Institute for Sustainability | University of Bath

Dynamic Reaction Monitoring FACILITY

5th Reaction Monitoring Symposium

Programme and Abstracts

Tuesday 4th July 2023

Chancellors' Building, University of Bath

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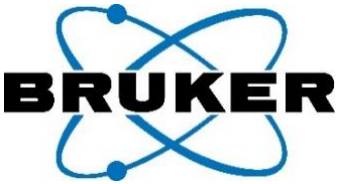


Programme

Time	Activity	Room
9:15	Registration, coffee, vendor exhibition	L1 foyer
	Morning session	
10:15	Welcome and opening remarks	1.10
10:30	**Prof. Ian Fairlamb, University of York, UK** "Deciphering complexity in catalytic cross-coupling chemistries" *Keynote talk sponsored by RSC Inorganic Reaction Mechanisms Group*	1.10
11:10	**Dr Enrico Luchinat, University of Bologna, Italy** "Monitoring ligand binding in human cells by real-time in-cell NMR"	1.10
11:40	Exhibitor flash presentations	1.10
12:00	Lunch and vendor exhibition	L1 foyer
12:30	Poster session and vendor exhibition	L1 foyer
	Early afternoon session	
13:30	**Dr Lorraine Bateman, University College Cork, Ireland** "The Highs and Lows of NMR Reaction Monitoring and Mechanistic Investigations Using InsightMR"	1.10
14:00	**Dr Evan Wenbo Zhao, Radboud University Nijmegen, Netherlands** "Operando NMR methods for monitoring redox flow battery chemistry"	1.10
14:30	Coffee and vendor exhibition	L1 foyer
	Late Afternoon Session	
15:00	**Dr Alejandro Bara Estaun, Bruker, France** "Benchtop NMR spectroscopy in pharma: the PIPAC project"	1.10
15:20	**Prof. Jason Hein, University of British Columbia, Canada** "Tips and Tricks for using Online HPLC as a Universal Reaction Interrogation Tool" *Keynote talk sponsored by Institute for Sustainability, University of Bath*	1.10
16:00	Closing remarks and poster prizes	1.10
16:10	Wine reception	L1 foyer
17:30	Close of meeting	

Exploiting Ultra-Fast Time-Resolved Infrared Spectroscopy in the Study of Mechanisms in Mn-Catalysed C-H Bond Functionalization reactions

Ian J. S. Fairlamb* and Jason Lynam*

University of York

In this presentation I will discuss our collaborative journey to study the reaction mechanisms of substrates possessing suitably activated C-H bonds, involving (primarily) Mn carbonyl species.[1] Using the photoactivation of Mn carbonyl species, and time-resolved infrared spectroscopy (TRIR) methods, one can observe excited states, ligand loss and substitution at Mn with both solvent and reagents (*e.g.* alkenes, alkynes, carbonyl and imine compounds), and migratory insertion processes into Mn-C bonds.[2] Valuable kinetic data has been generated. The information adds greatly to that gained through traditional organometallic mechanistic studies,[3] particularly about the intimate steps proposed for catalytic cycles. We have further exploited the protonation of Mn-C bonds enabling the first direct experimental evidence to be gathered for the microscopic reverse of the Concerted Metalation Deprotonation (CMD) mechanism, which has been proposed in an eclectic array of metal-catalyzed C-H bond functionalization reactions.[4] We have probed the *ortho*-fluorine effect[5] and examined the factors underpinning catalyst activation and deactivation more generally in Mn-catalyzed processes.[6] An exemplar recent transformation that we have studied is shown in Figure 1.[7] Our applied work very much takes advantage of the fundamental groundwork for ultrafast vibrational spectroscopy set out over 25 years ago.[8]

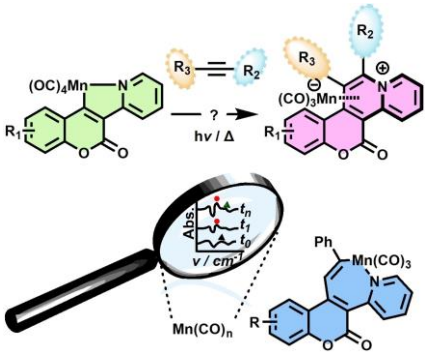


Figure 1: Exemplar process studied as part of our mechanistic work in Mn-catalyzed C-H bond functionalization processes.

1. I. J. S. Fairlamb and J. M. Lynam, (2023), *Acc. Chem. Res.* (**outline paper accepted**); C. Wang, (2018), *Acc. Chem. Res.* **59**, 816-827.
2. I. J. S. Fairlamb and J. M. Lynam, (2018), *Nature Catal.* **1**. 830-840; C. Wang et al. (2018), *Nature Catal.* **1**. 816-817;
3. I. J. S. Fairlamb and J. M. Lynam et al., (2016), *Angew. Chem. Int. Ed.* **55**, 12455-12459; I. J. S. Fairlamb and J. M. Lynam et al., (2019), *J. Am. Chem. Soc.* **141**, 2316-2328.
4. I. J. S. Fairlamb and J. M. Lynam et al., (2021), *J. Am. Chem. Soc.* **143**, 1356-1364.
5. I. J. S. Fairlamb and J. M. Lynam et al., (2022), *ACS Catal.* **12**, 1532-1544.
6. I. J. S. Fairlamb and J. M. Lynam et al., (2023), *Organometallics*, **in press**.
7. I. J. S. Fairlamb and J. M. Lynam et al., (2023), *Chem. Eur. J.* e202203038.
8. K. Wynne and R.M. Hochstrasser, (1995), *Chem. Phys.* **193**, 211-236.

Monitoring ligand binding in human cells by real-time in-cell NMR

Enrico Luchinat

University of Bologna and CIRMMP, Italy

In-cell NMR spectroscopy is a unique approach to study the structure and function of biological macromolecules in their native cellular environment at atomic resolution. At CERM/CIRMMP, an approach was developed for expressing and labelling proteins directly in human cells, which is ideally applied to monitor functional processes such as protein folding and maturation, metal binding, chemical modifications, and interactions with ligands or with specific partners.[1] A major limitation of in-cell NMR is the short lifetime of the cells once they are densely packed in a closed environment. NMR bioreactors overcome this issue by actively perfusing the cell sample with fresh nutrients and oxygen. We have implemented a modular NMR bioreactor which can greatly extend the lifetime of the sample, making possible to study intracellular processes in real time over the course of up to 72 hours.[2] Real-time in-cell NMR provides important information on protein-ligand interactions, such as intracellular ligand binding kinetics and thermodynamics, which are critical to optimize drug penetrance and potency.[3] We have recently developed ^{19}F in-cell real-time NMR methodologies, which allow protein-observed and ligand-observed screenings on targets that would be otherwise invisible by conventional ^{1}H in-cell NMR.[4] Such approaches hold great potential in the development of more effective drugs towards pharmacologically relevant targets.

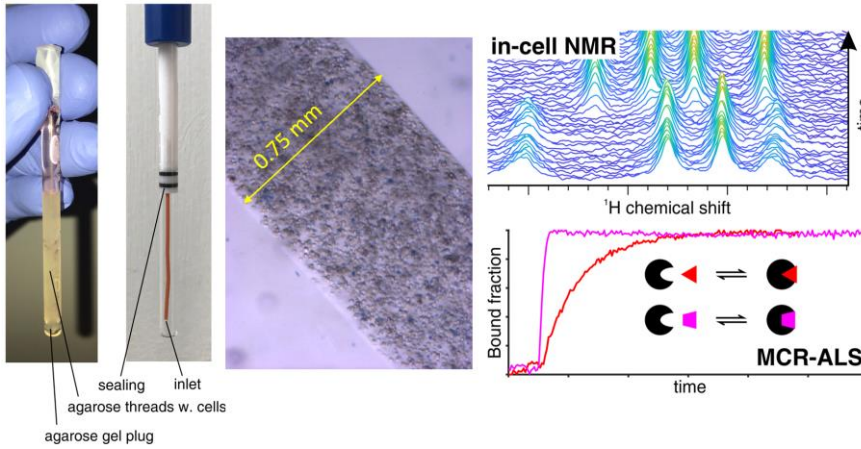


Figure 1: Time-resolved in-cell NMR spectroscopy of human cells embedded in agarose threads.

1. Barbieri, L., Luchinat, E., Banci, L. (2016), *Nat. Protoc.* **11**, 1101–1111.
2. Luchinat, E., Barbieri, L., Campbell, T. F., Banci, L. (2020), *Anal. Chem.* **92**, 9997-10006.
3. Barbieri, L., Luchinat, E. (2021), *J. Vis. Exp.* **169**, e62323.
4. Luchinat, E., Barbieri, L., Cremonini, M., Pennestri, M., Nocentini, A., Supuran, C. T., Banci, L. (2021), *Acta Crystallogr. D Struct. Biol.* **77**, 1270–1281.
5. Pham, L. B. T., Costantino, A., Barbieri, L., Calderone, V., Luchinat, E., Banci, L. (2023), *J. Am. Chem. Soc.* **145**, 1389–1399.

