Institute of Sustainability and Climate Change | University of Bath

Dynamic Reaction Monitoring FACILITY

7th Reaction Monitoring Symposium

Programme and Abstracts

29th January 2026

University of Bath

Dynamic Reaction Monitoring FACILITY

Institute of Sustainability and Climate Change | UNIVERSITY OF BATH

Reaction Monitoring Symposium Program – 29th January 2026

Time	Activity	Venue
9.30	Registration, coffee, vendor exhibition	CB L1 foyer
Morning session		
10.15	Welcome and opening remarks	CB 1.10
10.30	**Prof Jana Roithová, Radboud University, Netherlands** *Reaction mechanisms in electrocatalysis*	CB 1.10
11.10	**Dr Filepe Vilela, Heriot-Watt University, UK** *Towards Greener Photocatalysis: The Role of Enabling Technologies and Continuous Flow Systems*	CB 1.10
11.40	Exhibitor flash presentations	CB 1.10
12.00	Lunch and vendor exhibition	CB L1 foyer
12.30	Poster session and vendor exhibition	CB L1 foyer
Early afternoon session		
13.30	**Dr Rebecca Ruscoe, Keele University, UK** *New insights into biocatalysis: Inline high-field NMR analysis of enzymatic transformations*	CB 1.10
14.00	**Nouran Hamed, University of Manchester, UK** *What is my reaction intermediate? Resolving individual spectra in real-time NMR reaction monitoring*	CB 1.10
14.15	**Marcus Shanley, University of Bath, UK** *ASOP's Fables: A Tortoise & Hare Race for Mechanistic Understanding*	CB 1.10
14:30	Coffee and vendor exhibition	CB L1 foyer
Late afternoon session		
15.00	**Dr Dawid Drelinkiewicz, Syngenta UK** *Real-time Process Understanding: Harnessing FlowNMR and Online MS in Industry*	CB 1.10
15:30	**Prof Patrick Giraudeau, Nantes Université, France** *Gradient-based NMR pulse sequences for real-time reaction monitoring*	CB 1.10
16.10	Closing remarks and poster prize	CB 1.10
16.20	Reception	CB L1 foyer
17.30	Close of meeting	

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Speaker Abstracts

Reaction Monitoring by Mass Spectrometry

Jana Roithová

Radboud University, Nijmegne, The Netherlands, j.roithova@science.ru.nl

Understanding reaction mechanisms is the key to developing new chemical reactions. Electrospray ionization mass spectrometry has a unique dynamic range that allows for studying reaction mixture compositions, including low-abundant reactive intermediates, side products, and degraded forms of catalysts.[1] In the lecture, I will focus on mapping catalytic reactions and detecting and characterizing reaction intermediates.[2] I will present our approach to using advanced mass spectrometry methods, such as ion spectroscopy, to characterize reactive species by vibrational and electronic spectroscopy.[3] I will also show the use of all the methods to investigate electrocatalytic reactions (Figure 1).[4-7]

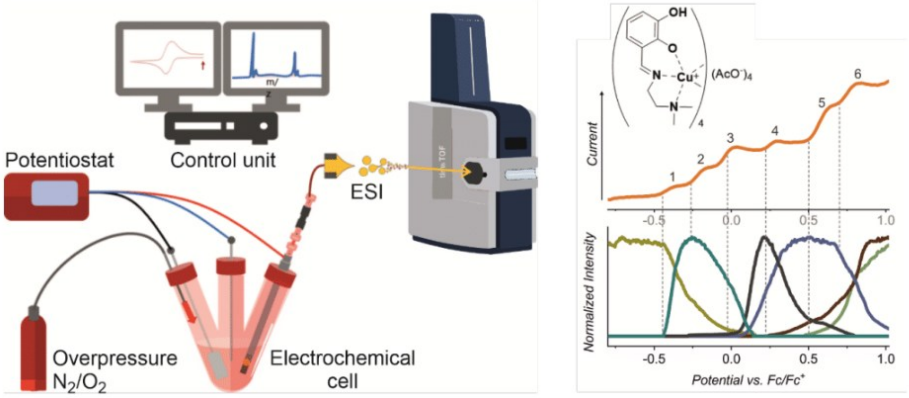

Figure 1. VESI-MS (Voltammetry–electrospray ionization mass spectrometry) setup and an example of a voltammogram coupled with ion abundances from mass spectra in dependence of the potential.

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1. J. Mehara, J. Roithova, Identifying reactive intermediates by mass spectrometry, *Chem. Sci.,* **2020**, *11*, 11960.
2. G. L. Tripodi et al., Tracking Reaction Pathways by a Modular Flow Reactor Coupled to Electrospray Ionization Mass Spectrometry, *Chem. Methods*, **2021**, *1*, 430.
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4. A. Koovakattil Surendran, J. Roithová, Decoding Voltammograms at the Molecular Frontier: Integration of Voltammetry and Mass Spectrometry, *Chem. Methods*, **2024**, *4*, e202400003.
5. A. Koovakattil Surendran et al., Host-guest tuning of the CO2 reduction activity of an iron porphyrin cage, *Nat. Sci.*, **2023**, *3*, e20220019.
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Towards Greener Photocatalysis: The Role of Enabling Technologies and Continuous Flow Systems

Filipe Vilela / / / f.vilela@hw.ac.uk / / / vilelalab.co.uk

Heriot-Watt University
School of Engineering and Physical Sciences, Edinburgh, Scotland
Keywords: flow chemistry, organophotocatalysis, polymer chemistry

Photocatalysis has emerged as a powerful methodology to achieve unique chemical transformations under mild conditions, enabling selective late-stage modification of complex and fragile compounds.[1] Development of efficient heterogeneous photocatalysts as a more sustainable alternative to state-of-the-art Ru and Ir transition metal complex photocatalysts, has been described as one of the greatest challenges within the field of photocatalysis.[2]

In the talk, I will present our recent work utilising enabling technologies to enhance photochemical synthesis, including flow chemistry, additive manufacturing, and real-time process analytical tools.[3-5] I will begin by discussing the rational design and synthesis of light-harvesting materials for photocatalytic applications in flow.[6] I will then present our recent work developing in-line flash chromatography for the automated synthesis and purification of organic molecules in continuous flow (Fig. 1) and the development of an automated continous flow system to monitor the degradation of polymers in real-time.[8]

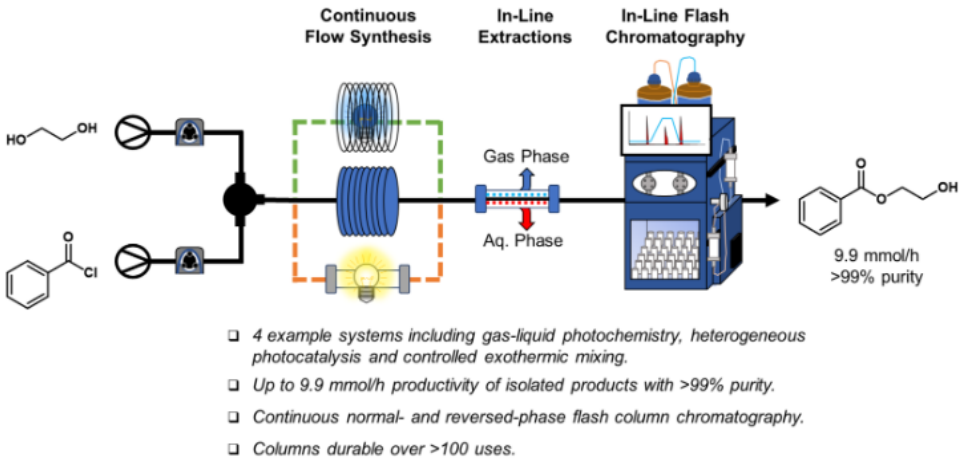

Figure 1: *Depiction of the continuous flow synthesis system with integrated in-line flash column chromatography.*

