chemistry research in the UK leading to i) the development of new feedstocks for complex molecules; ii) greater understanding of fundamental reaction parameters to facilitate the controlled manipulation of multiple bonds in a predictable fashion; iii) development of a wish list of new reactions with transformative impact; iv) a profound understanding of catalytic, thermal and photochemical reactions, solvent effects, redox manipulation and waste-stream management *etc.*; v) access to new chemical space through diversity

In the upcoming period Dial-a-Molecule will promote activities to take these projects forward. For more information and if you are interested in participating in any of the projects highlighted above please contact us at dialamol@soton.ac.uk or Prof. David Harrowven at dch2@soton.ac.uk.

Paper

NMR reaction monitoring during the development of an active pharmaceutical ingredient

Ian M. Clegg, Charles M. Gordon, David S. Smith, Roberto Alzaga and Anna Codina

***Anal. Methods*, 2012, Advance Article**

An interesting article about the use of NMR spectroscopy to develop detailed understanding of a reaction mechanism during development of a manufacturing process for an active pharmaceutical ingredient (API)was published on-line in the last week: (http://pubs.rsc.org/en/content/articlelanding/2012/ay/c1ay05384a).

The article includes structural elucidation of reaction starting materials, intermediates and products. Generally, the authors intended to tell a detailed story about industrially based development of a commercial synthesis route and how PAT (in this case NMR) can have a very powerful role to play.

The authors also make the point that calibration of Mid-IR instruments remains something of a problem in the sense that it is intrusive to operation of the process and is generally problematic (especially at manufacturing scale).

Catalytic paradigms for 100% efficient synthesis - Outcomes

A 2-day meeting entitled ***Selectivity, Sustainability, Predictability: Multi-Disciplinary Issues for 21st Century Catalysis*** brought together workers from a broad range of disciplines (organic and organometallic catalysis, heterogeneous catalysis, theoretical and computational chemistry, biocatalysis, synthetic biology, chemical engineering, spectroscopy, physical organic chemistry) from across academia and industry. The meeting was built around three general discussion themes. The first of these, **New Reactivity: Target Driven Catalysis** considered the issues of WHICH key new catalytic reactions are likely to be needed to meet the Dial-a-Molecule goals, and WHAT the key catalysts/technologies to address this would be. Three key messages evolved:

- ✓ **New catalytic transformations** of value will include increased focus on construction of complex 3D structures, on '*difficult*' transformations (eg selective fluorination of C–H bonds), and on reactions that multiply functionality (eg C–H activation) rather than consume it. The closer integration of chemo- and biocatalysis was recognised as a potentially key component
- ✓ **Sustainable catalysis** will be a key driver for medium-long term aspirations of the challenge. This manifests itself both in the need to move from '*at risk*' precious metals towards more abundant metals and organocatalysts (including biocatalysts) for key transformations, and in the need to develop catalysts to manipulate renewable feedstocks (biomass-derived, fermentation-derived, waste-stream derived). A role for next-generation heterogeneous catalysis (moving from classical feedstocks/bulk chemicals to applications in fine chemicals) with high turnover numbers was identified.
- ✓ **Development of a Knowledge-Exchange mechanism** (e.g. a UK Network of Excellence in Catalysis) is needed to share industrial issues and expertise with the broader community. A recurring theme was the failure of

many apparently '*standard*' catalytic processes when presented with molecules with the physicochemical properties found in pharmaceuticals, agrochemicals etc. A sub-group is investigating the possibility of a publication outlining the parameters that need to be covered for a reaction to be considered truly '*general*'.

The second theme, **Intervention-free Synthesis by Phase-Distinct Multi-Dimensional Catalysis** addressed the long-term goal of driving up efficiency (maximum speed, minimum waste) by sequencing catalytic reactions. Investigation of complementary approaches include:

- ✓ Sequenced catalytic processes addressed by three conceptual routes: mutually-compatible catalysts (eg sequential bio-/chemocatalysis) enabling "*one-pot*", multiple-step processing; phase-separated catalysts (solid-liquid or liquid-liquid) enabling flow/continuous processing engineering solutions but with no loss of activity; and stimulus-responsive "*switchable*" catalysts that can be programmed externally to activate at specific times/locations.
- ✓ Separation technology to underpin this will also be key. The development of smarter membranes for compound and/or catalyst segregation is seen as key, encompassing both traditional polymeric membranes and potentially '*softer*' membranes by analogy with compound transport in biological systems. Reactor design to facilitate robust and readily-integrated reaction/separation modules will also be important.

The final theme, **Engineering control through fundamental mechanistic understanding** is driven by the recognition that our ability to develop and optimise new catalytic reactions and ultimately to predict the most likely avenues for success of new reaction will be facilitated by a step-change in our fundamental mechanistic understanding of both homo- and heterogeneous catalysis. Three activity themes arise:

- ✓ **Advances in automation** mean that we can collect and collate data at increasing rates, and clear links to the need for integrated data capture protocols articulated in the ELN project were made. Quick gains will be made if intelligent database mining can be used to identify '*starting points*' for optimisation using eg statistical Design of Experiment techniques (eg linking to the **National Service and Virtual Centre for the Study of Reactions**).
- ✓ **Advances in analytical tools** for the *in situ* and operando analysis of reactions. This will comprise both improvements in relatively low-cost '*local*' equipment but also driving the increased use by workers in catalysis of national facilities eg Diamond, the proposed **National Service for the Study of Reactions**.
- ✓ **Advances in theoretical methods**, coupled with improvements in computational power, will ultimately bring the rapid analysis of transition states and comparisons of multiple possible pathways (important both for issues of selectivity and catalyst deactivation) for a much broader range of reactions into scope. The ultimate goal will be prediction a priori of new catalyst species for given reactions, with special value in the identification of sustainable catalysts.