The Highs and Lows of NMR Reaction Monitoring and Mechanistic Investigations using InsightMR

Lorraine M. Bateman[1,2,3], Aoife M. Kearney[1,3,4], Ciara Tyner[1,3,4], Denis Lynch[1,3,4], Stuart G.Collins[1,3,4], Anita R. Maguire[1,2,3,4]

[1]School of Chemistry, [2]School of Pharmacy, [3]Analytical and Biological Chemistry Research Facility, , [4]Synthesis and Solid State Pharmaceutical Centre, University College Cork, Ireland

Recent advances in low-field NMR spectrometers, have extended the scope and application to reaction monitoring. With access to both low (80 MHz, Fourier 80) and high-field (600 MHz, AVIII) Bruker NMR spectrometers equipped with Insight MR flow tubes, two comparative case studies were conducted to evaluate the potential of reaction monitoring at low- versus high-field.

Case Study A, investigated the latter stages of a telescoped multistep reaction sequence exploring the reactivity of α-sulfenyl-β-chloroacrylamides (Fig. 1), a key intermediate in the selective, efficient and mild oxidation of α-sulfanyl amides to β-hydroxyacrylamides, conducted without isolation of the intermediates.[1] Analogous to the high-field study, full profiling of the reaction species was possible at low-field. Comprehensive process understanding facilitates further scope for adaptation of this synthetically powerful oxidative functionalisation reaction.

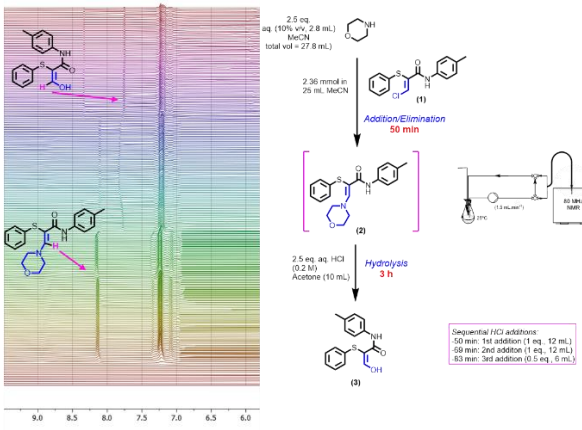


*Figure 1: Case Study A: 80 MHz InsightMR ^{1}H reaction profile of the formation and subsequent hydrolysis of β-morpholinoacrylamide **(2)**; CH_3CN, 25 °C*

In Case Study B (Fig. 2), the rhodium-catalysed intramolecular aromatic addition of α-cyano-α-diazoacetamides was investigated via InsightMR at 80 MHz, in tube and flow reactions. In spite of hazardous diazo starting materials and very low catalyst concentrations, a comprehensive detailed mechanistic and kinetic profile was established for the generation of a series of aza-azulenones.[2]

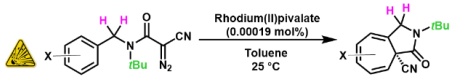


Figure 2: Case Study B: General synthetic scheme for rhodium-catalysed formation of aza-azulenone compounds, studied at 80 MHz via InsightMR; Toluene, 25 °C

1. M. Kissane, M. Murphy, L.M. Bateman, D.G McCarthy & A.R. Maguire, (2011), *Tetrahedron*, 5494-5499.
2. A.M. Buckley, D.C. Crowley, T.A. Brouder, A. Ford, U.B.R. Khandavilli, S.E. Lawrence, A.R. Maguire, (2021), *ChemCatChem*, *13*, 1–8.

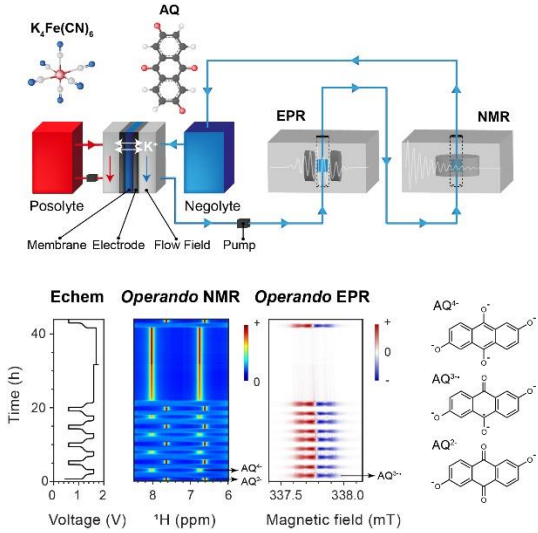
Operando NMR methods for monitoring redox flow battery chemistry

Evan Wenbo Zhao

Magnetic Resonance Research Center, Institute for Molecules and Materials, Radboud University Nijmegen

Redox flow batteries are promising battery technology for grid-scale energy storage due to their unique advantage of decoupled energy storage and power generation. In this presentation, I will introduce operando (inline) nuclear magnetic resonance (NMR) and electron paramagnetic resonance (EPR) methods that offer mechanistic insights into the rich electrochemistry of an anthraquinone-based redox flow battery. The utilization of operando methods enables us to understand and quantify a wide range of fundamental phenomena, including reaction intermediates and products, intermolecular electron transfer, and electrolyte degradation. By monitoring the battery's electrochemical processes in real-time, we have identified the electrochemical cycling conditions that regenerate the redox-active anthraquinone molecules, resulting in a seventeen-fold increase in the battery's lifetime. Last, I will demonstrate that a 40 MHz benchtop NMR system has sufficient, and even superior, spectral and temporal resolution for studying redox flow batteries.

By leveraging operando NMR and EPR methods and the accessibility of benchtop systems, we can gain a deep understanding of the electrochemistry underlying redox flow batteries. This knowledge will guide the design and optimization of battery chemistries, facilitating their broad implementation for efficient grid-scale energy storage.



1. Zhao E W, Liu T, Jónsson E, Lee J, Temprano I, Jethwa B J, Wang A, Smith H, Carretero-González J, Song Q, Grey C P "In situ NMR metrology reveals reaction mechanisms in redox flow batteries" *Nature* **2020,** *579,* 224-228.
2. Zhao E W, Jónsson E, Jethwa B J, Hey D, Lyu D, Brookfield A, Klusener P A A, Collison D, Grey C P "Coupled in situ NMR and EPR studies reveal the electron transfer rate and electrolyte decomposition in redox flow batteries" *J. Am. Chem. Soc.* **2021,** *143*, 1885-1895.
3. Jing Y,# Zhao E W,# Goulet M A,# Bahari M, Fell E, Jin S, Davoodi A, Jónsson E, Wu M, Grey C P, Gordon R D, Aziz M "In situ electrochemical recomposition of decomposed redox-active species in aqueous organic flow batteries" *Nature Chemistry* **2022,** *14,* 1103-1109. (#equal contribution)
4. Wu B, Aspers L E G R, Kentgens A P M, Zhao E W "Operando benchtop NMR reveals reaction intermediates and crossover in redox flow batteries" *J. Magn. Reson.* **2023,** *351,* 107448.

Benchtop NMR spectroscopy in pharma: the PIPAC project

Alejandro Bara-Estaún[3*], Vincenzo Fusillo[2], Matteo Pennestri[1] and Anna Codina[1].

[1]Bruker France SAS, 34 Rue de l'Industrie, 67160 Wissembourg, France [2]Bruker BioSpin GmbH, Rudolf-Plank-Straße 23, 76275 Ettlingen, Germany [3]Bruker UK Ltd, Banner Lane, Coventry CV4 9GH, UK

The companies NovAliX, Alysophil, De Dietrich Process Systems and Bruker have joined forces to bring to market a new approach to active pharmaceutical ingredient (API) production. Based on a Smart Production of Active Ingredients model, the PIPAc project aims to bring the API manufacturing to the next level, by breaking the long and often complex supply chains associated with pharmaceutical production and creating rapid-response mobile API production units that are ready to deploy worldwide. PIPAc combines breakthrough synthesis, continuous flow chemistry and *in-flow* IR and NMR analysis with artificial intelligence (AI).

In flow chemistry, chemical reactions are performed in a continuous flow, rather than in batch mode. This allows for better control and optimization of the reaction conditions, leading to higher yields and better product purity. AI takes the advantages of flow chemistry one step further by adapting synthesis parameters in real-time to an ever-changing environment. Autonomously piloted systems require an analytical technique to provide the progression of the chemical reaction. Infrared (IR) is the most used techniques for reaction monitoring due to their highly sensitive and fast measurements.[1] Nuclear Magnetic Resonance (NMR) is the most successful technique for identification, characterisation, and quantification of chemical components in relatively complex mixtures, which provides detailed structural and quantitative information at atomic level.