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1. C. K. Prier, D. A. Rankic and D. W. C. MacMillan, Chem. Rev., 2013, 113, 5322–5363.
2. M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, Chem. Rev., 2017, 117, 11796–11893.
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New insights into biocatalysis: Inline high-field NMR analysis of enzymatic transformations

Rebecca E. Ruscoe[1] and Sebastian C. Cosgrove[1]

Keele University, Keele, ST5 5BG, United Kingdom

Biocatalysis harnesses enzymes for chemical synthesis, providing a sustainable alternative to traditional methods due to their biodegradability and operation under mild conditions.[1] The integration of inline analytical technologies has significantly advanced many areas of chemistry, including biocatalysis, by enabling real-time monitoring of reactions.[2] Although NMR spectroscopy is widely used in synthetic chemistry, its application for analysing biocatalytic transformations using high-field instruments remains limited. This presentation will showcase pioneering work from the DReaM facility, where in vitro biocatalysts were studied using an inline high-field NMR spectrometer for the first time. Case studies include the enzymatic reduction of aryl nitro compounds to anilines,[3] low-concentration biocatalysis,[4] a two-enzyme cascade,[5] and a soluble alcohol oxidase reaction.[6] Inline NMR analysis provided unprecedented mechanistic insights and facilitated rapid optimization of these transformations, significantly reducing development timelines compared to conventional offline approaches.

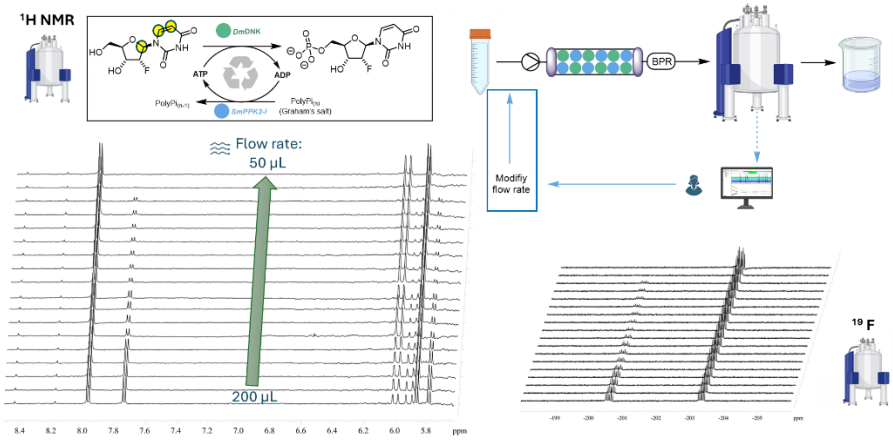

Figure 1: Kinase-mediated phosphorylation of nucleosides with ^{1}H and ^{19}F NMR analysis

References:

1. E. L. Bell, W. Finnigan, S. P. France, A. P. Green, M. A. Hayes, L. J. Hepworth, S. L. Lovelock, H. Niikura, S. Osuna, E. Romero, K. S. Ryan, N. J. Turner and S. L. Flitsch, *Nat. Rev. Methods Primer*, 2021, **1**, 46.
2. R. E. Ruscoe and S. C. Cosgrove, *Curr. Opin. Green Sustain. Chem.*, 2024, **49**, 100954.
3. S. C. Cosgrove, G. J. Miller, A. Bornadel and B. Dominguez, *ACS Sustain. Chem. Eng.*, 2023, **11**, 8556–8561.
4. A. Naramittanakul, S. Sari, C. Benckendorff, J. Cheang, Y. Sanghvi, G. Miller and S. Cosgrove, *ChemRxiv*, 2025, preprint, DOI: 10.26434/chemrxiv-2025-snvjk-v2.
5. T. L. Roberts, J. P. Dolan, G. J. Miller, M. A. D. Lima and S. C. Cosgrove, *React. Chem. Eng.*, 2025, **10**, 1221–1226.
6. P. Cinca-Fernando, C. Ascaso-Alegre, E. Sevilla, M. Martínez-Júlvez, J. Mangas-Sánchez and P. Ferreira, *bioRxiv*, 2024, preprint, DOI: 10.1101/2024.03.22.586125.

What is my reaction intermediate? Resolving individual spectra in real-time NMR reaction monitoring

Nouran A. Hamed*[1], Marshall J. Smith[1,2], Alexander P. Golovanov[1], Ralph W. Adams[1], Gareth A. Morris[1], and Mathias Nilsson[1]

1. *Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, United Kingdom*
2. *JEOL UK Ltd., Welwyn Garden City, AL7 1LT, U.K.*

NMR spectroscopy is widely used in live reaction monitoring as it provides rich structural information and quantitative concentration profiles; yet, extracting detailed insight from reaction mixtures remains a significant challenge. Combining NMR methods with chemometrics has shown great success in resolving pure component spectra of mixtures without requiring physical separation.[1-3] Here, we demonstrate the power of a simple matrix decomposition approach for continuous reaction monitoring using NMR. This approach facilitates the analysis of reaction pathways and mechanisms by providing individual spectra of all reaction mixture components.

We applied the method to a photodegradation study of betamethasone, a well-known anti-inflammatory drug, using the NMRTorch[4] for *in situ*, real-time reaction monitoring by NMR. Interleaved 1D ^{1}H and ^{19}F {^{1}H} NMR spectra were recorded, followed by matrix decomposition analysis. This decomposes the NMR dataset (X) into component spectra (S) and concentration profiles (C) according to the model $X = CS^{T} + E$, where E represents the experimental noise and ^{T} denotes the transpose. Using concentration profiles C from resolved ^{1}H or ^{19}F signals, the dataset X can be decomposed by solving the system of linear equations in a single step to yield pure component spectra S. In the case of betamethasone photodegradation, we successfully separated the spectra of the substrate, two intermediates, and major products.

Matrix decomposition analysis of NMR timecourse data enables a detailed understanding of complex reaction mixtures without physical separation, offering a novel computationally efficient multicomponent analysis broadly applicable to studies of reaction kinetics and catalysis.

References:

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ASOP's Fables: A Tortoise & Hare Race for Mechanistic Understanding

Marcus A. Shanley,[1] Kristaps Ermanis,[2] Stephen Harman,[2] Antonio Misale,[3] Alexander J. Cresswell*[1]

[1]Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, U.K.
E-mail: a.j.cresswell@bath.ac.uk.
[2]School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, U.K. [3]Johnson & Johnson Innovative Medicine, calle Río Jarama 75A, 45007 Toledo, Spain.

