Institute of Sustainability and Climate Change | University of Bath

Dynamic Reaction Monitoring FACILITY

6th Reaction Monitoring Symposium

Programme and Abstracts

28th January 2025

University of Bath

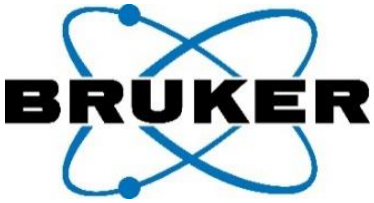
Dynamic Reaction Monitoring FACILITY

Institute of Sustainability and Climate Change | UNIVERSITY OF BATH

Reaction Monitoring Symposium Programme

Time	Activity	Venue
9.30 – 10.15	Registration, coffee, vendor exhibition	CB L1 foyer
Morning session chaired by Dr John Lowe		
10.15	**Prof Matthew Davidson and Dr Ulrich Hintermair, University of Bath, UK** Welcome and opening remarks	CB 1.10
10.30	**Dr Maxie Rößler, Imperial College London, UK** "Real-time reaction monitoring by EPR"	CB 1.10
11.10	**Dr Timothy McCabe, University of Strathclyde, UK** "Kineticolor: Non-contact Reaction Monitoring with Computer Vision"	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 chaired by Dr Anneke Lubben		
13.30	**Dr Kerstin Münnemann, University of Kaiserslautern-Landau, Germany** "Perspectives for Overhauser Dynamic Nuclear Polarization in Online NMR Spectroscopy"	CB 1.10
14.00	**Prof Alexander Forse, University of Cambridge, UK** "Online NMR studies of redox flow batteries and electrochemical CO_2 capture"	CB 1.10
14:30	Coffee and vendor exhibition	CB L1 foyer
Late afternoon session chaired by Dr Ulrich Hintermair		
15.00	**Annabel Flook, University of Edinburgh, UK** "Trust the Process: A Data Processing Technique to Improve Signal-to-Noise and Temporal Resolution of NMR Reaction Monitoring Data"	CB 1.10
15:30	**Prof Liam Ball, University of Nottingham, UK** "Dielectric Spectroscopy as a Tool for in situ Reaction Monitoring" ROYAL SOCIETY OF CHEMISTRY | INORGANIC REACTION MECHANISMS GROUP *RSC Inorganic Reaction Mechanisms Group Young Investigator Award Lecture*	CB 1.10
16.10	Closing remarks and poster prize	CB 1.10
16.20	Wine reception	CB L1 foyer
17.30	Close of meeting	

6th Reaction Monitoring Symposium made possible with generous support from our exhibitors:



Please visit our exhibitors in the L1 foyer during breaks

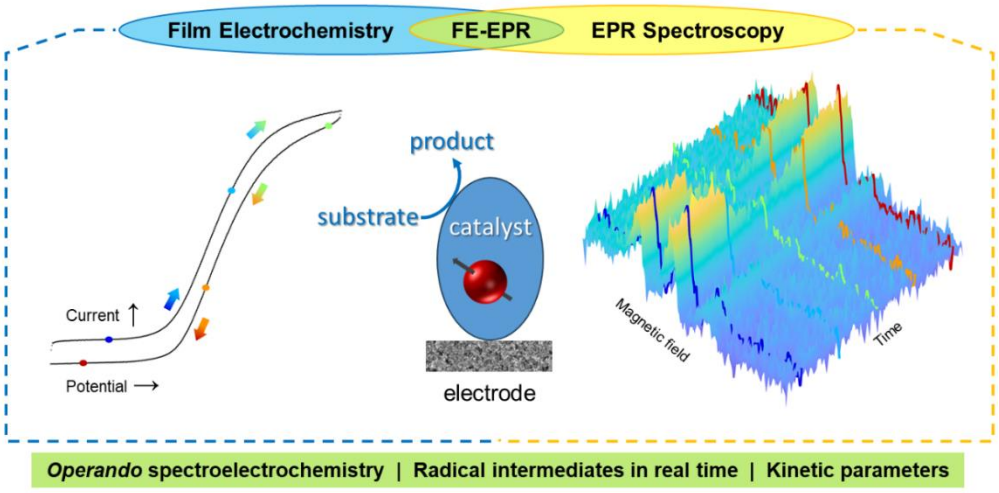
Real-time reaction monitoring by EPR

Maxie Rößler

Imperial College London
www.imperial.ac.uk/roessler-lab

Unpaired electrons play an important role in numerous redox-driven catalytic processes. Controlling their location and exploiting the interactions with their environment can provide key mechanistic information into these catalytic reactions.[1] In this talk, I will discuss how we are using electron paramagnetic resonance (EPR) derived techniques to gain mechanistic insights into redox-driven reactions.

Specifically, I will introduce film-electrochemical EPR spectroscopy (FE-EPR) as a new tool to investigate surface-bound molecular catalysts. With in situ and operando FE-EPR we can monitor the evolution of radicals during catalysis in real time, providing a novel way to benchmark such electrocatalysts.[2] Our current work is focused on extending FE-EPR to probe faster reactions and complex biological catalysts,[3] and to explore different electrode materials.



1. K. H. Richardson, M. Seif-Eddine, A. Sills, M. M. Roessler, Methods Enzymol 2022, 666, 233–296.
2. M. Seif-Eddine, S. J. Cobb, Y. Dang, K. Abdiaziz, M. A. Bajada, E. Reisner, M. M. Roessler, Nature Chemistry 2024 16:6 2024, 16, 1015–1023.
3. D. Facchetti, Y. Dang, M. Seif-Eddine, B. L. Geoghegan, M. M. Roessler, Chemical Communications 2024, DOI 10.1039/D4CC04013A.

Computer-vision Assisted Colorimetric Analysis of the UV-promoted Degradation of Polyurethane Foams

Timothy J. D. McCabe

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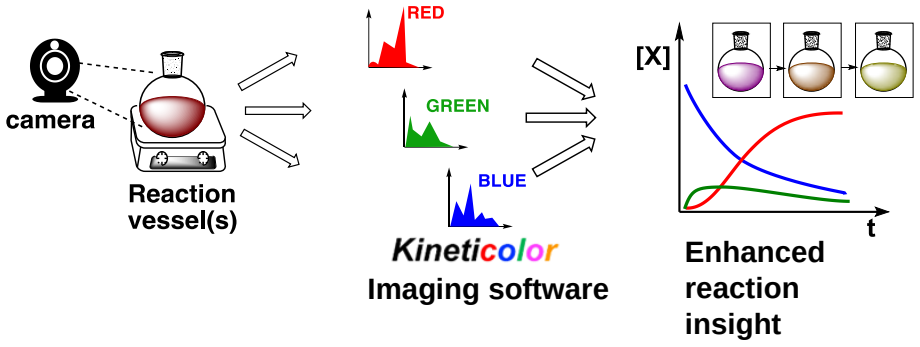
timothy.j.mccabe@strath.ac.uk ; https://www.linkedin.com/company/kineticolor/ .