In PIPAc, Process Analytical Technology (PAT) integrates the AI within the pharmaceutical manufacturing line to perform chemometric modelling for interpretation of results as well as online monitoring of chemical processes. The Fourier80[2] NMR system a fundamental component for this project as a compact, benchtop FlowNMR equipment, tailored to process monitoring and control, integrated into management software.[3]

1. Whyman R. et al., Phys. E: Sci. Instrum. (17), 559–561, (1984).
2. Benchtop NMR | System | Solutions | Bruker
3. https://www.syntq.com/

Tips and Tricks for using Online HPLC as a Universal Reaction Interrogation Tool

Jason E. Hein

Department of Chemistry, University of British Columbia, Vancouver Campus, 2036 Main Hall, Vancouver, BC, Canada V6T 1Z1

The integration of automation and real-time reaction monitoring in synthetic chemistry has sparked a revolution, enabling data-rich experimentation (DRE) that brings new depth to our understanding of chemical processes. This talk will particularly emphasize the pivotal role of real-time High-Performance Liquid Chromatography (HPLC) as a general and powerful tool, contributing significantly to reaction process optimization and discovery. Moreover, the potential of Artificial Intelligence (AI) and Machine Learning (ML) tools to augment automated real-time reaction monitoring will be explored.

DRE focuses on the extraction of real-time reaction progress data using techniques such as HPLC, allowing for detailed insights into reaction kinetics, intermediates, rate constants, and by-product reaction pathways. Automation plays an indispensable role in DRE, capturing and analyzing reaction aliquots accurately, processing complex analytical data, and executing precise reaction manipulations. This enhanced approach improves decision-making capabilities, reduces optimization time and resources, and aids in unraveling the intricacies of reaction mechanisms and dynamics.

This presentation will shine a light on the current paradigm of data-driven reaction investigation, which predominantly leans on human interpretation. We argue that the marriage of real-time HPLC monitoring data with AI and ML tools opens a new vista in accelerating process optimization and reaction discovery. Real-time monitoring telemetry equips automated systems to receive critical feedback and adapt to changing conditions, thus enabling flawless autonomous synthesis. ML-based predictive models and autonomous optimization platforms can reduce the number of required experiments and extend the scope of reaction parameters considered beyond simple yield measurements. By harnessing these advanced technologies, we are poised to push the boundaries of synthetic chemistry further than ever before.

Poster Presentations

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Adam Khan	1
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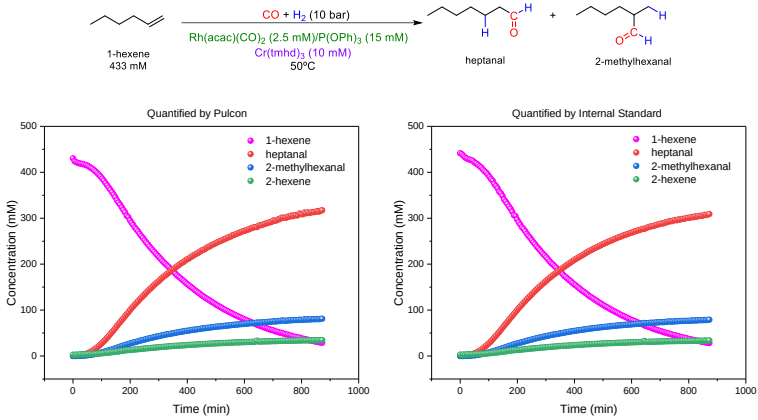
Poster 1:

NMR Goes with The Flow: Multi-nuclear Operando FlowNMR Investigations Using Standardless Pulcon Methodology

Adam Khan,[1,2,3] Alejandro Bara-Estaún[1,2], Catherine L. Lyall,[1,2] John P. Lowe[1,2] and Ulrich Hintermair*[1,2,3]

[1]Department of Chemistry, University of Bath, Claverton Down, BA2 7AY, UK [2]Dynamic Reaction Monitoring Facility, University of Bath, Claverton Down, BA2 7AY, UK [3]Institute for Sustainability, University of Bath, BA2 7AY, UK.

Accurate information of complex homogenous reaction mixtures can be obtained under native conditions using multinuclear high-resolution FlowNMR spectroscopy. The use of internal standards is however still required for quantitative concentration determination. Identifying suitable internal standards that are physically, chemically, and spectroscopically compatible with a given reaction system can be challenging, especially when several different nuclei are to be quantified, which adds extra time and cost to FlowNMR investigations. With careful calibration purely pulse length-based concentration determination can be achieved (PULCON) [2, 3]. Provided the same NMR spectrometer and tube are used PULCON is a non-invasive technique which can reproducibly measure solution concentrations using standard NMR equipment. As FlowNMR uses an unchanging Flow-tip it makes a perfect candidate for the application of PULCON. The viability of PULCON was examined using different nuclei (^{1}H, ^{19}F, ^{31}P) and was found to be accurate at ~5 % error for >1 mM concentrations. An acceptable margin for most FlowNMR experiments. Investigation into its effectiveness across different temperatures and in different protonated solvents has resulted in a refinement of the literature known PULCON equation [4] by the inclusion of a suitable solvent density correction factor term.



Hydroformylation reaction scheme

PULCON methodology was applied to the FlowNMR analysis of the Rh catalysed hydroformylation of hexene (see above). Overall, the reproducibility of reaction concentration profiles quantified by PULCON were found to be excellent compared to those quantified by an internal standard.

1. React. Chem. Eng., 2021,6, 1548-1573
2. Toxins 2016, 8(10), 294
3. J. Agric. Food Chem. 2014, 62, 12, 2506–2515
4. J. Am. Chem. Soc. 2006, 128, 8, 2571–2576

Poster 2:

Investigation into the Cp*Ir catalysed reductive amination reaction

Adam Khan,[1,2,3] Catherine L. Lyall,[1,2] John P. Lowe,[1,2] Matthew Harper,[4] David Sale,[4] Ulrich Hintermair*[1,2,3]

[1]Department of Chemistry, University of Bath, Claverton Down, BA2 7AY, UK [2]Dynamic Reaction Monitoring Facility, University of Bath, Claverton Down, BA2 7AY, UK [3]Centre for Sustainable & Circular Technologies, University of Bath, BA2 7AY, UK [4]Syngenta, Jealott's Hill International Research Centre Backnell, RG42 6EY, UK.

From an industrial perspective the methanolic Cp*Ir catalysed reductive amination (RA) of carbonyl compounds using $HCOONH_4$ is an irresistible green protocol for the synthetic output of primary amines due to relatively available and inexpensive feedstocks and its single one-pot nature [1]. Knowledge of its mechanism and chemoselective origin is crucial for efficient lab to plant scalability and translation of use in other (possibility asymmetric) metal catalysed RA frameworks. In this Project we have applied *operando* FlowNMR spectroscopy for the real-time reaction monitoring of the RA process in its native conditions.

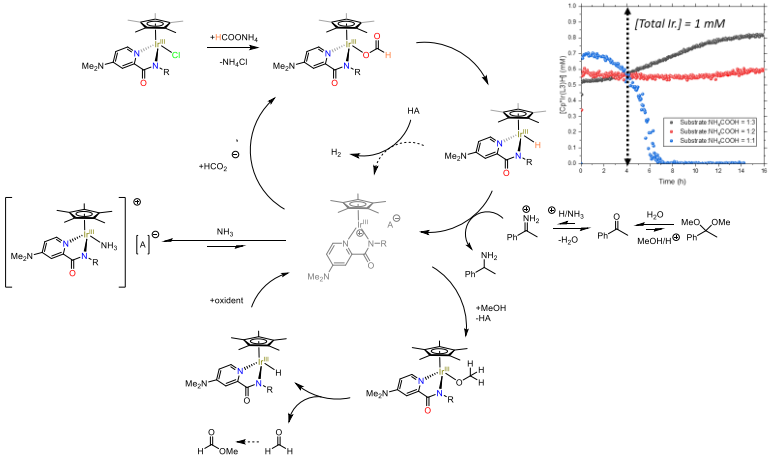


*Figure: Cp*Ir catalysed RA reaction and FlowNMR data*

A mixture of batch and FlowNMR investigations has discovered Iridium hydride dehydrogenation pathway and acid catalysed diketal-ketone equilibrium. Also identified a subsidiary alcohol oxidation pathway which contributes minimally to conversion relative to the formate consumption. If the system is starved of formate, then we observe a majority conversion of Iridium content to a cationic Iridium amino complex which is in equilibrium with an Iridium acetate complex. Furthermore, the origin of amine and alcohol chemoselective control is currently being investigated. Herein we have disentangled the kinetics and thermodynamics linked to the amine condensation pathway, as well as the selectivity of amine and alcohol facilitated by the metal on-cycle catalysis.

1 J. Org. Chem. 2019, 84, 17, 10962–10977

Poster 3:

MaDDOSY: Mass Determination Diffusion Ordered Spectroscopy on the Bench Top

Owen Tooley[1], William Pointer[1], Rowan Radmall[1], Mia Hall[1], Daniel Lester[1], Paul Wilson[1] and David Haddleton[1*]

[1]University of Warwick, Department of Chemistry, Coventry, United Kingdom

Control over molecular weight is one of the most important parameters in polymer synthesis, and yet often only once a reaction has finished is the molecular weight of the polymer determined. Here we present a universal, solvent-independent [1] calibration curve for the rapid determination of polymer molecular weight using a benchtop NMR spectrometer, which provides a system in which no external calibration is required prior to measurement. We show results of calculated molecular weight for a wide range of polymer types and solvent systems.