Precise control over the spatial orientation of functional groups within small-molecule drug candidates is critical to maximising drug potency and minimising undesirable off-target effects. Towards this goal, the incorporation and functionalisation of rigid three-dimensional, Fsp^3-rich spirocyclic frameworks is an attractive drug development strategy.[1] However, existing methods for spirocycle synthesis are challenging or lack generality, frequently requiring a near case-by-case retrosynthetic disconnection.[2,3] The development of a general, modular synthetic route for spirocycle construction — suitable for automation/library synthesis and harnessing abundant, commercially available reaction feedstocks — would greatly accelerate the drug discovery process.

To address this challenge and facilitate access to currently unexplored chemical space, we have recently developed a new modular reaction for the assembly of α-(hetero)arylated spiropyrrolines, termed the **Amino Sulfoxide Protocol (ASOP).** The two-component process is operationally simple, executed entirely at ambient temperature and exhibits a broad substrate scope, including halogens and many pharmaceutically relevant heteroaromatics (**Figure 1**). A subsequent (asymmetric) pyrroline reduction step — performed either before or after scaffold diversification — provides streamlined access to valuable chiral α-(hetero)arylated spiropyrrolidines. Our preliminary efforts to elucidate the mechanistic pathway of the transformation using ^{1}H-NMR kinetic reaction monitoring are presented, including the origins of an **unusually mild and regioselective sulfoxide *syn*-elimination step**.

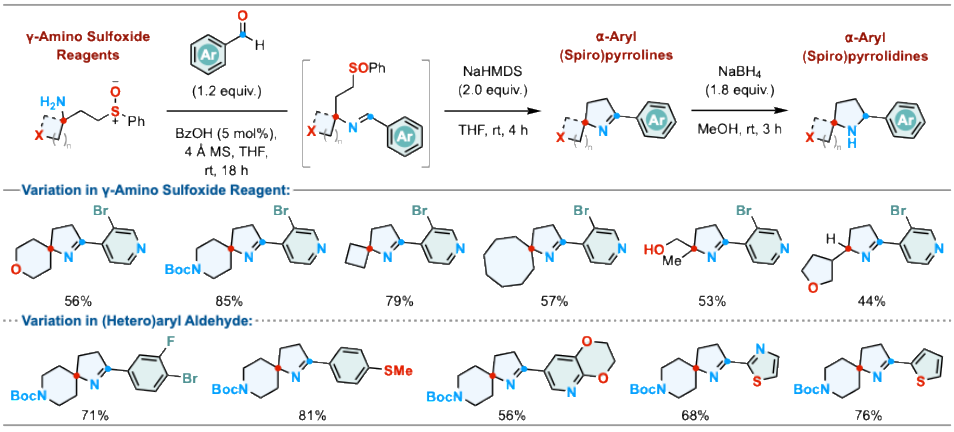

Figure 2: Amino Sulfoxide Protocol (Cresswell)

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Real-time Process Understanding: Harnessing FlowNMR and Online MS in Industry

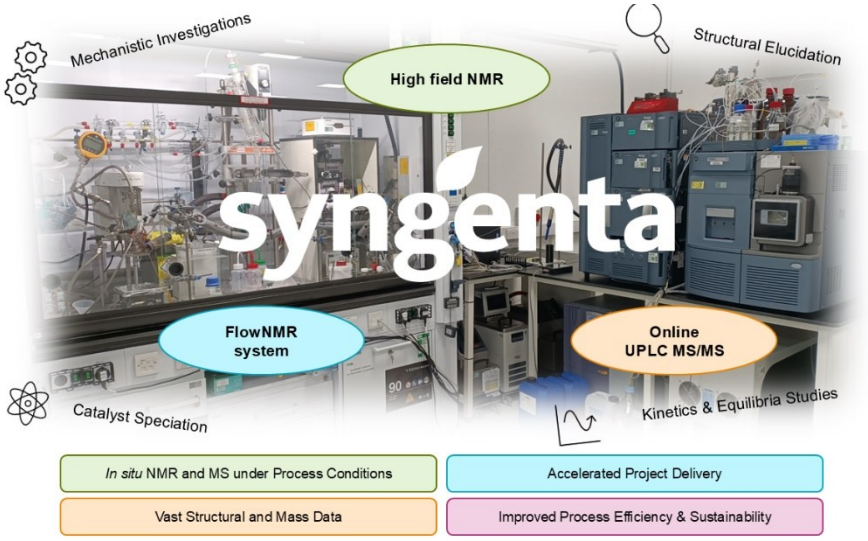
Dawid Drelinkiewicz

Syngenta UK

Syngenta's advancements in fundamental process understanding and chemical process analysis are presented with FlowNMR Facility at Jealott's Hill being central to these efforts, offering *in situ* reaction monitoring via high-field NMR and MS used for mechanistic investigations, structural elucidation of low-level and labile species, and detailed characterization of complex kinetics and equilibria.

The utility of FlowNMR system is demonstrated through real-world applications. Studies of a Pd-catalysed reaction revealed the persistence of Pd-containing species through various process stages, providing valuable insights that led to process control strategies. The presentation also explores the application of exotic nuclei NMR, such as ^{27}Al NMR for aluminium catalysed processes and ^{1}H NMR for detecting hydride species in hydrogenation reaction, further enhanced by online MS/MS for comprehensive catalyst speciation understanding. Advanced NMR techniques, such as ^{13}C broadband decoupled ^{1}H NMR and pure shift ^{1}H NMR, are employed to improve data quality, resolution, and address challenges like overlapping signals when acquiring data on low-level species.

FlowNMR and online MS are presented as powerful tools providing vast structural and mass data on reaction components, including reactive and unstable species, enabling enhanced mechanistic understanding and accelerated project delivery.



Gradient-based NMR pulse sequences for real-time reaction monitoring

Patrick Giraudeau

Nantes Université, CNRS, CEISAM, 44000 Nantes, France

Real-time reaction monitoring requires NMR methods that meet several stringent requirements. NMR spectra used for reaction monitoring need to be sensitive, well resolved, solvent-suppressed, and compatible with flow, and the experimental duration must match the timescale of the monitored reaction. Therefore, most NMR reaction monitoring studies rely on one-dimensional experiments which are rapid and simple, but are often limited by overlap between multiple peaks from reactants and products. While the NMR toolbox offers a great diversity of 1D and 2D experiments that can resolve individual components from complex mixtures, these methods are often time-consuming and not compatible with flow.