Kineticolor, a software platform developed by Reid Group Research at the University of Strathclyde provides a rare and chemistry-agnostic example of a non-contact analytical tool that can provide quantifiable insights on reaction bulk. Using computer-vision technology, we are enabling chemists and technologists to extract data-rich, time- and space- resolved trends from any visible reaction, using any camera. This technology is applicable to processes where recourse to more traditional in-contact, probe-based technologies, is not possible. It can also be used as a complimentary tool giving insight on the reaction bulk, rather than the molecular specifics of a process. Kineticolor has already been used in advancing the understanding of catalyst activation, deactivation, forensic spot testing, amidation chemistry, as well as providing a computer-vision enabled platform for the analysis of mixing phenomena in chemical and non-chemical processes at different scales.[1-5] Kineticolor analysis has also been applied to understanding of dynamic, electrochromic performance of electro-active polymer films.[6]



1. Computer Vision as a New Paradigm for Monitoring of Solution and Solid Phase Peptide Synthesis. Chem. Sci. 2023, DOI: 1039/D3SC01383A.
2. Computer Vision for Non-contact Monitoring of Catalyst Degradation and Product Formation Kinetics. Chem. Sci. 2023, DOI: 10.1039/D2SC05702F.
3. Teaching old presumptive tests new digital tricks with computer vision for forensic applications. Digital Discovery 2023, DOI: 1039/D3DD00066D.
4. Computer Vision for Kinetic Analysis of Lab- and Process-Scale Mixing Phenomena. Org. Process Res. Dev. 2022, DOI: 10.1021/acs.oprd.2c00216.
5. A Computer Vision Approach toward Verifying CFD Models of Stirred Tank Reactors. Org. Process Res. Dev. 2024 DOI: 10.1021/acs.oprd.4c00229
6. Non-contact computer vision enables analysis of the dynamic performance of naphthalene diimide electrochromic films. J. Mater. Chem. C. 2024, DOI: 10.1039/d4tc02096k

Perspectives for Overhauser Dynamic Nuclear Polarization in Online NMR Spectroscopy

Kerstin Münnemann

Laboratory for Advanced Spin Engineering, Core Facility Magnetic Resonance (LASE-MR), RPTU Kaiserslautern, Germany

NMR spectroscopy is an attractive analytical technique for reaction and process monitoring. Robust benchtop NMR spectrometers have extended the applicability of the method to industrial processes. Process monitoring is often carried out on-line: the mixture that is to be analysed is pumped through the analytic instrument, which is operated in flow mode. In these setups, the volume of the line between process and analysis should be small and flow rates should be high to enable a fast transport to the analytic instrument. In NMR spectroscopy, this is in conflict with the time needed for sufficient polarization build-up, which is particularly problematic for benchtop NMR spectrometers because of their compact design. However, hyperpolarization methods like Overhauser Dynamic Nuclear Polarization (ODNP) are well suited to overcome this problem because hyperpolarization build-up happens on very short timescales and can be performed under continuous flow [1, 2, 3].

However, a challenge in combining online NMR with ODNP is quantitative analysis, because the ODNP efficiency varies greatly depending on the solvent, receptor molecule, type of radical, sample temperature, measured nucleus, and polarization field. To take these effects into account and to understand the underlying physical effects in detail, Molecular Dynamics (MD) simulations combined with quantum mechanical calculations can be performed [4]. However, these simulations are tedious and were demonstrated so far only for a radical dissolved in a pure solvent. For more complex and temporarily changing systems, as being present in chemical reactions, simulations would be extremely time-consuming if possible at all. A better strategy is to enable quantitative analysis by means of calibration which is the topic of this lecture. We demonstrate continuous-flow ODNP enhanced 1H and 13C NMR measurements in binary solvent mixtures (acetonitrile + water, acetonitrile + 1,4-dioxane, acetonitrile + chloroform) with varying compositions. Quantitative analysis of the hyperpolarized mixtures is enabled by means of calibration and the benefits and drawbacks of the method are discussed (see Figure 1).

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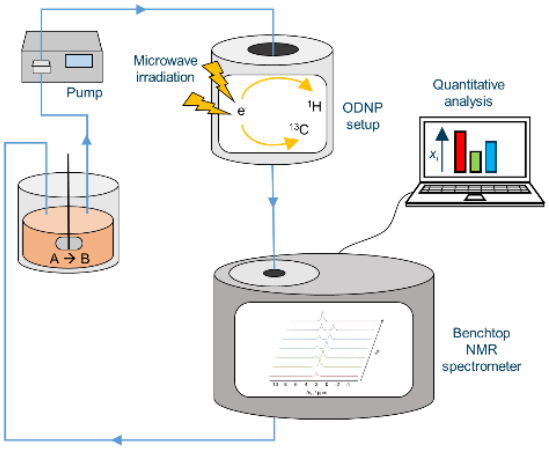


Figure 1: Sketch of ODNP for process monitoring applications

1. R. Kircher, H. Hasse, K. Münnemann, Analytical Chemistry 93, 25, 8897–8905 (2021).
2. R. Kircher, S. Mross, H. Hasse, K. Münnemann, Molecules 27, 6402-6418 (2022).
3. J. Phuong, B. Salgado, T. Labusch, H. Hasse, K. Munnemann, Analytical Chemistry (2025). https://doi.org/10.1021/acs.analchem.4c03985.
4. D. Sezer, M.J. Prandolini, T.F. Prisner, Physical chemistry chemical physics 11 (31), 6626-6637 (2009).

Developing online NMR to understand electrochemically-driven CO_2 capture

Alexander Forse, Jack Taylor, Emma Latchem, Alex Thom, Suzi Pugh

University of Cambridge, Yusuf Hamied Department of Chemistry

We are in a climate change crisis and urgently need efficient greenhouse gas mitigation. Electrochemical carbon dioxide capture is an emerging energy efficient approach that can overcome some of the limitations of traditional thermally driven processes.

A promising strategy is to employ redox active molecules that become activated for CO_2 capture following electrochemical reduction, though the mechanisms of the electrochemical and chemical steps remain unclear in this process.

We show that online NMR can be used to follow the electrochemical CO_2 capture process when using anthraquinone capture agents, and we find new insights into the capture mechanism. Challenges and opportunities for the field of electrochemical CO2 capture will be discussed.