We also present an automated sampling method for the monitoring of monitoring molecular weight as a reaction proceeds using rapid diffusion-ordered spectroscopy (DOSY) measurements. We evidence the reaction monitoring capability of this system through the monitoring of 4 polymerizations in non-deuterated solvents using a range of mechanisms. We see the results are comparable to those obtained by offline GPC, while providing a much shorter measurement time, and requiring the use of no additional solvent, whilst being able to return the sample to the reaction mixture following measurement.

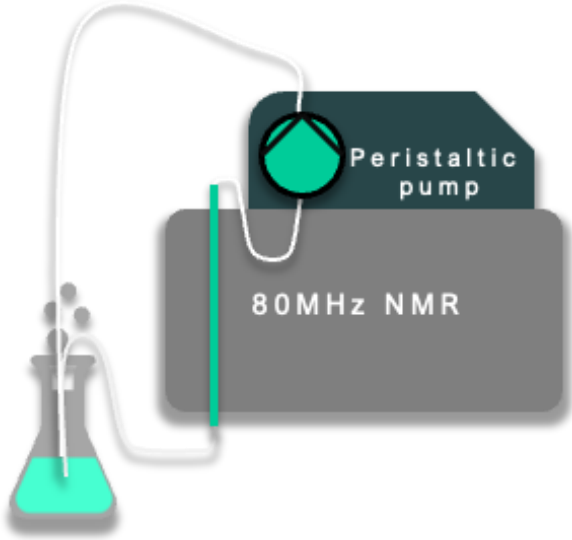


Figure 1 – DOSY Online Reaction Monitoring Setup

[1] P.-J. Voorter, A. McKay, J. Dai, O. Paravagna, N. R. Cameron and T. Junkers, Angew. Chem. Int. Ed., 2022, 61, e202114536.

Poster 4:

Automated transient kinetic screening of continuous flow photoRAFT polymerization using inline NMR

Magdalena A. Bereś,[a] Tanja Junkers*[b], Sébastien Perrier*[acd]

[a]Department of Chemistry, University of Warwick, Coventry, CV4 7AL, United Kingdom [b]School of Chemistry, Monash University, Clayton, VIC 3800, Australia [c]Warwick Medical School, University of Warwick, Coventry, CV4 7AL, United Kingdom [d]Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia

Photo Reversible Deactivation Radical Polymerization (photoRDRP) methods are widely applied in the synthesis of well-defined materials. Simple and more sustainable protocols as well as spatiotemporal control contributed to the popularity of photoRDRPs which was further aided by development of scalable protocols using flow polymerization platforms. Despite this popularity, we are still lacking many fundamental investigations concerning mechanism and kinetics of such reactions. Lack of accurate descriptions and inconsistencies of photoreaction set ups such as, but not limited to, light intensity and maxima of light wavelength used, lead to conflicting and irreproducible data. Herein, we apply an automated continuous flow platform featuring inline NMR analysis which allows for rapid kinetic screening via transient timesweep experiments for detailed investigation of photoRAFT (Reversible Addition-Fragmentation chain Transfer) of common acrylic monomers. Automatisation of experiments, data acquisition and analysis are achieved using a combination of Python and LabView scripts, allowing for rapid data acquisition under reproducible conditions. Variable direct current power supply is used to control light intensity of light sources of different wavelengths to establish a relationship between light wavelength and intensity on control and rate of polymerization.

Poster 5:

Extracting Chemical Kinetics from a Single Scan NMR Experiment

Annabel Flook[a], Guy C. Lloyd-Jones[a]

[a]*University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh EH9 3FJ*
Annabel.Flook@ed.ac.uk

Solution-phase NMR spectroscopy provides a powerful, yet accessible tool to monitor reaction progress with quantitative concentrations, detailed structural information and suitable sensitivity across several nuclei common in organic reactions. Through mechanistic study, reactions can be evaluated and classified, which can further chemical understanding, support optimisation of known reactions and guide the discovery of new chemical systems. [1]

However, for fast reactions (lifetimes < 10 s), the number of NMR spectra that can be acquired in one reaction becomes a limiting factor. Obtaining meaningful kinetic information for fast reacting systems is more challenging, and requires specialist hardware, such as stopped-flow or rapid-injection coupled with the NMR system. In these cases, experiments must be repeated with increasing pre-scan delay, to obtain suitable data density. This method is both time consuming and susceptible to problems with reproducibility. [1][2]

In this work, we show that a single NMR experiment holds kinetic information of an irreversible reaction with a lifetime shorter than the acquisition time (5 s). One method to extract kinetic data is through truncation of the start of the FID followed by typical NMR processing (Fourier transform, phasing, baseline correction and integration). This method allows for an increased temporal resolution in the order of 0.1 ms and a window into the reaction kinetics of much faster reactions using a comparable number of experiments and data density to slower reactions.

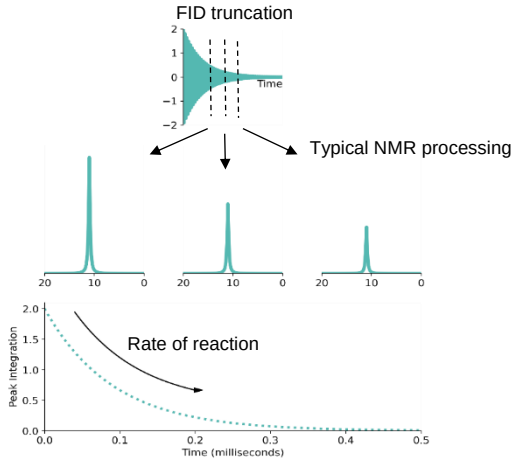


Figure 1: *A single FID can be truncated at intervals and upon Fourier transform, spectra are obtained corresponding to changing concentration over time, over milliseconds.*

[1] Y. Ben-Tal et al, Prog. Nucl. Magn. Reson. Spectrosc., **2022**, 129, 28-106
[2] R. Wei, Eur. J. Org. Chem. **2021**, 2021, 2331

Poster 6:

Renewable cyclic monomers for ring-opening polymerisation and co-polymerisation with L-lactide

Anita Plumley

University of Bath, United Kingdom

The reliance of plastic synthesis on fossil fuels is highly unsustainable. Polymers from renewable sources such as sugars are a highly attractive alternative due to their functionality and abundance. Poly(lactic acid) (PLA) is a commercial bioplastic made from the ring-opening polymerisation (ROP) of L-lactide[1, 2] and is currently one of the most successful commercially available sustainable polymers.[3] PLA's low melting point and high mechanical strength make it an attractive alternative to traditional plastics in applications such as 3D printing and packaging.[4] However, PLA has a fairly simple polymer structure with little functionality, therefore limiting its applications and degradation potential.

Our group has been focusing on synthesising and investigating sugar-based monomers. These are biocompatible, bio-degradable and are highly functional. By adding these sugar units into PLA, their desired properties can be incorporated to the resulting co-polymer. This poster focuses on the ring-opening co-polymerisation (ROCOP) of L-lactide with sugar-derived co-monomers. The conditions of this reaction have been optimised; varied temperatures have been investigated, along with varied co-monomer ratios. The influence of the composition of the co-polymers on thermal stability and mechanical properties have been explored.

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Poster 7:

Design and optimisation of a high-throughput automated workflow for the accelerated discovery of porous organic cages

Annabel Basford,[1] Steven Bennett,[1] Muye Xiao,[1] Kim Jelfs,[1] Becky Greenaway[1]

[1]*Department of Chemistry, Imperial College London, London, UK, W12 0BZ.*

The acceleration of materials discovery plays a role in solving global problems, particularly within molecular separations and purification processes, which account for 10-15% of the world's energy consumption.[1] One solution lies within the use of supramolecular porous materials, to create high-dimensional systems with accessible void spaces that can be tailored for separations. Porous organic cages (POCs), have emerged as an important subclass of porous materials.[2] They are discrete molecules containing a permanent internal cavity, remain shape-persistent (do not collapse into a higher density structure), and may pack together in the solid state to form a low density porous state. POCs have a range of applications including molecular separations, as sensors and in gas storage.[3]

To access novel POCs with new emergent properties, we need to further explore the chemical space. Typically, POCs are formed using dynamic covalent chemistry (DCvC), but the reversibility of DCvC makes the targeted design and prediction of reaction outcome particularly difficult. Traditional experimental design methods, such as trial and error screening, and relying on serendipitous discovery, are labour intensive and time consuming.[3] Even with the aid of automation and high-throughput experimentation, bottlenecks remain in data acquisition and characterisation on a reasonable timescale.[4] This work presents a streamlined hybrid automated workflow for the synthesis and characterisation of POCs via the combination of high-throughput experimentation, robotics, computer vision and computational modelling (Figure 1). By utilising a combination low-cost robotic automation and open-source software, we hope to facilitate the dissemination and uptake of digital chemistry within supramolecular materials discovery.