We have developed and optimized a set of NMR experiments that make it possible to analyse complex reacting mixtures in real time. Most of these experiments rely on spatially-encoded pulse sequences that combine frequency-swept pulses with magnetic field gradients. These include ultrafast 2D NMR methods,[1] whose application to reacting mixtures under flow conditions was optimized by using gradients orthogonal to the sample flow combined with solvent-suppression schemes.[2] We successfully applied these methods to online and in-line reaction monitoring, both at high magnetic field and on benchtop NMR spectrometers.[3,4,5] Other recent developments include pure-shift NMR experiments in continuous flow,[6] as well as time-resolved diffusion NMR experiments that provide clean, individual spectra of newly formed compounds in reacting mixtures.[7]

We will describe these recent NMR methods for real-time reaction monitoring, and their application to the online study of chemical reactions and to the in-line optimization of flow chemistry processes. The integration of these methods into autonomous flow chemistry settings also offers an interesting perspective.[8]

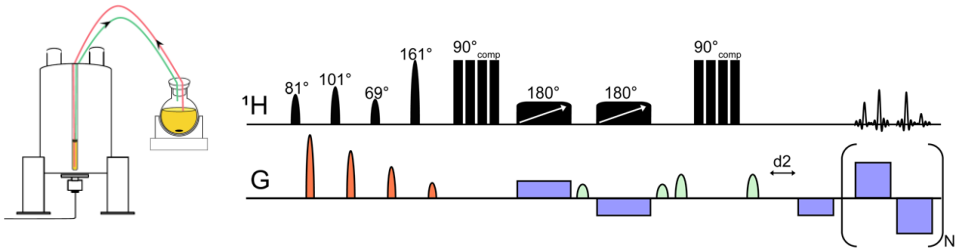


Figure 3: Ultrafast COSY pulse sequence for online reaction monitoring[3]

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Poster Presentations

Presenter	Poster Number
James Beeston	1
Yuan Gao	2
Izzy Hehir	3
Seren Hewer	4
Claire Jepsen	5
Trey Koev	6
Chen Li	7
Ben Morgan	8
Roisin O'Dea	9
Maximilian Pollar	10
Kawarpal Singh	11
Matthew Wallace	12
Annabel Flook	13
Aleksandr Ostudin	14
Claire Jones	15

Kinetics and Mechanism of the Corey-Winter Reaction

James H. Beeston, Dr Gary Nichol and Dr Andrés García-Domínguez

School of Chemistry, The University of Edinburgh, Joseph Black Building, David Brewster Road, King's Buildings, Edinburgh, EH9 3FJ, UK

The Corey-Winter reaction is a two-step protocol to convert 1,2-diols to their corresponding alkene, stereospecifically and without the use of heavy metals.[1, 2] The reaction has demonstrated utility for derivatising carbohydrates, for the synthesis of strained and highly-substituted alkenes and in natural product synthesis.[3] However, the second step, the conversion of a thionocarbonate to alkene by refluxing in trialkyl phosphite as solvent at high temperatures for extended reaction times, has restricted overall uptake. Recent computational work has proposed a mechanism for the second step.[4] However, experimental evidence for this mechanism is currently limited. A detailed mechanistic study would guide future reaction development and increase application to the wider synthetic chemistry field.

In this work, the mechanism of the second step of the Corey-Winter reaction has been investigated using a range of NMR spectroscopy techniques, reaction monitoring and kinetic analyses. NMR spectroscopy (^{1}H, ^{19}F and ^{31}P) in particular has been vital for structural elucidation, quantitation and characterising intermediates within the system under reaction conditions. The effects of the substrate sterics and electronics on rates of reaction have been uncovered and parametrised, where electron-deficient and less sterically demanding thionocarbonates react faster. Thionocarbonates which cannot eliminate to their corresponding alkene but still react with trialkyl phosphite have provided insight into the reactivity of a zwitterionic intermediate and, potentially, a 1,3-dioxacarbene intermediate.

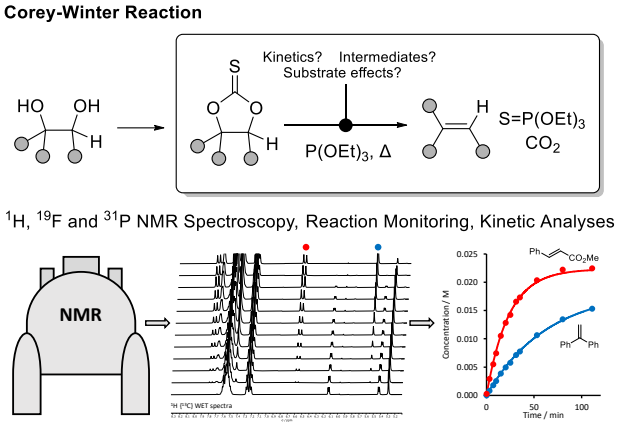

Figure 4: Kinetic and Mechanistic Study of the Corey-Winter Reaction using NMR Spectroscopy

References:

1. E. J. Corey and R. A. E. Winter, *JACS*, 1963, **85**, 2677-2678.
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To Flow or Not to Flow? Pulsed-Flow NMR

Y. Gao, C. Lyall, J. Lowe, and U. Hintermair.

Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK.
Dynamic Reaction Monitoring Facility, University of Bath, Claverton Down, Bath BA2 7AY, UK.

NMR spectroscopy is a powerful technique for reaction monitoring due to its high chemical specificity, quantitative nature, and non-invasive character. FlowNMR extends these capabilities by enabling *operando* measurements under representative reaction conditions and alleviating the limitations of conventional static NMR experiments.[1] However, continuous flow inherently introduces flow effects that compromise sensitivity and spectral quality,[2] and several advanced NMR experiments require a static sample environment. In current practice, flow is typically paused manually to perform such experiments, introducing variability in pause and restart timing and limiting reproducibility and automated operation.

To address this, we have developed a pulsed-flow NMR approach, in which the flow is repeatedly stopped and restarted using precisely controlled timing and flow rates (**Figure 1**). This method combines the advantages of flow and static NMR while maintaining automated reaction monitoring and well-defined temporal control. Preliminary experiments show excellent reproducibility and robust synchronisation between flow and NMR acquisition.

Preliminary experiments show that optimisation of pulsed-flow parameters can enable improved signal-to-noise ratios within reduced experimental times. We are also exploring the combination of pulsed-flow NMR with advanced reaction monitoring experiments, including diffusion-ordered spectroscopy (DOSY) and solvent suppression. We propose that pulsed-flow NMR provides a practical intermediate operating mode between static and continuous flow, enabling reproducible, high-quality NMR data acquisition for reaction monitoring.

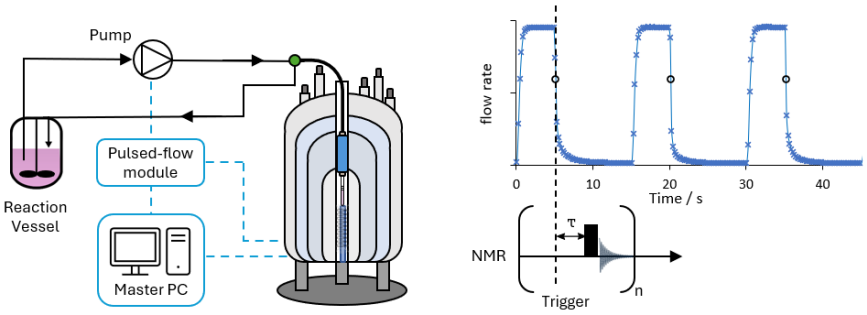

Figure 5: Left: a schematic of a recirculating flowNMR setup with a pulsed-flow module. Right: example of a pulsed-flow experiment showing flow modulation and synchronised NMR acquisition.