Trust the Process: A Data Processing Technique to Improve Signal-to-Noise and Temporal Resolution of NMR Reaction Monitoring Data

Annabel Flook, Guy Lloyd-Jones

University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh, EH9 3FJ

Solution-phase NMR spectroscopy provides a powerful, yet accessible tool to monitor reaction progress with quantitative concentrations, detailed structural information and high sensitivity across several nuclei common in organic reactions. For reaction monitoring, analytically useful spectra should aim to have a) suitably high signal-to-noise ratio (S/N) to resolve both high and low concentration species present in the reaction and b) high temporal resolution to well describe the reaction with high data density.[1]

Increasing the number of scans applied during acquisition (signal-averaging) is often employed to improve S/N, but is also detrimental to temporal resolution. Alternatively, signal-averaging can be applied flexibly in post-acquisition processing, which is now feasible due to the developments in computer storage and computational power over the last 50 years.[2]

Several benefits for reaction monitoring were realised by changing signal-averaging to be a processing technique rather than an acquisition parameter. The power of this technique can be appreciated during processing; signal-averaging can be applied with a moving or rolling window, which maintains the temporal resolution with which the data was acquired and enhances S/N. Additionally, S/N can be maximised by applying signal-averaging over all FIDs, allowing low concentration intermediates to be identified. This method can also be applied to more complex pulse sequences, such as solvent suppression, with the same results.[3]

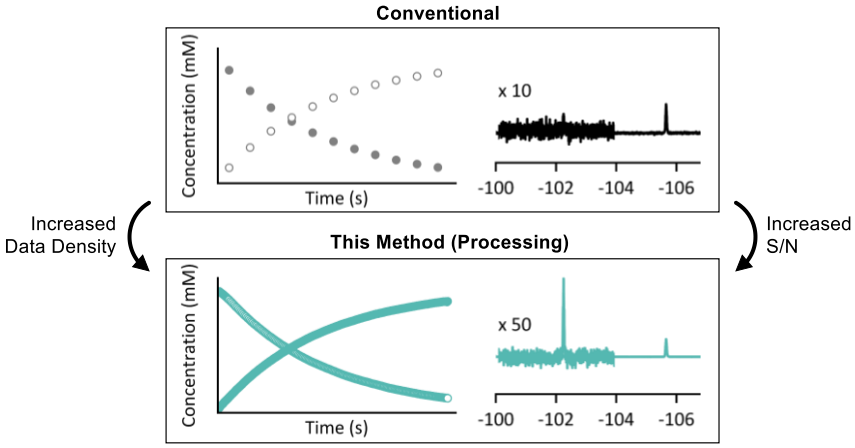


Figure: Using an alternative method for reaction monitoring to acquire spectra, the number of kinetic data points can be increased (top left: conventional, this method: bottom left), as well as S/N (top right: conventional, this method: bottom right).

1. Y. Ben-Tal et al, Prog. Nucl. Magn. Reson. Spectrosc., 2022, 129, 28-106
2. Ernst, R. R., Rev. Sci. Instrum. 1965, 36, 1689–1695
3. Flook, A., Lloyd-Jones, G. C., J. Org. Chem., 89, 16586 – 16593, 2024

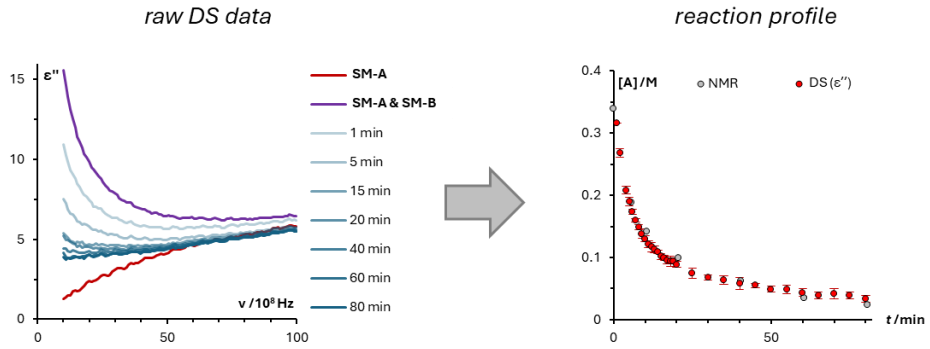
Dielectric Spectroscopy as a Tool for in situ Reaction Monitoring

Desiree M. Dalligos,[a] Michael J. Pilling,*[b] Georgios Dimitrakis,*[c] and Liam T. Ball*[a]

a) School of Chemistry, University of Nottingham, Nottingham NG7 2RD, U.K. b) Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield SK10 2NA, U.K. c) Department of Chemical and Environmental Engineering, University of Nottingham, Coates Building, Nottingham NG7 2RD, U.K.

In situ reaction monitoring is essential for the development of new synthetic methodology and robust manufacturing processes, and as the basis for experimental mechanistic studies. Although many process analytical tools exist for *in situ* reaction monitoring, there is no single technique that can be applied to every reaction system, and there thus remains need for new tools that complement the mainstream analytical methods

This lecture will introduce broadband dielectric spectroscopy (DS) as a technique, and will discuss its strengths and limitations as a tool for *in situ* reaction monitoring.[1] The workflows for collecting DS data, and the importance of using multivariate data analysis to ensure that the data are both precise and accurate, will be described.



1. D. M. Dalligos, M. J. Pilling, G. Dimitrakis and L. T. Ball, Coaxial Dielectric Spectroscopy as an In-Line Process Analytical Technique for Reaction Monitoring, Org. Process Res. Dev., 2023, 27, 1094–1103.

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Poster Presentations

Presenter	Poster Number
Christina Wartmann	**1**
Alexander Echtermeyer	**2**
Patrick J. Boaler	**3**
Molly I. Parry	**4**
Pedro H. Helou de Oliveira	**5**
Yuliia Horbenko	**6**
Roisin O'Dea	**7**
Rucha S. Medhekar	**8**
Jan-Dominik H. Krueger	**9**
Oliver R. J. Nedderman	**10**
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Faidra Batsaki	**12**
Charlie Parfitt	**13**
Yuan Gao	**14**
Sooyeon Moon	**15**

Poster 1:

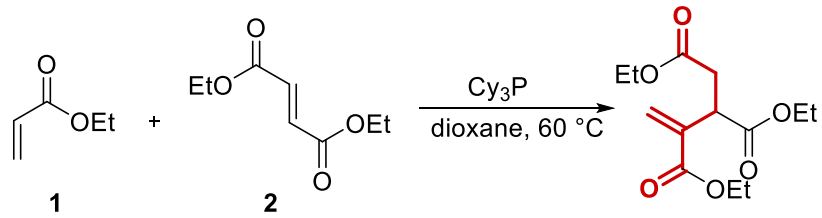
Mechanistic Investigations on the Rauhut-Currier Reaction

C. Wartmann, G. C. Lloyd-Jones

University of Edinburgh, David Brewster Rd, Edinburgh EH9 3FJ

The Rauhut-Currier (RC) reaction describes the reaction of two Michael acceptors in the presence of a nucleophilic phosphine catalyst and was first reported by Rauhut and Currier in 1963.[1] An example for such a RC reaction is the coupling of ethyl acrylate (**1**) and diethyl fumarate (**2**), first reported by Kobayashi.[2] While the structural motive obtained in the RC reaction (highlighted in red) is found in an abundance of natural products,[3] its application is still limited by a lack of product selectivity. This study aims to elucidate the mechanism of the RC reaction and to gain a better understanding of the mechanism, especially of the proton transfer, and the origin of product selectivity – or lack thereof.