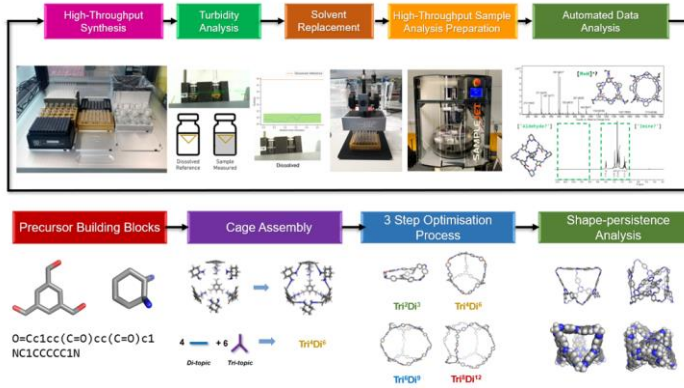

Figure 1: The designed, low cost, automated high-throughput (HT) automated workflow for the synthesis, characterisation, and analysis for the discovery of POCs that combines automation, computational modelling and computer vision.

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Poster 8:

Investigation of additive influence on selective biomass oxidation catalyzed by $H_5PV_2Mo_{10}O_{40}$

Jan-Dominik Krueger [a], Maximilian J. Poller [a], Ulrich Hintermair [b], Catherine Lyall [b], John Lowe [b], Jakob Albert [a]

[a] Universität Hamburg, Germany; [b] University of Bath, United Kingdom

Global warming due to man-made CO_2 emissions and the increasingly difficult geopolitical situation push our societies to move away from the use of fossil resources and instead produce fuels and chemicals from renewable raw materials, such as biomass. One process for such valorisation of biomass is the OxFA process, in which biomass is oxidized to formic acid and CO_2, using $H_8PV_5Mo_7O_{40}$ as a catalyst and O_2 as an oxidant.[1,2] Although this process is already commercially applied, further research is necessary to improve this process, specifically the selectivity towards formic acid. A recent publication has shown, that the formation of CO_2 can be supressed by the addition of methanol.[3] However, the influence of methanol on the catalyst is not fully understood yet on a molecular level, which makes a rational choice of additives for further improvement difficult.

In order to study the influence of additives on this process, we observed a model reaction using ^{31}P, ^{51}V, and ^{1}H NMR spectroscopy at the Dynamic Reaction Monitoring Facility at the University of Bath. To facilitate interpretation of the spectra we used the lower substituted $H_5PV_2Mo_{10}O_{40}$ catalyst for the oxidation of the model substrate glycolaldehyde, which has been observed as an intermediate in the OxFA process.[4] This reaction was carried out either with or without the addition of methanol. Through these experiments we were able to identify, which positional isomers of $H_5PV_2Mo_{10}O_{40}$ are influenced by the additive.

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Poster 9:

Integrated control of a chemical reactor and a high-field NMR spectrometer for autonomous reaction optimization

N. El Sabbagh, M. Bazzoni, C. Lhoste, Y. Horbenko, A. Bernard, D. Cortés-Borda, P. Giraudeau, F.-X. Felpin, J.-N. Dumez

Nantes Université, CNRS, CEISAM, UMR6230, F-44000 Nantes, France

Flow chemistry involves the continuous pumping of reactants through a temperature-controlled reactor. Automated reactors have become increasingly prevalent in assisting synthetic chemists, from self-optimizing reactors[1] to whole autonomous flow optimization systems[2,3]. In-line analysis techniques such as IR spectroscopy[4], HPLC[5], and benchtop NMR[6] are commonly employed to track reaction yields, conversions, and optimize experimental conditions on-the-go. High-field NMR is also a powerful tool for real-time monitoring, and its higher resolution and sensitivity are needed for reactions that cannot be addressed with benchtop NMR.

This work focuses on the integration of a flow chemical reactor with a high-field NMR spectrometer to obtain detailed, real-time information about flow reactions. Overcoming several challenges is necessary for successful implementation. First, the mixture from the reactor must be delivered to the NMR spectrometer. Second, the experiments need to be created, launched, monitored, and their acquired spectra analyzed in an automated and integrated approach.

To address these challenges, a custom flow reactor was connected to a commercial flow tube (Bruker, InsightMR), which was inserted into a 500 MHz spectrometer (Bruker, AvanceIII). To enable autonomous experiments, a MATLAB-based graphical user interface (GUI) was developed to remotely control the high-field spectrometer. The GUI allows for programming experiments, collecting and analyzing spectra, as well as tracking and detecting mixture deliveries for subsequent study. This interface was integrated into a software dedicated for reaction control and optimization.

We will describe the design of the program, the experimental challenges and how to overcome them and examples of applications.

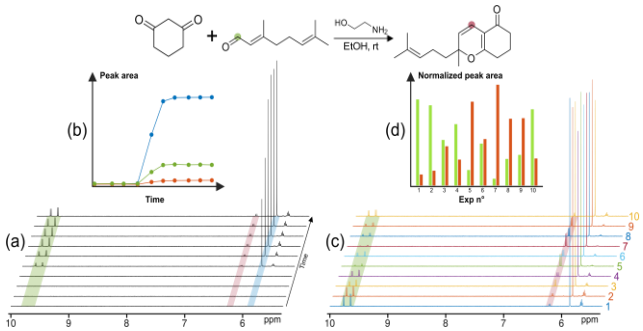

Figure 1: ^{1}H NMR spectra acquired during the optimization of the reaction between Citral and 1,3-Cyclohexanedione: (a) spectra acquired in order to monitor the arrival of the mixture of interest during one reaction run; (b) area evolution over time of the peaks corresponding to the Citral (green), the produced molecule (red) and the internal reference (blue); (c) spectra acquired to analyze the outcome of consecutive reaction runs; (d) normalized peak area of the Citral (green) and the produced molecule (red) during each experiment.

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Poster 10:

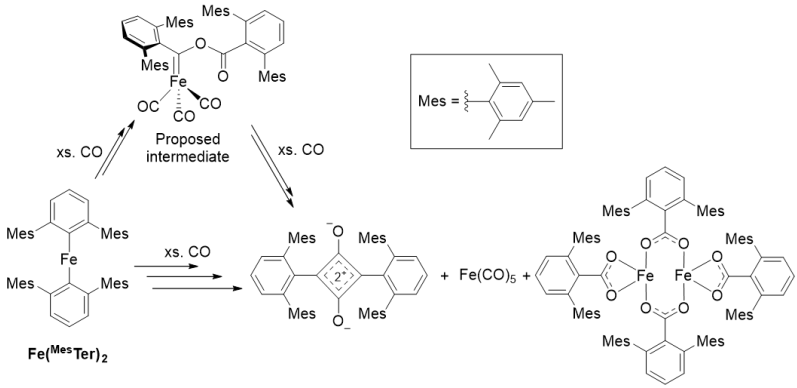
Mechanistic insights into CO scission and homologation by highly unsaturated iron complexes

Nathan T. Coles, Yu Liu, Laurence J. Taylor, E. Stephen Davies, Patrick J. Morgan, Kevin Butler, Ben Pointer-Gleadhill, Stephen P. Argent, Jonathan McMaster, David Robinson and Deborah L. Kays

University of Nottingham, Nottingham Trent University

CO is an abundant source of both carbon and oxygen and utilising this could lead to a wealth of organic molecules that could have applications within the fields of medicinal and agricultural chemistry. Industrial use of CO as a chemical feedstock through the Fischer Tropsch process usually requires heterogeneous catalysts which can present issues with reaction selectivity. However, the development of homogeneous compounds which can stoichiometrically cleave and homologate CO is a vibrant and diverse research area.

Power *et al.* have shown that CO can insert into bulky iron terphenyl bonds, yielding a diacyl iron dicarbonyl complex.[1] However, when applying this methodology to smaller *m*-xylyl or *m*-mesityl iron terphenyls, scission and homologation of the CO occurred resulting in the formation of squaraines (Scheme 1).[2] These squaraine analogues are a relatively rare species that are difficult to synthesise by alternative routes. Reaction monitoring and labelling experiments allowed the provenance of the carbon atoms in the products to be determined, which, together with the structure of a proposed intermediate allowed a mechanism to be tentatively postulated.



Scheme 1 *– General reaction scheme for the reaction of Fe(^{Mes}Ter)$_2$ with CO including proposed intermediate carbene*

The work presented looks to detail further mechanistic studies of the reaction of CO with Fe(^{Mes}Ter)$_2$ using IR and NMR spectroscopic monitoring. These studies are supported by crystallographic characterisation of many intermediate species, allowing development of the initially proposed mechanism. Isotopic labelling has also been conducted to determine products that are derived directly from the CO and highlight the side reactions that can occur in this system, including key ketene intermediates and some degradation products.

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Poster 11:

Photoactivated Catalysts for Hydrosilylation

Helena G. Lancaster[1*], Andrew S. Weller[1], Simon B. Duckett[1], Robin N. Perutz[1], Laura Ashfield[2] and Samuel Douglas[2].

[1]*Department of Chemistry, University of York, UK*
[2]*Johnson Matthey Technology Centre, Blounts Ct Rd, Sonning Common, Reading.*

Hydrosilylation is an industrially important addition reaction of an Si–H bond across an unsaturated bond.[1] Various transition metal-ligand complexes have been used to catalyse this reaction, including those based on platinum[2], rhodium[3] and iridium[4]. Commercially, complexes of platinum are most commonly employed; typically Karstedt's[5] and Speier's catalysts[6], owing to their high activity, selectivity, and tolerance to processing conditions. Since the 1960's, hydrosilylation reactions have been widely used in the production of functional organosilicones and have found application in paper release coatings, automotive parts and adhesives[7].