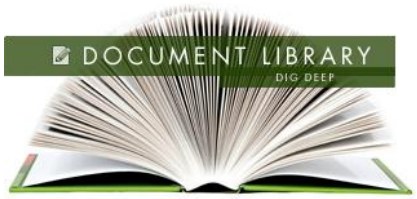
In the upcoming period Dial-a-Molecule will promote activities to take these projects forward. For more information and if you are interested in participating in any of the projects highlighted above and please contact us at dialamol@soton.ac.uk or contact Prof. Steve Marsden at s.p.marsden@leeds.ac.uk.

Upcoming Dial-a-Molecule meeting

Title: Data exchange format meeting
Date: End November 2011– beginning December 2011
Place: Southampton, UK
Synopsis:
A working group will convene to take the first steps in making data exchange based on ELN data possible. This group will propose a model for exchange that will then be made open to the Dial-a-Molecule (and wider) communities for comment, review and ratification. In this first instance the group will develop a descriptive data model that scopes the question "What comprises an ELN record?". This will probably take the form of a core metadata model with an extensible dictionary. The whole model will be set in the context of the purpose of exchanging or sharing this data and will therefore be mindful of research funder, research group, institutional and publication/dissemination requirements and the various interactions that take place around an ELN such as archival, team sharing, collaboration, public engagement and commercialisation.
In order to pave the way for the next stage of implementation some recommendations on formats, method of expression, machine accessibility, automatic processibility and scope will be made.

If you are interested in participating in the development of a standard please let us know by email at dialamol@soton.ac.uk or contact Dr. Simon Coles at S.J.Coles@soton.ac.uk

Dial-a-Molecule Document repositories



The recent thematic meetings held by the Dial-a-Molecule network raised a need of sharing documents easily between various Dial-a-Molecule members. To answer this need we have created two repositories to be used by Dial-a-Molecule members:

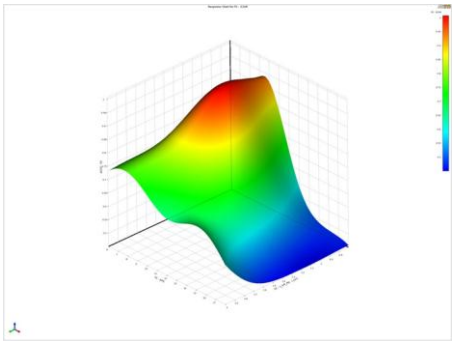
1. Our own platform at www.dial-a-molecule.org . The documents can be accessed through the Forum link on our website. After introducing a valid username and password (please request one from our network coordinator at dialamol@soton.ac.uk) users are able to access a modern Document Library with enhanced capabilities such as sorting data into folders, tagging of folders and individual documents, versioning, online viewing of standard document formats (PDF, Word, Excel, Powerpoint) as well as associating comments with documents. The direct link to the Document library is: http://dialamolecule.chem.soton.ac.uk/share/page/site/dialamolecule/documentlibrary
2. On Connect platform from the Technology Strategy Board. A mirror of the documents from our platform is held on the Connect platform at https://ktn.innovateuk.org/web/dial-a-molecule1/document-library. Please note that each of the Dial-a-Molecule themes have its own document library accessible to only to members interested in that particular theme.

Please note that you need to be a member of these platforms to be able to access the documents. At the moment we do not have an online registration form for the restricted part of our website so if you would like to gain access please let us know by email at dialamol@soton.ac.uk .

For members interested in joining the Connect platform the link to the registration form is:
https://ktn.innovateuk.org/c/portal/create_account_forward?redirect=%2Fweb%2Fguest&joinOrg=

Dial-a-Molecule is a group in the Chemistry Innovation network so please be sure to join us at https://ktn.innovateuk.org/web/dial-a-molecule1 .

Use of modified DoE software for automated "telescoping" of multiple reaction steps



Challenge: Even if reactions achieve near 100% efficiency (so that product yield is effectively independent from the length of the synthetic route) the cost of implementing lengthy multi-step synthesis where isolation is needed between steps will be too high for such procedures to be sustainable in the long-term. Routes which contain extended sequences of reactions that can be performed without work-up are needed. The current challenge is to enable "telescoping" of multiple reaction steps by developing novel automated procedures to identify and optimise sections of reaction sequences that can be brought to convergent reaction conditions without sacrificing yield and product purity.

Achievement: New sustainable synthetic chemistry and process chemistry methods become available that have low environmental costs because reaction work-up stages are minimised by the use of automation to identify and optimise sections of synthetic routes so that reactions have compatible conditions, and so sequence them in a single reaction vessel.

If you are interested in this project and you would like more information please let us know by email at dialamol@soton.ac.uk or contact Dr. G. Richard-Stephenson at g.r.stephenson@uea.ac.uk .