Here, our mechanistic studies on the coupling of ethyl acrylate (**1**) and diethyl fumarate (**2**) are presented. Using *in situ* NMR, detailed kinetic analyses and D-labelling studies have been performed. From these inferences on the turnover limiting step and the mechanism of the proton transfer are made.



1. M. M. Rauhut, H. Currier, Patent No. US307499A, 1963, United States
2. K-i. Morita, T. Kobayashi, Bull. Chem. Soc. Jpn. 1969, 42, 2732-2732.
3. a: A. B. Smith, Q. Han, P. A. S. Breslin, G. K. Beauchamp, Org. Lett. 2005, 7, 5075-5078; b: S. Hatakeyama, M. Kawamura, E. Shimanuki, S. Takano, Tetrahedron Lett. 1992, 33, 333-336; c: Y. Guo, T. Quan, Y. Lu, T. Luo, J. Am. Chem. Soc. 2017, 139, 6815-6818; d: M. M. Littleson, C. M. Baker, A. J. Dalençon, E. C. Frye, C. Jamieson, A. R. Kennedy, K. B. Ling, M. M. McLachlan, M. G. Montgomery, C. J. Russell, A. J. B. Watson, Nature Commun. 2018, 9, 1105.

Poster 2:

Spectroscopic Insights into Biorefinery Processes

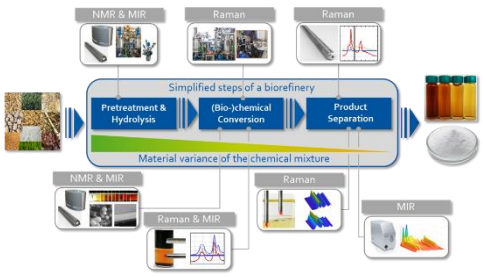
Alexander Echtermeyer, Clemens Minnich

S-PACT, Aachen, Germany

The transition from a fossil-based chemical industry to a circular, sustainable bioeconomy is one of the crucial steps toward a sustainable future economy. First, closed carbon cycles must be established, i.e., by chemical utilization of biogenic raw and residual materials. Second, a joint product-process-development targeting highly efficient and selective production technologies needs to be followed. This can be achieved with biorefinery and biotechnology processes that are among the key technologies to provide versatile molecular building blocks, fine and tailored molecules, or even complex biopharmaceuticals to the chemical and life science industry. In contrast to established (petro-)chemical processes, biorefineries are built on innovative processing concepts at rather mild reaction conditions, requiring flexible operation to quickly adjust to different types and seasonal qualities of raw materials.

To provide the necessary process data for a flexible and efficient plant operation, inline process spectroscopy techniques, such as Raman, mid-infrared (MIR), or nuclear magnetic resonance (NMR) spectroscopy, are well suited because they yield time-resolved multivariate data in a fast, robust, reliable, and automated manner. The transformation of the raw data into interpretable results such as component concentration profiles and other mixture properties is done with chemometric software such as PEAXACT, which provides a comprehensive set of spectra analysis methods including mechanistic and robust Spectral Hard Modelling. Coupling of the spectrometer with the chemometric model by in-build interfaces or the PEAXACT ProcessLink creates a powerful process analyser that acquires valuable multi-component information for process control units and plant operators.

This work highlights successful applications of process monitoring solutions employing spectroscopic techniques combined with comprehensive chemometric methods to gain insight into different biorefinery and biotechnology process steps.



Technique	Pro/Con
MIR	✓ unaffected by turbidity and coloration ✓ excellent chemical stability ⊘ fouling on ATR element ⊘ limited flexibility of fibers
Raman	✓ resolution of similar components ✓ heterogeneous media ⊘ fluorescence, coloration, and complex scattering ⊘ advanced safety considerations
NMR	✓ highly specific and well-resolved ✓ unaffected by coloration ⊘ critical in heterogeneous media ⊘ no inline but bypass installation

Figure 2: Application examples for process spectroscopy at different steps in biorefinery and biotechnology processes with pro and contra technique comparison [1]-[3].

1. A. Echtermeyer, (2022), Doctoral Dissertation, RWTH Aachen University, DOI: 10.18154/RWTH-2022-09155.
2. A. Milewska et al., (2023), Eng. Life Sci. 23(2), e2200050.
3. K. Saur et al., (2023), Bioengineering 10(6), 723-767.

Poster 3:

Extracting Microkinetic Rate Constants Directly from Reaction Monitoring Data using Cumulative Temporal Concentrations

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

School of Chemistry, The University of Edinburgh, David Brewster Road, Edinburgh EH9 3FJ

Despite impressive advances in spectroscopic capabilities and resolution over the past three decades, there have been comparatively few innovations in data processing techniques to aid in formulating quantitative models of reaction kinetics. Because of this, full-system kinetic modelling of reactions with complex mechanisms remains a challenging and laborious process, even with access to high quality data.

This project presents Cumulative Temporal Concentrations (CTCs) – quantities derived directly from temporal NMR data by summation – which establish a direct link between raw spectroscopic data and a subset of the rate constants within a reaction network describing the chemistry (a mechanism). Through exploring the underlying mathematics that describe this relationship, we show that CTCs can provide access to certain microkinetic rate constants directly from reaction monitoring data, vastly simplifying the kinetic modelling process and sometimes circumventing it altogether. Alongside an introduction to the theoretical framework that we have developed for CTCs, several experimental examples will be presented in which microkinetic rate constants forming part of a multistep mechanism are reconstructed using only NMR reaction monitoring data and initial concentrations.

Poster 4:

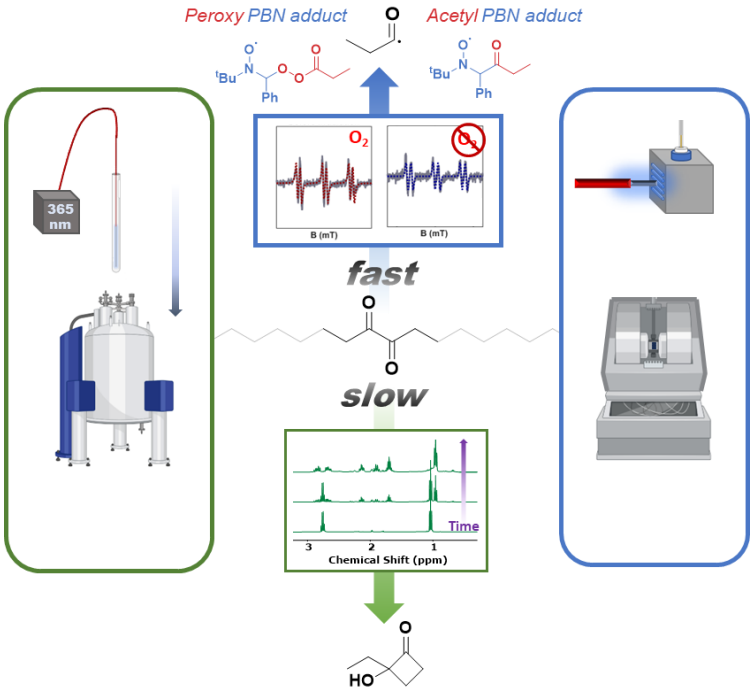
Revealing Polymer Degradation Mechanisms by EPR and NMR in Tandem

Molly I. Parry,[a,b] Gavin Hill,[c] Ali Salehi-Reyhani,[d] Maxie M. Roessler,[a,b] and George J. P. Britovsek[a]

a) Department of Chemistry and b) Centre for Pulse EPR Spectroscopy (PEPR), Imperial College London, Molecular Sciences Research Hub, 82 Wood Lane, London, W12 0BZ, United Kingdom. c) Polymateria Ltd., London, W12 0BZ, United Kingdom and d) Department of Surgery & Cancer, Imperial College London, Hammersmith Campus, W12 0HS, United Kingdom.