The design of a catalytic system that exhibits latency: near-zero rates under ambient conditions but hugely accelerated rates upon triggering with heat or UV-light, at low catalyst loadings, is particularly useful for manufacturing processes that require temporal and spatial control. An example of such a process is provided by UV-photocuring hydrosilylation reactions. Here we report the development of a new suite of hydrosilylation catalysts that show excellent latency and UV-photocuring characteristics, as studied by quantitative NMR. We also demonstrate a mechanistic study which has been facilitated by ^{1}H NMR reaction monitoring.

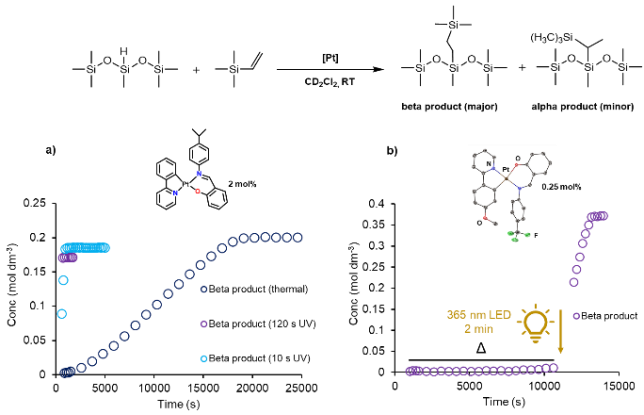

*Figure 1: Concentration versus time plots for beta hydrosilylation product formation. Figure **1a** depicts thermal product formation, alongside that with 120 s and 10 s irradiation for catalyst loadings of 2 mol%. Figure **1b** shows latent reaction kinetics at 0.25 mol%.*

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Poster 12:

Shedding Light on Photochemical Reactivity with LED-NMR

Yael Ben-Tal[1,2], Marcel Utz[1], Guy C. Lloyd-Jones[2]

[1]School of Chemistry, Building 30, University of Southampton, United Kingdom [2]School of Chemistry, Joseph Black Building, University of Edinburgh, United Kingdom.

NMR is well-established as a particularly powerful tool for reaction monitoring and mechanistic study.[1] In recent years, photochemistry has become an increasingly important tool for synthetic chemistry, with many new reactions being developed and implemented in both industrial and academic settings. However, the mechanisms of many of these reactions remain poorly understood and few mechanistic studies have been conducted; in part because of the intrinsic challenges of gathering robust kinetic data on photochemical systems. Here we present the results of a detailed NMR kinetic study conducted on the silane-mediated cross-electrophile coupling developed by the MacMillan group (figure 1.a).[2] This was conducted via a bespoke in-situ illumination NMR spectroscopy system (LED-NMR) that we constructed in-house (figure 1.b).

The simultaneous direct monitoring of a large number of components in the reaction solution by ^{19}F LED-NMR has enabled several important mechanistic observations. One particularly important outcome of this monitoring was the direct observation of a key intermediate that is the major resting state of the Ni catalyst throughout the cycle. The role of this intermediate species in the reaction was further elucidated through sophisticated isotope labelling studies, taking advantage of the unique properties of NMR. A subsequent combination of control experiments, systematic variation of the reaction conditions and kinetic modelling to fit 35 unique datasets has enabled mechanistic conclusions to be drawn.[3]

This case study demonstrates how LED-NMR is a powerful tool for enabling understanding of photochemical reactivity. Further innovations in hardware for NMR reaction monitoring may also be discussed.

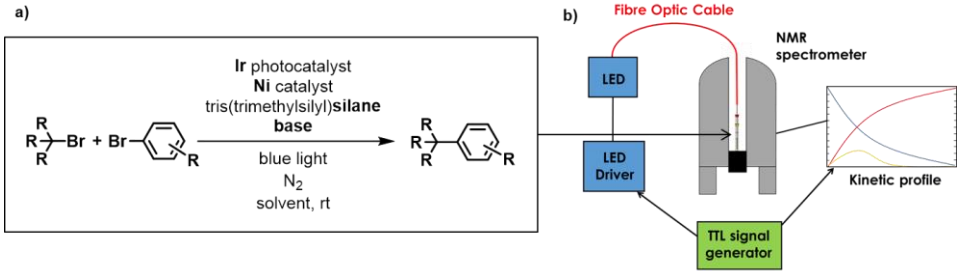

Figure 1: a) The Ni/photoredox cross-coupling studied in this work. b) A scheme of the LED-NMR setup.

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Poster 13:

Tackling Ligand Deactivation in Molecular Catalysis: Insights from *Operando* FT-IR and NMR Spectroscopy

Niklas Wessel[a], Sebastian Obst[a], Katrin Köhnke[a], Andreas J. Vorholt[a], Walter Leitner[a,b]

[a] *Max Planck Institute for Chemical Energy Conversion, 45470 Mülheim an der Ruhr, Germany.*
[b] *Institute of Technical and Macromolecular Chemistry, RWTH Aachen University, 52074 Aachen, Germany.*

Catalyst deactivation is a frequently observed problem in molecular catalytic systems which can strongly inhibit the practical use of catalysts. [1] In the past, combining multiple spectroscopic techniques has contributed to a deeper mechanistic understanding of various catalytic reactions. [2]

Previous work in our group has proven that one of such techniques, transmission FTIR spectroscopy, is a useful tool in detecting catalysts in hydroformylation. [3] Also, the application of FlowNMR has become more widespread in recent years and has already shown its usability in exploring new deactivation pathways in transfer hydrogenation reactions. [4]

By the use of *operando* transmission FTIR and NMR spectroscopy ligand degradation mechanisms that have previously been only studied with *ex situ* methods were revised, with ligand oxidation or P-C-bond cleavage as examples. More specifically, the Pd-catalyzed oxidation of phosphine ligands is such a deactivation mechanism in molecular catalysis [5] and can be tracked via ^{31}P NMR and FTIR spectroscopy.

It can be shown that both NMR and FTIR spectrometry are suitable methods to follow the oxidation of triphenylphosphine to triphenylphosphine oxide. Both methods do not only provide kinetic information but also further insight into the evolution of different Pd-species throughout the reaction. A rapid change in the present species can be observed with varying Pd:TPP ratios.

The addition of low amounts of acid has shown to slow down this deactivation path. Investigations utilizing aforementioned *operando* techniques show how this countermeasure works.

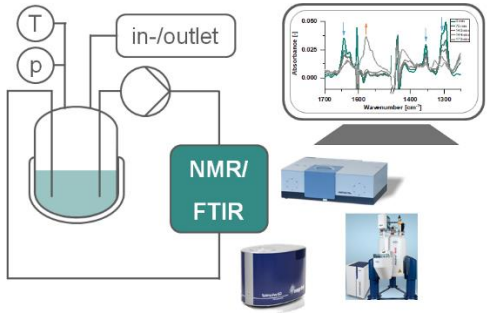

Figure 1: Scheme of the operando set-up containing a NMR and transmission IR spectrometer.

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Poster 14:

Importance of Material Selection in Flow Set ups and Developments of FlowNMR equipment

Owen Harper,[1] Catherine Lyall,[3] John Lowe,[3] Ulrich Hintermair*[1,3]

[1]Institute for Sustainability, University of Bath, Claverton Down, BA2 7AY, UK [3]Dynamic Reaction Monitoring Facility, University of Bath, Claverton Down, BA2 7AY, UK.
e-mail: ojh50@bath.ac.uk

Monitoring a reaction under flowing conditions is a valuable technique for understanding mechanistic and kinetic details due to the high data density gathered under realistic reaction conditions. However, careful consideration must be taken to engineering aspects when constructing a flow set up.[1] Although many robust reactions with mild conditions can be easily and accurately followed by using a standard HPLC pump and Polyetheretherketone (PEEK) polymer tubing combined with a flow tube for insertion into an NMR magnet,[2] scientists are becoming more adventurous with what conditions are possible.[3]

Reactions that are very sensitive to moisture will require a different tubing material such as PTFE due to a leaching effect that introduces water into the solution. Furthermore, when studying pressurized systems, the softer fluoropolymer tubing can be prone to slippage meaning termination of the experiment on top of safety implications. A glass/silicate tubing lined with PEEK (PEEK-Sil) can resolve this issue and still retain good inertness to external moisture. As well as being a more expensive option, PEEK-Sil tubing has the downside of less flexibility owing to its brittle nature so users must adopt the material most suitable for their application.

Improvements can also be made in the area of pumps with smaller and more withstanding designs being needed for different solvent combinations or working with less soluble compositions particularly under pressure. This applies also to the inner connections of a flow tube to improve consistency and resolution.