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In situ SABRE hyperpolarisation in benchtop NMR spectroscopy

Izzy Hehir, Daniel. A Taylor, James M^{c}Call, Gregory Yule and Meghan E. Halse

University of York

Benchtop spectrometers present an exciting addition to reaction monitoring technology, offering the rich chemical information of NMR whilst being compact enough for diverse applications.[1] However, the lower magnetic field presents challenges of lower sensitivity and resolution compared to high-field spectroscopy. This work focuses on overcoming these limitations using Signal Amplification By Reversible Exchange (SABRE), a hyperpolarisation technique in which spin order is transferred from *para*-hydrogen (*p*-H_2) onto a substrate of interest *via* an iridium catalyst.[2] SABRE can create large amounts of polarisation in seconds and is relatively cheap when compared to other hyperpolarisation methods. SABRE also allows repeated hyperpolarisation of the sample as the substrate molecules remain chemically unchanged. However, standard SABRE methods are arduous to perform and can give irreproducible enhancements.

In this work, an entirely *in situ* method was developed by automatically delivering the gas *via* a capillary and using radio-frequency (RF) irradiation to satisfy the polarisation transfer conditions. This method, RF-SABRE, has previously been successful for proton spectra at high-field,[3] but the lower B_0 field and robust hardware of benchtop spectrometers have allowed greater enhancements (450-fold) to be achieved. The automation of the *in situ* method gives suitable repeatability for two-dimensional experiments, which contribute towards overcoming spectral overlap.

The capability to investigate nuclei with greater chemical shift dispersion is another vital tool in combatting the low resolution of benchtop NMR spectrometry. Here, a new, highly effective method to hyperpolarize ^{13}C nuclei using RF-irradiation *in situ* has been developed, allowing ^{13}C spectra to be obtained on natural abundance samples in as little as 1 scan.

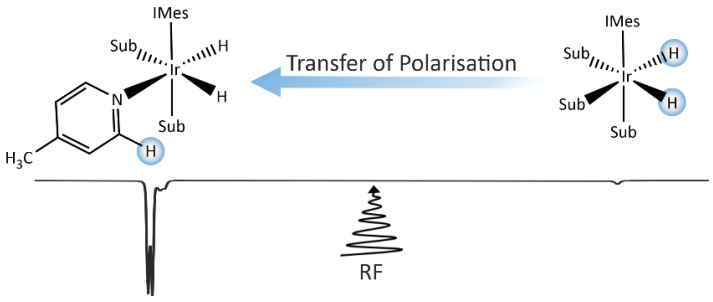

Figure 6: Schematic representation of the hyperpolarisation of substrate protons via RF-SABRE

References:

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Piecing Together Hiyama Cross-Coupling

Seren Hewer, Dr Andrés García-Domínguez

University of Edinburgh, School of Chemistry

Biaryls are a fundamental structural motif found in many agrochemicals, pharmaceuticals, and materials with diverse applications. The synthesis of such structures has been widely facilitated by cross-coupling reactions. However, challenges arise when employing 2-pyridyl derivatives as nucleophilic coupling partners due to their instability leading to a phenomenon known as the '2-pyridyl problem'.[1] The high stability of 2-silylated pyridyl derivatives has been suggested as an alternative to couple these motifs in the so-called Hiyama cross-couplings. The available literature on these reactions is limited and inconsistent, and key considerations include solvent, a nucleophilic activator (typically a source of fluoride anions), occasional use of metal additives (such as copper or silver salts), and only a narrow scope of pyridines explored. Additional complexities arise from limited understanding of the palladium catalyst, ligands, and the effect of water and oxygen on the reaction. My research seeks to address these challenges with the development of a model system that provides insight into these reactions, using experimental techniques (primarily ^{19}F NMR spectroscopy) for reaction monitoring and kinetic analysis.[2, 3]

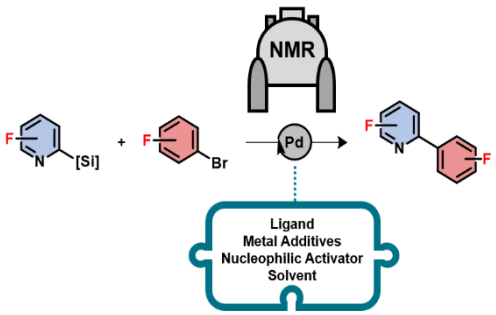

Figure 7: Overview of the key pieces to understand the cross-coupling of 2-silylated pyridyl derivatives.

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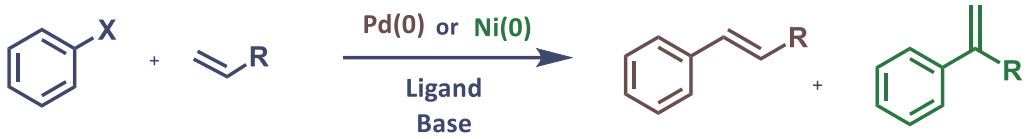
What the Heck?! The Mechanism of the Ni-Catalysed Mizoroki-Heck Reaction

Claire Jepsen[a], Andrés García-Domínguez[a], David Sale[b], Harvey Dale[b]

a. University of Edinburgh, Joseph Black Building, Edinburgh EH9 3FJ
b. Syngenta, Jeallot's Hill, Warfield, Bracknell RG42 6EY

The Mizoroki-Heck reaction, typically catalysed with Palladium, is a pillar of organic chemistry as it couples aryl/vinyl/benzyl electrophiles with terminal alkenes to form new sp^2 bonds under relatively neutral conditions and with high functional group tolerance. Nickel can achieve results comparable to Palladium, although it's selectivity and mechanism are not well understood experimentally. Dictated in the migratory insertion step, Nickel has high selectivity for the branched alkene product while Palladium mainly yields the linear alkene. To help deduce the regioselectivity relationship between the metal, ligands, electrophiles, and substrate electronics, the coupling of a benzyl chloride and an electronically unbiased alkene is used as the initial model system[1]. Using a Ni(II) precatalyst[2] allows for a homogeneous, air- and moisture- stable synthesis in just 4 hours at room temperature. This is an ideal system for reaction monitoring via in-situ ^{19}F NMR and UV-Vis. Combining UV-Vis and NMR techniques allow for the observation of catalyst oxidation states and speciation alongside the substrate and product kinetics. Understanding the factors that dictate regioselectivity will help showcase Nickel's reactivity and mechanistic differences from Palladium while allowing greater control of selectivity in synthesis.

Mizoroki-Heck Reaction



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Peering Inside the Gut: Real-Time Spatially Resolved Analysis of Pharmaceutical Degradation in the Human GIT

Trey T. Koev[1], Joseph Mauracheea[1], Fred J. Warren[2] and Matthew Wallace[1]

School of Chemistry, Pharmacy and Pharmacology, University of East Anglia, Norwich Research Park, NR4 7TJ
Food, Microbiome and Health, Quadram Institute Bioscience, Norwich Research Park, NR4 7UQ

Understanding how pharmaceutical materials degrade within the human gastrointestinal (GI) tract is critical for optimising drug delivery, bioavailability, and therapeutic outcomes. Conventional *in vitro* or bulk sampling methods often fail to capture the complex, dynamic environment of the GI system, leaving a critical gap between formulation design and *in vivo* performance. We present a novel platform enabling real-time, spatially resolved monitoring of pharmaceutical material degradation within a simulated human GI tract. By integrating advanced chemical shift imaging NMR with *in situ* data acquisition, our approach provides unprecedented insight into where, when, and how degradation occurs along the digestive pathway. This capability not only reveals site-specific variations in excipient stability and dissolution but also informs predictive models of parenteral drug delivery. The methodology opens new avenues for personalised medicine, improved formulation strategies, and regulatory science, bridging a longstanding disconnect between laboratory testing and real-world physiological conditions.