The resistance of plastics to degradation is part of their appeal, but their environmental persistence is an increasingly pressing issue. By studying photodegradation, we can exploit our understanding of these pathways for polymer design.[1] The carbonyl group is the target site for Norrish type photoreactions. These radical-forming reactions initiate C—C cleavages and reductions in polymer chain length. Here, we use EPR and NMR spectroscopy to unravel the photoreactivity of α,β-diones. The diketo group is deliberately incorporated into polyethylene analogues to accelerate their photodegradation. Hexane-3,4-dione is used as a model compound to study the photoreactivity of such diketo groups.

We have developed EPR- and NMR-based methodologies to study these photoreactions. Fibre-coupled LEDs allow irradiation of the model compound and *in situ* monitoring of its reactivity by both EPR, in conjunction with spin trapping, and NMR spectroscopy.[2] *In situ* and *ex situ* NMR studies using hexane-3,4-dione have shown the major irradiation product to be the cyclobutanone shown below. However, PBN-trapped radicals are not consistent with the expected radical intermediate for this process. Instead, peroxy and acetyl radicals are trapped in the presence and absence of oxygen, respectively. These results show that the cyclisation reaction is slow, and it is the products of the faster but reversible C—C cleavages that are spin-trapped. Thus, our work shows how *in situ* NMR and EPR can be used successfully in tandem to understand photodegradation pathways. Future work will look at exploiting this mechanistic understanding to design suitable polymer keto-derived additives for controlled photodegradation.



1. A. Ammala et al., Prog. Polym. Sci., 2011, 36 (8), 1051–1049
2. S. Ho et al. ChemPhotoChem, 2023, 7, e202200290.
3. Figure created with BioRender.com.

Poster 5:

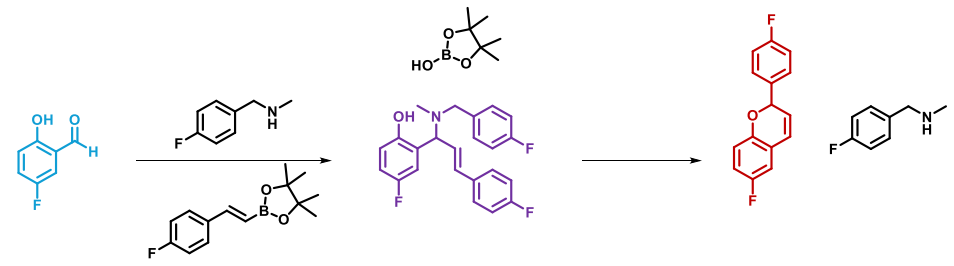
Mechanistic and Kinetic Studies on the Petasis borono-Mannich Reaction

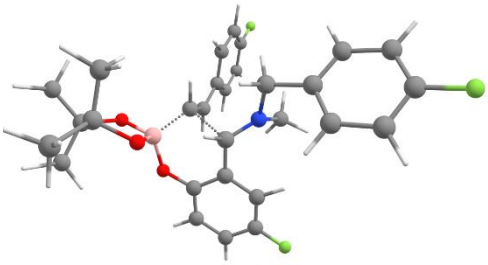
Pedro H. Helou de Oliveira[a], Prof Guy C. Lloyd-Jones FRS[a]

a) EaStChem, University of Edinburgh, School of Chemistry, Joseph Black Building, Edinburgh, EH9 3FJ, UK

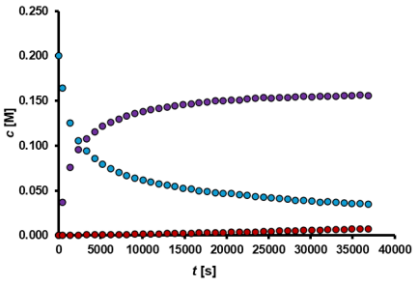
email: s2016373@ed.ac.uk

Multicomponent reactions are a widely used method to access complex scaffolds with high atom-economy and selectivity.[1, 2] The Petasis borono-Mannich (PBM) reaction involving formaldehyde, secondary amines, and vinyl boronic acids was first reported in 1993 in the synthesis of naftifine reported by Petasis and co-workers.[3] Herein we present out results from kinetic studies on the PBM reaction of 5-fluorosalicylaldehyde, *N*-methyl-4-fluorobenzylamine, and *p*-fluorostyrylpinacolboronic ester. From insight obtained through computational studies, mechanistic experiments, and kinetic measurements employing in situ NMR Monitoring (^{1}H, ^{19}F) we present a pathway for the condensation of the salicylaldehyde, amine and organoboron species as well as for subsequent reactions involving condensation products.





Calculated Transition State



Concentration-Time Profile

1. C. Marques, P. Brandão, (2023), Catalysts 13, 1022.
2. N. R. Candeias, F. Montalbano, P. M. S. D. Cal, P. M. P. Gois, (2010), Chem. Rev. 110, 6169.
3. N. A. Petasis, I. Ankritopoulou, (1993), Tet. Lett. 34, 583.

Poster 6:

Multi-way analysis of diffusion NMR data for the monitoring of a click chemistry reaction

Yuliia Horbenko,[a] Martin Jaudronnet,[a] Nour El Sabbagh,[a] Margherita Bazzoni,[a] Aurélie Bernard,[a] Mathias Nilsson,[b] Patrick Giraudeau,[a] François-Xavier Felpin,[a] and Jean-Nicolas Dumez[a]

a) Nantes Université, CNRS, CEISAM UMR 6230, F-44000 Nantes (France).
b) Department of Chemistry, University of Manchester, Oxford Road, Manchester, UK M13 9PL.