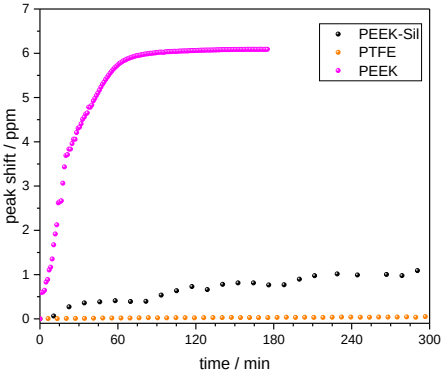

Figure 1: ^{19}F NMR shift of ortho peak of $B(C_6F_5)_3$ in dry toluene into its water adducts from environmental moisture for different polymer tubing options when flowing at 4 mLmin^{-1} (δ, ppm). A larger shift indicates more water absorbed.

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Poster 15:

Rapid Study of Organic Reactions in Flow Systems

Dawid Drelinkiewicz

University of Southampton

Continuous flow chemistry offers unique ways to investigate chemical transformations, however one of the drawbacks is that separate experiments are required for different reaction times. A method for studying photochemical reactions irradiance times in single experiment, termed “Switch-Off” is presented. It relies on switching off the light source during a working photochemical transformation, allowing for measurement of exposure times from initial, down to zero.

Solvents are used in almost all manufacturing processes and are important factor to be considered for reaction development, but optimisation of solvents mixtures is rarely ever performed, due to the laborious nature. A method using flow systems with real-time monitoring for determining the best binary and ternary solvents mixtures composition in organic reactions is proposed, which was successfully used in two model reactions, showing various non-linear effects, and confirming that for studied processes the mixtures are higher yielding than just pure solvents.

Additives, e.g. ligands or chiral molecules, are crucial components of various transformations. Method for screening additives effects on heterogeneous catalysts in flow with in-line PAT is presented, which removes the catalyst degradation issue that limits such studies in batch. Determination of the positive, neutral, or negative effect on the process outcome is presented, alongside with determination of reversibleness of the additive action.

Poster 16:

Synthesis of polyaminoborane using Iridium POCOP catalysts

C. van Beek,[a] A. S. Weller[a] and R. E. Douthewaite[a]

[a]*Department of Chemistry, University of York, York, YO10 5DD*

Polyaminoboranes (PAB) are analogous to polyolefins through the isoelectronic relationship between C—C and B—N bonds. However, they have different chemical properties due to polarity of the B—H and N—H bonds.[1,2] Several catalyst systems have been developed utilising transition metals such as Ir(POCOP)H_2 (POCOP = [μ^3-1,3-(OP^{t}Bu$_2$)$_2$C$_6$H$_3$]) which was reported by Manners in 2008 to produce high molecular weight polymer (Mw = 150,000 g mol^{-1}, Đ = 2.9).[3] Investigation into the materials properties of these inorganic main chain polymers and their possible applications as precursors for B,N-based preceramics[4,5] are currently in their infancy. The materials properties of polyaminoboranes are underdeveloped, this is because the controlled synthesis of polymer on-scale has only recently been reported.[6]

Despite recent advances in other catalyst systems in delivering PAB on scale with mechanistic insight from our laboratories, mechanistic understanding and optimisation of Manners' original catalyst Ir(POCOP)H_2 is still unresolved. In this contribution we report both preliminary mechanistic studies and optimisation experiments that reveal speciation, kinetics and our ability to control molecular weight over a 100,000 g mol^{-1} range.

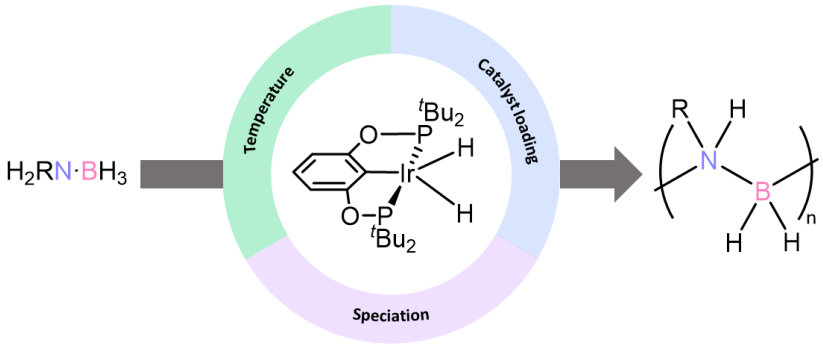

Figure 1: Amine-borane dehydropolymerisation.

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Poster 17:

Engineering aspects of FlowNMR spectroscopy setups for online analysis of solution-phase processes

Asad Saib,[1,2] Alejandro Bara-Estaún,[1,2] Owen J. Harper,[1,2,3] Daniel B. G. Berry,[1,2] Isabel A. Thomlinson,[1,2,3] Rachael Broomfield-Tagg,[1,2] John P. Lowe,[1,2] Catherine L. Lyall[1,2] and Ulrich Hintermair*[1,2,3]

[1]Department of Chemistry, University of Bath, Claverton Down, BA2 7AY Bath [2]Dynamic Reaction Monitoring Facility, University of Bath, Claverton Down, BA2 7AY Bath, UK [3]Centre for Sustainable & Circular Technologies, University of Bath, Bath BA2 7AY, UK

A variety of flow cells and setups have been developed that allow a continuous stream of sample solution to be pumped through the NMR active region of the spectrometer at both low and high magnetic field strengths for various applications, and the choice of materials, dimensions and components can have a profound impact on the quality and relevance of the data obtained.[1-8] Whatever the application, key to obtaining NMR data relevant to the process occurring within the external vessel is an appropriately designed flow system (Fig. 1) that fulfils the following criteria:

a) Full chemical compatibility
b) Provide reaction conditions with appropriate control over key process parameters
c) Deliver a smooth, controlled sample flow throughout the system
d) Safe to use

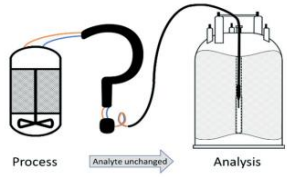

Fig. 1 Schematic illustration of the engineering challenges associated with efficiently interfacing a reaction vessel with an NMR spectrometer

With these considerations belonging more to the realm of chemical reaction engineering, teams of molecular scientists and NMR spectroscopists seeking to use FlowNMR spectroscopy for a given application may lack the expertise and practical experience required for efficiently interfacing the reaction vessel with the spectrometer. Here we show the important and fundamental engineering considerations and selection of components of FlowNMR setups to help avoid common pitfalls and work towards establishing good practice quality guidelines (GxP) for FlowNMR investigations in academia and industry.

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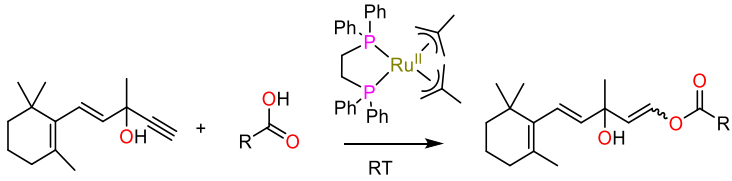
Poster 18:

Catalyst Speciation and Deactivation in the Ru-mediated Meyer-Schuster Rearrangement of Ethynyl-β-Ionol for Vitamin A Production

Asad Saib,[a,b] Roman Goy,[c] Jonathan Medlock,[c] Gabriele Kociok-Köhn,[d] Catherine L. Lyall, [a,b,d] John P. Lowe, [a,b,d] Ulrich Hintermair[a,b,e]*

[a]Department of Chemistry, University of Bath, Claverton Down, BA2 7AY Bath, United Kingdom [b]Dynamic Reaction Monitoring Facility, University of Bath, Claverton Down, BA2 7AY Bath, United Kingdom [c]DSM Nutritional Products AG, Wurmisweg 576, 4303 Kaiseraugst, Switzerland [d]Materials and Chemical Characterisation Facility (MC2), University of Bath, Bath BA2 7AY, United Kingdom [e]Institute for Sustainability, University of Bath, Bath BA2 7AY, United Kingdom.

The ruthenium-catalysed isomerisation of propargylic alcohols into α, β-unsaturated carboxylates (Meyer-Schuster rearrangement, MSR)[1] is an effective and atom-economic method for the derivatisation of a range of terpenoids used in the production of vitamins and aroma compounds. The MSR of ethynyl-β-ionol was found to be efficiently catalysed by [$Ru^{II}(\eta^3\text{-}CH_2C(Me)CH_2)_2$(dppe)] in moderately polar organic solvents, such as ethyl acetate or acetone, in the presence of carboxylic acids to give near complete conversion after 10 hours at room temperature with 2mol% catalyst loading. The use of lower loadings and attempts at catalyst recovery and recycling, as economically required for process development, were met with limitations in catalyst turnover number (TON) however.



Catalytic addition of carboxylic acids to ethynyl-β-ionol

Online reaction monitoring by multinuclear high-resolution FlowNMR spectroscopy, a powerful tool for interrogating complex and dynamic catalytic systems in solution,[2] allows reaction systems to be studied under realistic conditions and allows for straightforward reaction progress kinetic analysis (RPKA)[3] by way of variable time normalisation (VTNA)[4] of the concentration profiles. Here we apply these methods to better understand the mechanism of the Ru-catalysed MSR of ethynyl-β-ionol with the aim of devising optimal process conditions and gain insight into catalyst speciation during turnover. This will hopefully enable the process to reach the challenging performance targets for industrial application and bring about new reactivity of relevance to industrial fine chemical synthesis.