Kinetics and Mechanism of Boroxine Alcoholysis

Chen. Li,[a] L. Sotorrios,[b] P. J. Boaler,[a]

A. García-Domínguez,[a,*] A. G. Leach,[b,*] G. C. Lloyd-Jones[a,*]

a School of Chemistry, University of Edinburgh, Edinburgh EH9 3FJ, U.K.
b School of Health Sciences, The University of Manchester, Manchester M13 9PT, U.K.

Fast, readily controlled equilibria between boroxines and boryl derivatives underpin their physicochemical behavior and diverse applications.[1] While the equilibrium and boryl species are well-known and extensively applied,[1,2] the mechanism and kinetics governing these multistep interconversions remain poorly defined. Following on our prior detailed studies of arylboronic acids / arylboroxines exchange in aqueous THF,[3] the kinetics and mechanism of the additional alcohols promoted transformation between boroxines and boronic esters is investigated in this study using $^{1}H/^{19}F$ NMR and UV–vis spectroscopy, including titrations, stopped-flow kinetics, magnetization transfer, numerical simulations of reaction kinetics and equilibria, and DFT calculations with explicit solvation. The seven-membered cyclic intermediate, containing a 1,3,5,2,4-trioxadiborepane core, is identified in the interconversion with boronic esters. The amount of the seven-membered ring intermediate that accumulates depends on the ring strain in the ester ring. Two competitive pathways are illustrated, distinguished by whether the diol hydroxyl groups attack the same or different boron centers within the boroxine ring. Hydroxylic species, water and alcohols, act both as reagents and as catalysts in each step. These findings clarify the speciation of boryl species in complex media, and have implications for the use of boroxine derivatives as reagents, catalysts, and pharmaceuticals, as well as the design of materials, polymers, and dynamic architectures with new boryl skeletons.

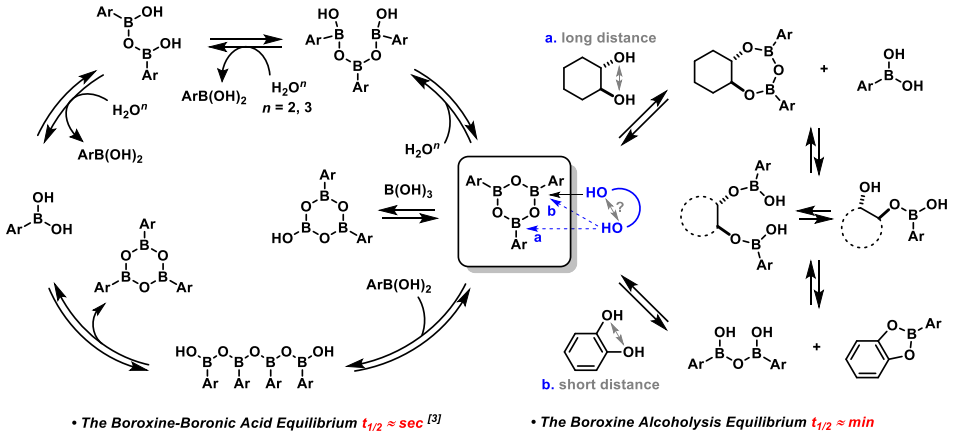

Figure 8: Proposed Mechanism of Boroxine Formation and Solvolysis

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Large Language Models for Small Molecule NMR Elucidation

Ben Morgan[1], Craig Butts[1], Markus Schade[2], Andrew McClusky[1], Richard Cox[1], Calvin Yiu[1]

1) University of Bristol, 2) AstraZeneca

There has been promising success in other groups using LLMs to interpret 1-D proton and carbon spectra.[1,2] It is believed this can be improved upon by incorporating 2D experiments into the inputs which has been used with great success in the Butts groups during prior research using CNNs, and GNNs.[3,4] This project tackles the elucidation of small molecule NMR spectra using large language machine learning models (LLMs). Initially a CNN was written which could assign the functional groups in a molecule with a high degree of accuracy (86.6% - 99.9% for the worst to best groups) from 1D proton and carbon spectra combined with COSY, HSQC, and HMBC. An LLM is now being developed to expand the capabilities and to fully elucidate 2D structures. This will be done by encoding spectra a series of tokens and then training an LLM to output a series of SELFIES string tokens corresponding to the 2D structure.[5] This will build on inverse IMPRESSION and hopefully create a leading tool for small molecule NMR elucidation.[3,4]

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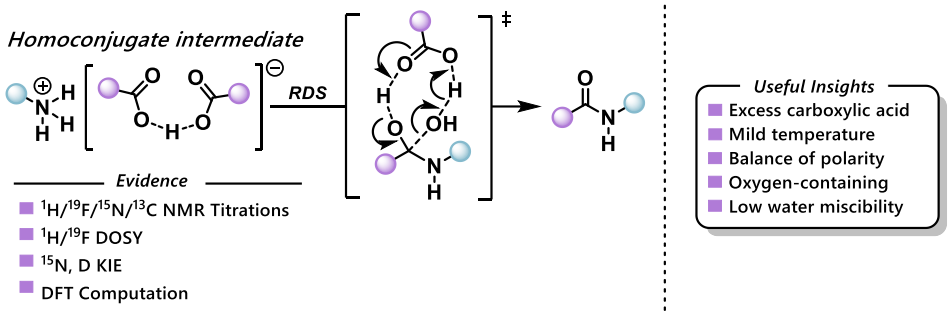
The Mechanism of Direct Amide Formation

Róisín O'Dea[a*], George Hodges[b], Guy C. Lloyd-Jones[a]

aUniversity of Edinburgh, UK, bSyngenta, UK.

Amide bonds are everywhere. In fact, their formation is the most frequently used chemical transformation in medicinal chemistry.[1] It is commonly taught in undergraduate chemistry that you cannot prepare an amide directly from a carboxylic acid and amine without pre-activation (*e.g.,* via acid chloride or by addition of carbodiimides/catalysts) due to unreactive salt formation. However, previous reports have shown that certain substrate combinations can react in the absence of additives [2] – offering a cleaner, cheaper, and more atom-efficient route. Despite its potential, the underlying mechanism of this reaction remains under-explored and poorly understood.

This work employs *in-situ* ^{19}F-NMR spectroscopy to continuously monitor additive-free direct amide formation, all in one NMR tube and without the need for water removal! ^{1}H/^{19}F DOSY and chemical shift NMR titrations provide information about the speciation under different conditions, and provide evidence for a homoconjugate intermediate which appears to correlate with enhanced reactivity. Additionally, ^{15}N/^{13}C NMR titrations and ^{18}O incorporation experiments probe the nature of the intermediates and various inhibitive pathways taking place in the background. Kinetic isotope effects (^{15}N, D KIEs) reveal surprising information about the rate-determining step, which is in agreement with a computed free energy profile. A kinetic model has been constructed which successfully fits rate data for > 80 reaction conditions, and includes multiple contributing equilibria which influence the overall reaction outcome. Ultimately, these results show an un-appreciated complexity which underlies this deceptively simple reaction, and that a delicate balance of polarity accounts for the specific conditions required for successful direct amide formation.