Diffusion NMR can be used to separate the spectra of mixture components and has been used successfully to monitor reactions,[1] provided that the data can be collected on a timescale that is short enough compared to that of the reaction of interest. Its most common data representation, Diffusion-Ordered Spectroscopy (DOSY), makes it possible to separate the 1D spectra of individual mixture components and access their diffusion coefficients.[2] However, the traditional DOSY approach is strongly limited by peak overlap which prevents it from getting clean spectra and true values of diffusion coefficients. For a reaction time course followed by diffusion NMR there are powerful alternatives including multi-way analysis methods such as Parallel Factor Analysis (PARAFAC), which exploit the trilinear nature of the data and can often recover the sought spectra, time course, and diffusion information.[3]

Here we describe the monitoring of a Cu-Catalyzed Azide−Alkyne Cycloaddition (CuAAC) reaction,[4] carried out in a tube or monitored by flow NMR. For the diffusion NMR experiment, we use a convection-compensated one-shot double-stimulated echo pulse sequence for the diffusion experiments, which provides high quality data with good time resolution (~ 1 min).[5] Univariate DOSY analysis results in partial spectrum separation due to significantly different diffusion coefficients of reactants and a product, whereas PARAFAC decomposition gives clean product spectrum and accurate (3 %) estimates of its diffusion coefficient. This work illustrates the potential of multi-way methods in reaction mixture analysis.

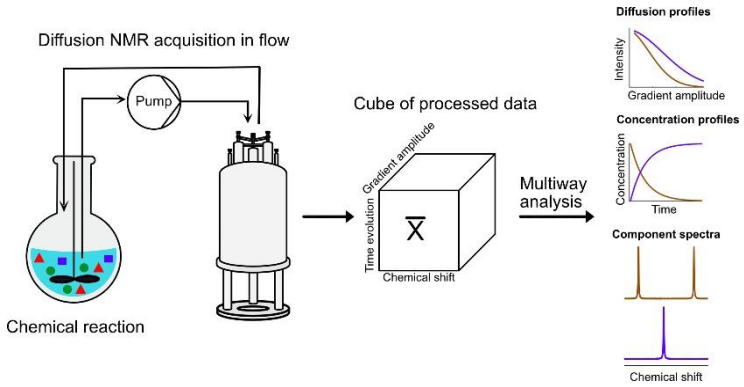


Figure 3: General strategy: real-time diffusion NMR and multi-way analysis yields product spectrum, concentration and diffusion profiles.

1. G. Pagès, V. Gilard, R. Martino, M. Malet-Martino, (2017), Analyst 142, 3771–3796.
2. C. S. Johnson, (1999), Prog. Nucl. Magn. Reson. Spectrosc. 34, 203–256.
3. M. Nilsson, M. Khajeh, A. Botana, M. A. Bernstein, G. A. Morris, (2009), Chem. Commun. 10, 1252–1254.
4. C. D. Hein, X.-M. Liu, D. Wang, (2008), Pharm Res 25, 2216–2230.
5. A. Marchand, R. Mishra, A. Bernard, J.-N. Dumez, (2022), Chem. Eur. J. 28, e202201175.

Poster 7:

Mechanistic Insights in the Direct Formation of Amides

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The amide bond is fundamental to nature, industry, and the entire scientific world. Its formation is the most frequently used chemical transformation in medicinal chemistry. 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 or catalysts) due to the formation of unreactive salt pairs. However, previous reports have shown that certain combinations of substrates can react in the absence of additives.[1] This direct coupling reaction offers a simpler, cheaper and atomically efficient route, with water being the only by-product. Despite its potential, mechanistic studies into this additive-free reaction remain extremely limited.

This work employs *in-situ* ^{19}F-NMR spectroscopy to continuously monitor and analyse the kinetics of additive-free direct amide formation within a single NMR tube[2], and without the need for water removal. Observation of how chemical shift and diffusion behaviour change in different conditions with NMR titrations provide insight into substrate interactions, and enable equilibrium constants (K_1, K_2) to be extracted for each combination. These findings suggest the presence of this homoconjugate intermediate is required for enhanced reactivity. Isotopic entrainment (^{13}C, ^{15}N, ^{18}O) and computational studies contribute to additional mechanistic insight and show this to be a more complex reaction than first appears, with multiple equilibria processes contributing to the overall reaction rate.

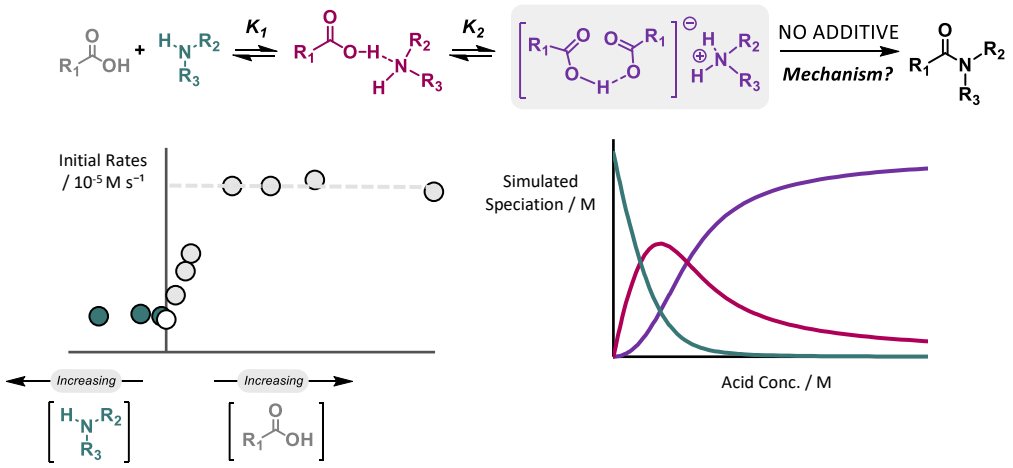

Figure 4: Evidence to suggest build-up of homoconjugate accounts for enhanced reactivity.

1. H. Charville, D. A. Jackson, G. Hodges, A. Whiting, M. R. Wilson, (2012), Chem. Comm., 48, 666.
2. G. C. Lloyd-Jones, and co-workers, (2022), Prog Nucl Magn Reson Spectrosc, 129, 28.

Poster 8:

Operando Spectroscopy: An important tool for catalyst deactivation studies

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High catalyst stability is extremely necessary for good catalytic performance, especially when continuous processes with physical separation steps are considered. [1] Catalyst deactivation greatly affects the catalyst performance leading to reduced conversion and selectivity. This can result in varied product streams, reduced reaction, and higher process costs, and in general a reduced process performance. [2] Studying the catalytic system and understanding the deactivation mechanisms, to then control the reaction conditions before the product quality actually declines, could result in more stable product qualities. Operando spectroscopy is an emerging tool for studying the catalytic system, which utilizes real-time analytical techniques, carried out under reaction conditions. [3]

Figure 1: The operando miniplant, containing a GC, NMR, and FTIR.

In our work, operando spectroscopic techniques are used to investigate the catalytic cycle of hydroformylation of 1-decene, catalyzed by a Rh catalyst complex. For this purpose, a miniplant is set up in which the reaction mixture from the reactor is pumped through the NMR, FTIR and GC. With this operando setup, it is possible to detect unstable intermediates formed during the reaction and thus analyze the catalytic cycle. In this work, the hydroformylation of 1-decene was successfully monitored. In addition, methods for prolonging and restoring catalytic activity are to be developed and used for process control, in order to obtain more stable product streams.

This work is funded by the Deutsche Forschungsgemeinschaft under project number 537105915.