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Poster 19:

Polymerisation-Induced Self-Assembly in Continuous Flow Systems

Alexandre M. Soares Gomes[a], Sébastien Perrier[abc], Timothy Smith[d]

[a]Department of Chemistry, University of Warwick, Coventry, CV4 7AL, United Kingdom [b]Warwick Medical School, University of Warwick, Coventry, CV4 7AL, United Kingdom [c]Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia [d]Lubrizol Limited, The Knowle, Nether Lane, Hazelwood, Derbyshire, DE56 4AN, United Kingdom

Flow chemistry has come to prominence in recent years as an enabling technology for the safe, efficient, and scalable synthesis of polymers in a sustainable and cost-conscious manner. In spite of this, the synthesis of polymeric nanoparticles is yet to be well established in flow as a result of the challenges associated with the heterogeneity of Polymerisation-Induced Self-Assembly (PISA) formulations.[1] To overcome this, careful consideration must be given to reactor design, mixing, and in situ characterisation if PISA is to be successfully implemented under continuous flow. In this work, the facile and efficient synthesis of a DDMAT-PEG precursor is reported using the easy-Polymer E-Series developed by Vapourtec as an all-in-one continuous flow solution.[2] When conducting the Reversible Addition-Fragmentation chain Transfer (RAFT) mediated emulsion polymerisation however, the results are less promising, and the limitations of the easy-Polymer system are highlighted. Further discussions regarding the implementation of In-/On-line analysis techniques and how Life Cycle Assessment (LCA) methodologies may be employed to evaluate the sustainability of such continuous processes are also presented.[3-6]

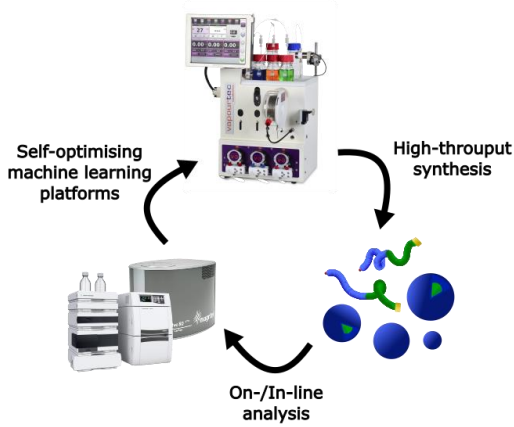

Figure 1: Schematic representation describing the interplay between On-/In-line analysis tools and self-optimising machine learning platforms for the high-throughput synthesis of polymeric nanoparticle architectures.

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Poster 20:

Stability analysis of commercial formulations using in-situ 1D and 2D NMR techniques at elevated temperatures

Dr Tomris Coban[1], Dr Robert Lucas[2], Professor Adam Le Gresley[1]

1. Kingston University, Kingston-Upon-Thames, Surrey, KT1 2EE, UK 2. Haleon ,The Heights, Weybridge, KT13 0NY

Consumer health companies are becoming more aware of a world that is getting smaller. This has led to more interest in the stability of their products and to confirm that the effectiveness of their products is still shelf stable in less-than-ideal conditions.

Here we demonstrate the use of NMR in stability measurements of APIs relevant in oral health. This allows us to exploit not only ^{1}H NMR but also ^{19}F and ^{31}P NMR experiments which allows investigation over a wider range of compounds and give a much better scope of analysis through the larger chemical shift ranges afforded by these techniques. The use of 2D ^{1}H/^{19}F/^{31}P DOSY experiments allows us to correlate changes in diffusion coefficient values and extracted peaks from overlapped 1D ^{1}H spectra using references, which have both ^{1}H/^{19}F and ^{1}H/^{31}P nuclei. Therefore, monitoring of new derivatives in these complex mixtures is made possible through overcoming overlapping issues in ^{1}H NMR with relatively fast alternative 1D experiments and pseudo 2D DOSY experiments[1].

This current research is exploring the end point of stability for products where the stabilisers of predominantly fluoride-based APIs are either ^{31}P based or ^{1}H based. The advantage of this heteronuclear approach and NMR stability measurement is that temperature (40/60C^{o}) can be maintained even during data acquisition, therefore giving an in-situ dynamic understanding of the breakdown process. This has allowed the observation of effects of different ions on stabilisers where the fluoride-based API can be kept stable by ion supplementation of stabilisers. The screening of ^{31}P data shows that the rate of degradation observed can be used as a predictive tool to when the fluoride-based API will breakdown.

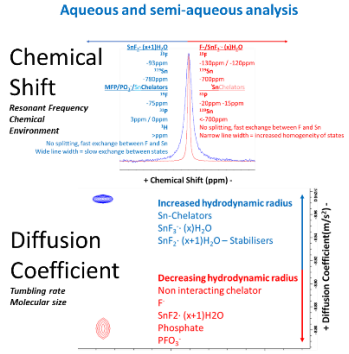

Figure 1: Heteronuclear NMR methodology and DOSY summary relevant to oral health stabilisation studies

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Poster 21:

Benchtop NMR spectroscopy in pharma: the PIPAC project

Alejandro Bara-Estaún[3*], Vincenzo Fusillo[2], Matteo Pennestri[1] and Anna Codina[1]

[1]Bruker France SAS, 34 Rue de l'Industrie, 67160 Wissembourg, France [2]Bruker BioSpin GmbH, Rudolf-Plank-Straße 23, 76275 Ettlingen, Germany [3]Bruker UK Ltd, Banner Lane, Coventry CV4 9GH, UK

The companies NovAliX, Alysophil, De Dietrich Process Systems and Bruker have joined forces to bring to market a new approach to active pharmaceutical ingredient (API) production. Based on a Smart Production of Active Ingredients model, the PIPAc project aims to bring the API manufacturing to the next level, by breaking the long and often complex supply chains associated with pharmaceutical production and creating rapid-response mobile API production units that are ready to deploy worldwide. PIPAc combines breakthrough synthesis, continuous flow chemistry and *in-flow* IR and NMR analysis with artificial intelligence (AI).

In flow chemistry, chemical reactions are performed in a continuous flow, rather than in batch mode. This allows for better control and optimization of the reaction conditions, leading to higher yields and better product purity. AI takes the advantages of flow chemistry one step further by adapting synthesis parameters in real-time to an ever-changing environment. Autonomously piloted systems require an analytical technique to provide the progression of the chemical reaction. Infrared (IR) is the most used techniques for reaction monitoring due to their highly sensitive and fast measurements.[1] Nuclear Magnetic Resonance (NMR) is the most successful technique for identification, characterisation, and quantification of chemical components in relatively complex mixtures, which provides detailed structural and quantitative information at atomic level.

In PIPAc, Process Analytical Technology (PAT) integrates the AI within the pharmaceutical manufacturing line to perform chemometric modelling for interpretation of results as well as online monitoring of chemical processes. The Fourier80[2] NMR system a fundamental component for this project as a compact, benchtop FlowNMR equipment, tailored to process monitoring and control, integrated into management software.[3]

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Poster 22:

Introduction of bespoke linewidth and diffusometry based methods for specific target assay development in commercial formulations

Dr Cameron Robertson[1], Dr Robert Lucas[2], Professor Adam Le Gresley[1]

1. Kingston University, Kingston-Upon-Thames, Surrey, KT1 2EE, UK 2. Haleon, The Heights, Weybridge, KT13 0NY

Consumer health products are becoming more important in our everyday lives and the increasing use of these products has led Industry to know, not only how well a new formulation works, but why it works and how this can affect not only us but the world around us[1]. This has led to a significant increase in the development of methods to interrogate the physiochemical interplay between different components of a formulation.

Changes in linewidth, self-diffusion coefficients and chemical shift of actives within proprietary formulations were measured through simple titration of formulations with proposed new excipients[2]. These results were subsequently correlated to MicroKill assays and specific available API quantifiable assays to determine which data type gives the greatest predictability of new formulation effectiveness and performance in regulatory assays.

The method developed here looks at the screening of cationic surfactants and how different excipients affect the pool of available surfactants through diffusion and binding kinetics-based NMR titrations. We observe that DOSY NMR allows us to differentiate between micellation state of cationic surfactants and predict the bactericidal efficacy of new formulations through measured degree of free API. Addition of parabens, specific co-block polymers were observed to negatively affect the performance.

This work has led to prospective AP generation for the methodology where these NMR methods are being used as a pre-screening tool. It also aided in the expedited release of a new product in the US market by giving pre-indications of regulatory assay performance.

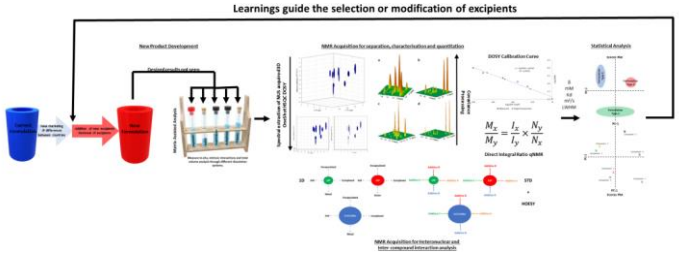

Figure 1: Simplified workflow for new product development and screening

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