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In Situ Observation of Polyoxometalate Formation by Vibrational Spectroscopy

Pegah Saedi [a], Jan-Dominik H. Krueger [a], Jan-Christian Raabe [a], Zainab Yusufzadeh [a], Andreas Berger [b], Jakob Albert [a], Maximilian J. Poller [a]

a Department of Chemistry, University of Hamburg, Germany; b Mettler-Toledo Sales & Marketing GmbH, Germany

The sustainable transformation of biomass into value-added chemicals is a central challenge for future energy and chemical supply chains. Polyoxometalates (POMs), and in particular vanadium-substituted phosphomolybdates, have emerged as highly promising molecular catalysts for selective oxidative biomass valorisation, owing to their tuneable redox properties and high selectivity.[1] Their relevance for sustainable catalysis, however, critically depends on the availability of efficient, robust, and scalable synthesis routes that provide well-defined and reproducible catalyst materials. This aspect is essential for widespread use and eventual industrial application.

In this contribution, we present an in-situ vibrational spectroscopic study of the synthesis of different POM structures, aimed at elucidating key reaction steps and intermediate species formed during their assembly in aqueous solution.[2] Continuous infrared (IR) monitoring of the synthesis process enables direct, time-resolved observation of structural evolution in solution, providing unprecedented mechanistic insight into the formation of the POM framework. These measurements reveal that POM formation proceeds rapidly, even at low temperatures, rendering prolonged reflux conditions unnecessary and challenging long-established synthetic protocols.

A special focus of this study is placed on vanadium-substituted phosphomolybdates. Different synthetic strategies for the incorporation of vanadium into the phosphomolybdate Keggin structure were systematically investigated, providing insight into the underlying substitution mechanisms. Based on the real-time spectroscopic information obtained, synthesis parameters such as temperature and reaction time were optimised, resulting in a simplified synthetic procedure with significantly reduced synthesis times. This represents an important step towards the scalable production of vanadium-substituted POM catalysts.

These findings directly support the development of highly selective POM-based catalytic systems for sustainable biomass conversion, as pursued within advanced biomass valorisation strategies. More generally, this work highlights the power of in-situ reaction monitoring as a key tool for rational catalyst synthesis, mechanistic understanding, and process optimisation in molecular catalysis.

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In-Situ and Ex-Situ NMR Reveal Temperature-Dependent Degradation and Regeneration in Organic Redox Flow Battery Electrolytes

K. Singh and C. P. Grey

Yusuf Hamied Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

Aqueous organic redox flow batteries (AORFBs) are promising for grid-scale energy storage, but their performance is limited by temperature-dependent electrolyte degradation and incomplete regeneration. Here, we use in-situ and ex-situ NMR spectroscopy to obtain molecular-level insight into degradation and regeneration pathways and electrochemical kinetics in AORFBs under operating conditions. Anthraquinone-based anolytes (DHAQ) [1-3] were studied using real-time in-situ 1H NMR under continuous flow (Fig. 1), combined with multidimensional ex-situ NMR, over temperatures from 25 to 65 °C. The measurements reveal temperature-dependent degradation mechanisms, irreversible dimer formation, and kinetic processes governing capacity fade and regeneration limits. This integrated NMR framework links molecular transformations, kinetics, and electrochemical behaviour, providing design guidelines to improve the stability and cycle life of AORFBs.

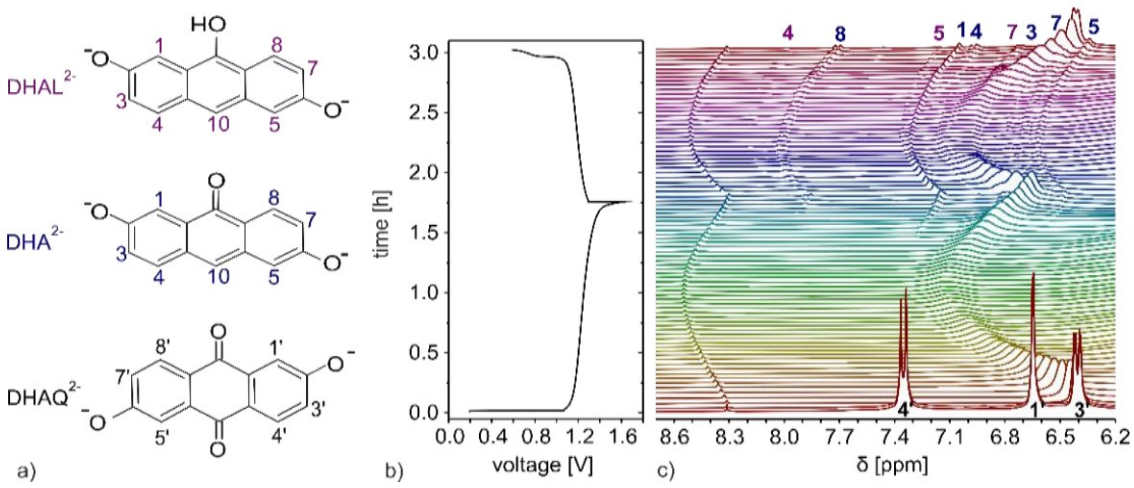

Figure 1. In situ 1H NMR during electrochemical cycling at 65 °C. (a) Molecular structures of DHAQ2-, DHA2-, and DHAL2- with proton assignments. (b) Cell voltage during the first charge–discharge cycle of a full cell. (c) In situ 1H NMR spectra of the anolyte aromatic region (64 s temporal resolution).

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Needs more base: an NMR mixing deck for reaction optimisation

Matthew Wallace,[a*] Serena Monaco[b] Claire F. Jones[a] and Valeria Tamburrini[a]

a: School of Chemistry, Pharmacy and Pharmacology, University of East Anglia, Norwich, NR4 7TJ, UK

b: Quadram Institute, Norwich Research Park, Norwich, NR4 7UQ, UK

Many reactions, including with enzymes, require the optimum conditions of pH, solvent composition and reagent concentrations to proceed at an acceptable rate. However, selection of these parameters is a tedious task with choices often based on intuition and guesswork. Many hours are wasted on setting, monitoring and working up reactions that fail to yield the correct products. In our group, we are developing ultrafast NMR methods to study systems as a function of the sample conditions using chemical gradients. These experiments provide high-resolution spectra at different vertical heights of a sample, enabling the progress of a reaction to be monitored across a range of conditions simultaneously as each vertical 'slice' of the NMR tube has a different pH, solvent or reagent concentration. For example, we can determine the optimum conditions for an enzymatic reaction by monitoring reaction progress at different positions along a pH gradient (Figure 1).