1. J. M. Dreimann, E. Kohls, H. F. W. Warmeling, M. Stein, L. F. Guo, M. Garland, T. N. Dinh, A.J. Vorholt, ACS Catalysis, 2019, 9 (5), 4308–4319.
2. R. H. Crabtree, Chem. Rev., 2015, 115, 127–150.
3. K. Köhnke, N. Wessel, J. Esteban, J. Jin, A. J. Vorholt and W. Leitner, Green Chem., 2022, 24, 1951–1972.

Poster 9:

Enhanced Biomass Valorisation by Engineering of Polyoxometalate Catalysts (BioValCat)

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Producing fuels and chemicals from renewable raw materials, such as biomass, is needed to reduce our ecologic footprint and especially the CO_2 emissions. Therefore, the development of sustainable processes to produce e.g. platform chemicals based on biomass as renewable resource is currently one of the most important challenges of our society.

One process for such valorization of biomass is the Erlanger OxFA process, where even complex biomass is selectively oxidized to formic acid and its derivatives, using a homogeneous polyoxometalate ($H_8PV_5Mo_7O_{40}$) catalyst and O_2 as an oxidant.[1,2] Although this process is already commercially applied by the OxFA GmbH since 2015, novel insights promised to drastically improve this technology further.

A recent publication has shown that the formation of undesired CO_2 can be almost completely suppressed by the addition of methanol.[3] Mechanistic insights proved the catalyst-solvent interactions as main reason.[4] Interestingly, changing reaction parameters as type of gas, temperature and solvent systems can broaden the product scope,[5] e.g. formic acid can be converted to green H_2 or green CO (syngas equivalent) and lactic acid can be used to form polylactic acid (PLA) as biological degradable plastic. These aspects, which are the key of the BioValCat project, are summarized in **Error! Reference source not found.** and are under current focus of our research.

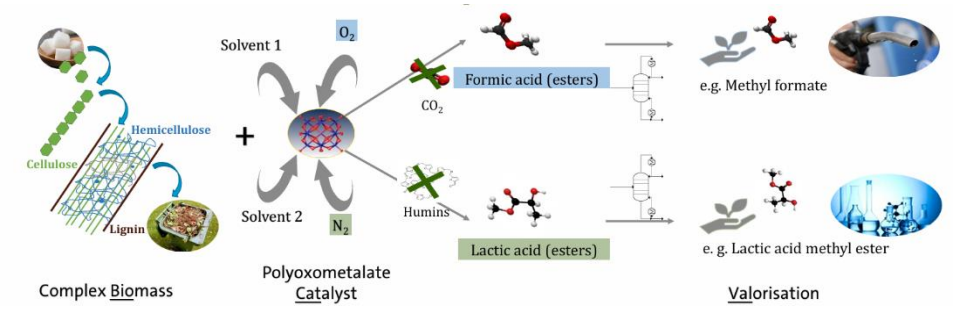

Figure 5: Summarised aspects of the BioValCat project (ERC Consolidator Grant No. 101086573)

1. Voß, D.; Kahl, M.; Albert, J. ACS Sustain. Chem. Eng. 2020, 8 (28), 10444–10453.
2. Raabe, J.-C.; Poller, M. J.; Voß, D.; Albert, J. ChemSusChem 2023, 16, 202300072–202300073.
3. Wesinger, S.; Mendt, M.; Albert, J. ChemCatChem 2021, 13 (16), 3662–3670.
4. Krueger, J. D. H.; Poller, M. J.; Lyall, C.; Lowe, J.; Hintermair, U.; Albert, J. ChemCatChem 2024, e202400402.
5. Voß, D.; Dietrich, R.; Stuckart, M.; Albert, J. ACS Omega 2020, 5 (30), 19082–19091.

Poster 10:

Chiroptical Growth and Circularly Polarised Luminescent Properties of Cyanine Dye J-Aggregates

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Cyanine dyes are known to form *H*- and *J*-aggregates in aqueous solution.[1,2] In our work, we have shown that the cyanine dye, TDBC, can form vortex induced-chiral *J*-aggregate assemblies in water.[3,4] In these studies, we showed that the chirality of the *J*-aggregates depend on the directionality of the stirring. This was studied using benchtop spectropolarimeters and Mueller matrix polarimetry (MMP). We probed the mechanism of formation and linear dichroism effects in the formation of the *J*-aggregates. We observed how the vortex caused growth of the *J*-aggregate resulting in large CD signals as the stirring of the solution continued over many hours. Herein, we also report the first case of solution-phase *J*-aggregates displaying circularly polarised luminescence.

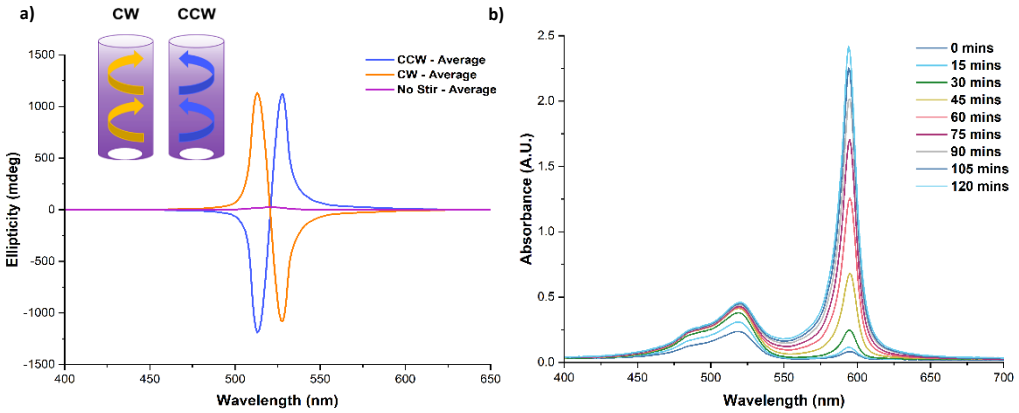

Figure 1: a) CD spectra from stirring solutions of TDBC at 25 µM in Milli-Q water in opposite directions, the non-stirred is highlighted in purple. b) Absorption spectra for solution of TDBC at 25 µM in Milli-Q water demonstrating growth of J-aggregate as the solution is continuously stirred.

1. Place, J. Perlstein, T. L. Penner and D. G. Whitten, Langmuir, (2000), 16, 9042–9048.
2. E. E. Jelley, Nature, (1936), 138, 1009–1010.
3. K. A. Clark, E. L. Krueger and D. A. Vanden Bout, The Journal of Physical Chemistry C, (2014), 118, 24325–24334.
4. L. Arrico, L. Di Bari and F. Zinna, Chemistry – A European Journal, (2021), 27, 2920–2934.