Similarly, taking advantage of the different densities of organic solvents and aqueous-organic mixtures, we can continuously vary the composition of the solvent across a tube just by layering two mixtures and leaving ca. four hours for diffusion. We can thus determine aqueous pK_a of water-insoluble compounds, identify tautomers and seamlessly convey challenging spectral assignments from one solvent to another.[1]

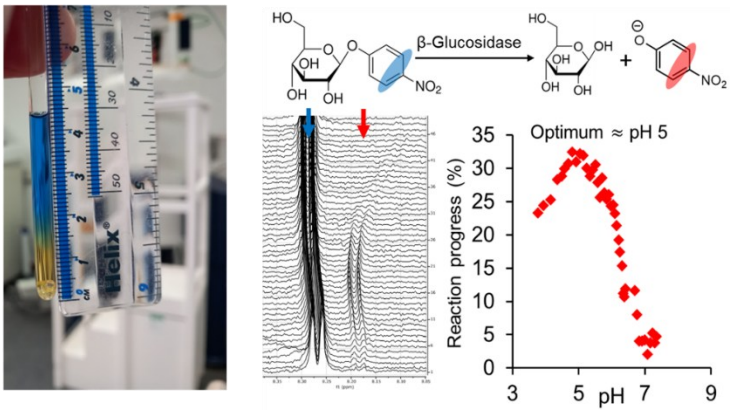

Figure 9: A concentration gradient of pH, solvent, reagent (or potentially all three) is generated within a standard 5 mm NMR tube. By monitoring reaction progress under a range of conditions simultaneously, hours of tedious screening is condensed into a single NMR experiment.

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The Total Reaction NMR Spectrum: A Direct Measurement of Chemical Kinetics

Annabel Flook[+], Patrick J. Boaler[+] and Guy C. Lloyd-Jones*

School of Chemistry, The University of Edinburgh, Edinburgh EH9 3FJ

Solution-phase NMR spectroscopy serves as a powerful, accessible tool for reaction monitoring, with quantitative potential and the ability to provide structural information across organic and organometallic chemistry.[1] However, reaction monitoring data is not always easy to analyse and multi-step chemical processes present a particular challenge due to the presence of intermediate species. The identity and kinetics of these species are crucial in building a robust understanding of a given reaction system, but are not captured in common approaches to kinetic analysis, such as linearisation techniques, steady state approximation or visual analysis approaches.[2,3]

Recently, our group has reported the Total Reaction Spectrum (TRS), which is generated by applying signal-averaging over all spectra acquired during quantitative *in situ* NMR reaction monitoring.[4] The procedure maximises signal-to-noise and facilitates identification of low-concentration intermediates formed during the monitored reaction. In this work, we demonstrate that the TRS is also a measurement of the area under the concentration-time profiles. Through a number of experimental case studies, we relate the TRS to a new kinetic framework: Cumulative Temporal Concentrations (CTCs), which describe the relationship between the TRS and reaction kinetics. The CTC framework provides a powerful handle for understanding chemical kinetics, can be extended and combined as building blocks to describe complex multi-step reactions, and allows the reactivity of intermediate species to be probed in both catalytic and stoichiometric reactions under synthetically realistic conditions.

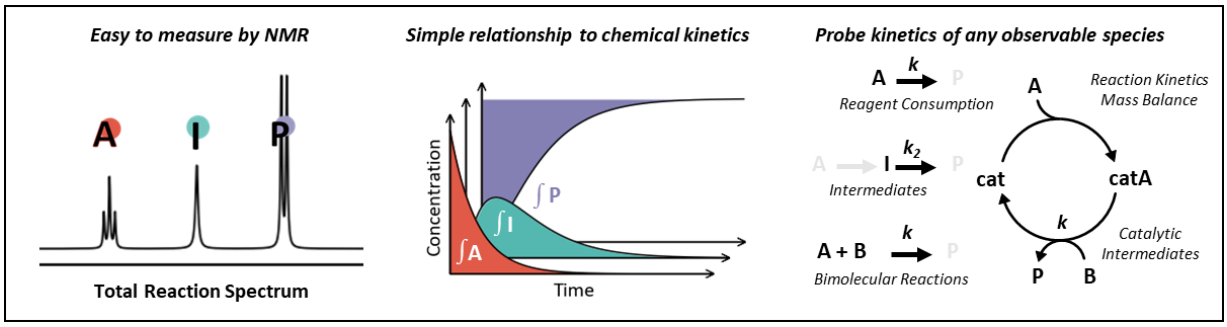

***Figure**: A Total Reaction Spectrum (left) describes the area under a concentration-time profile and can be related to chemical kinetics through a new kinetic framework (centre). The new framework allows the kinetics of observable species to be probed under synthetically realistic conditions.*

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Unsupervised kinetics tracking for online NMR scanning

Aleksandr Ostudin (ao1423@ic.ac.uk), Dr. Becky Greenaway, Prof. Kim Jelfs

Department of Chemistry, Imperial College London, Molecular Sciences Research Hub, London W120BZ, UK

We introduce an automated framework for tracking NMR peaks across time-resolved experiments that formulates peak evolution as a global assignment problem rather than a set of local heuristics, preserving maximal information from the original spectrum. Algorithm uses multi-objective optimisation for the initial peak detection, Kuhn-Munkers algorithm for the linear sum assignment and Gaussian Process models for the refining. Obtained kinetic profiles are clustered and compared with the existing database of NMR spectrums. This allows to detect in unsupervised manner the reaction outputs and kinetics, which can be used for the automated workflows with no human in the loop.

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NMR monitoring of fluorescein-based dye syntheses

Claire Jones and Matthew Wallace

University of East Anglia, School of Chemistry, Pharmacy and Pharmacology

Fluorescein-based dyes are used as pH indicators because the tautomeric equilibrium between the lactone and quinoid (fluorescent) is pH-dependent.[1] We can control the conversion using pH gradients in an NMR tube and monitor the change in conformation of the molecule(s).

Here we present chemical shift imaging (CSI) pH gradient ^{1}H-NMR spectra of each of the intermediate products of a four-step synthesis of a fluorophore [Fig. 1] Differences in the solubility of the molecules meant we had to convert from working in pure D_2O to pure d^6-DMSO necessitating the use of different chemical shift pH indicators.[2] The upfield shift of the indicators upon deprotonation is used to measure pH at different heights of the NMR sample. This work was useful to the synthetic chemist to correlate between products isolated in acidic and basic conditions. The spectra appear very different due to the large change in conformation of the molecule between lactone and quinoid forms, but by TLC they appear to be the same.

The obvious differences are very useful to determine if a base is strong enough to deprotonate the molecule in different solvents. We wish to take this idea forward to use these chromophores and other molecules that exhibit significant pH-dependent conformational changes to monitor deprotonation with common bases in green solvents providing a way to optimise switching reactions from the original solvent to the greener solvent in a single-tube.

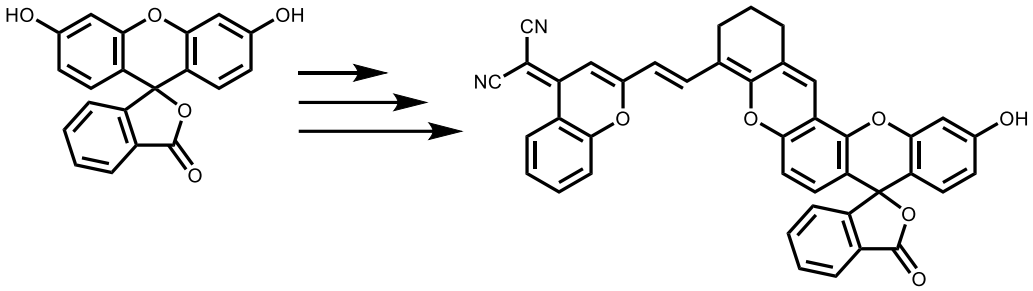

Figure 10: All intermediate products of the multistep synthesis exhibit pH-dependent tautomeric equilibria that can be imaged using chemical shift imaging NMR

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