Poster 11:

Quantitative Analysis in Online Benchtop NMR Spectroscopy by Paramagnetic Relaxation Enhancement

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Nuclear magnetic resonance (NMR) spectroscopy is a powerful tool for monitoring chemical reactions and processes. Compact benchtop NMR spectrometers are particularly suitable for such applications, allowing installation close to the process being monitored. In online analysis, measurements are often performed on flowing samples, resulting in short residence times in the spectrometer's magnetic field, which prevents efficient polarization build-up, reduces the signal and limits the flow velocities that are viable for accurate quantitative measurements using benchtop NMR spectrometers. Paramagnetic relaxation enhancement (PRE) offers a solution by accelerating polarization build-up in continuous flow NMR spectroscopy. By passing the sample through a fixed bed containing the PRE agent prior to NMR detection, the build-up of nuclear polarization can be significantly accelerated, enabling quantitative measurements even at high flow velocities. For process monitoring, robust and chemically inert PRE agents are essential for process monitoring.

In this work, stable nitroxide radicals immobilized on controlled porous glass (CPG) were synthesised and used as PRE agents [1]. In the experiments, mixtures of common solvents like water, acetonitrile, 1,4-dioxane were quantitatively analysed using flow PRE ^{1}H NMR spectroscopy with a 1 T instrument. The flow velocity was systematically varied. The results show that quantitative ^{1}H NMR measurements are possible with benchtop instruments even at very high flow velocities.

1. R. Kircher (2023), Appl. Magn. Reson. 54, 1555-1569

Poster 12:

Monitoring the early stages of protein aggregation as a diagnostic tool against neurodegeneration

Faidra Batsaki, Christopher Coxon*, Dusan Uhrin*

A hallmark of neurodegenerative diseases is protein misfolding and amyloidal aggregates (eg. α-synuclein for Parkinson's and amyloid-β for Alzheimer's). These aggregates are known to form via polymerisation of the corresponding protein but the fibrillisation mechanism, its kinetics, and intermediates still remain unknown. Recent evidence on α-synuclein aggregation, suggests that the oligomers formed during the first steps of the fibrillisation are more toxic than the final aggregates (Lewy bodies). Hence, new diagnostic tools are needed in order to study the early stages of amyloid formation.

The aim of this study is to explore protein aggregation through the lenses of ^{19}F NMR by both protein-observed and ligand-observed techniques. ^{19}F NMR is an emerging field in medicinal chemistry as it allows for high signal to noise ratio, high sensitivity, no background signals and easy analysis. The protein-observed study is based on designing a fluorinated tag with high fluorine content which can be covalently bound to a mutated form of α-synuclein. Upon aggregation the fluorinated protein is hypothesised to produce different chemical shifts that would relate to aggregates of different chemical environments. The signal-observed study is based on designing ligands that are known to selectively bind to amyloidal aggregates and not their monomeric forms. By incorporating fluorine moieties within these ligands we allow for the use ^{19}F NMR analysis during all stages of fibrillisation. The two novel ^{19}F NMR studies of protein aggregation may provide more insight on oligomer formation, with extended applications on any neurodegenerative disorder as an early diagnosis.

Poster 13:

Waste to Racing Fuel: Dimethyl Ether to High Octane Hydrocarbon Fuel Streams

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Conversion of Dimethylether-to-Gasoline (DTG) range hydrocarbons represents an interesting method of producing synthetic fuels.[2] Unlike the closely related Methanol-to-Gasoline (MTG) process it remains underdeveloped, despite exploiting the thermodynamic advantage that comes from direct DME synthesis from syngas.[3] MTG and DTG processes are typically performed at higher temperatures (> 350 °C) favouring cracking of branched *iso*-alkanes rather than further methylation which results in low rates of formation of highly branched, high-octane compounds, *i.e.*, triptane. By a combination of engineering (reactor design and process optimisation) and chemical (modification of catalyst composition and morphology) techniques we aim to select for highly branched alkanes and monitor changes in product distribution over time.

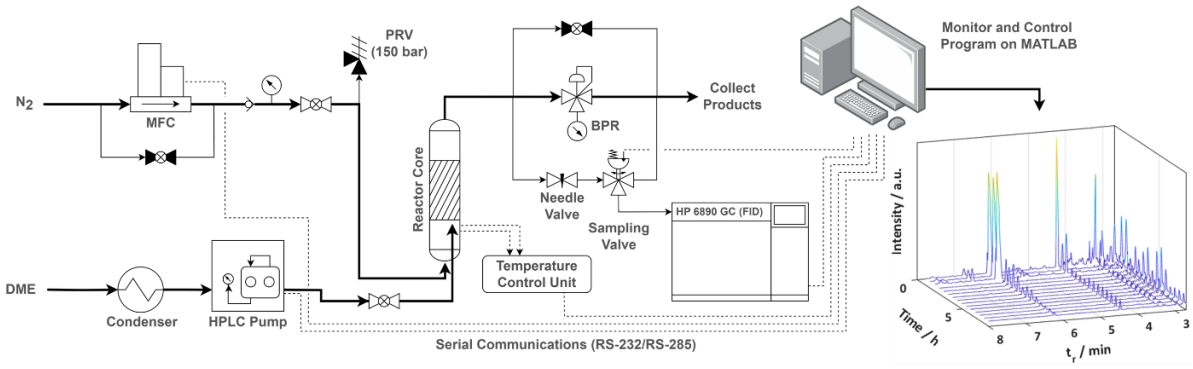

Figure 1. Plug flow reactor for the conversion of DME/Methanol to gasoline range hydrocarbons.

1. S. N. Khadzhiev, M. V. Magomedova and E. G. Peresypkina, *Petroleum Chemistry*, 2016, **56**, 181–196.
2. J. H. Ahn, B. Temel and E. Iglesia, *Angewandte Chemie International Edition*, 2009, **48**, 3814–3816.
3. D. Kubas, M. Semmel, O. Salem and I. Krossing, *ACS Catal*, 2023, **13**, 3960–3970.

Poster 14:

From solid-liquid to liquid-liquid: Advancing *in-situ* NMR reaction monitoring

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Liquid-liquid biphasic reactions are widely used in pharmaceuticals, fine chemicals, and materials due to their advantages in product separation, catalyst recovery, and using green solvents.[1] Despite their significance, *in-situ* monitoring of such reactions by NMR spectroscopy remains challenging due to inefficient mixing and sever peak broadening from magnetic inhomogeneity. Consequently, most studies rely on *ex-situ* methods, which require manual sampling and phase separation, making data collection laborious and potentially missing fragile intermediates.

To overcome these challenges, we are adapting an NMR-based *in-situ* mixing device,[2] initially developed for solid-liquid reactions, to liquid-liquid biphasic systems (**Figure 1**). By adjusting the reaction conditions of the liquid-liquid biphasic system and optimising mixing parameters, efficient mixing can be achieved without significant formation of immiscible droplets. Additionally, incorporating slice-selective NMR methods enables spatially resolved data acquisition,[3] which not only mitigates the impact of field inhomogeneity on spectral resolution, but also allows simultaneous monitoring of both phases. Preliminary studies showed that by combining both, reasonably good spectral resolution can be achieved, and quantitative kinetic data can be obtained. While further studies are required to validate the robustness of this *in-situ* monitoring approach, we anticipate that it will enable high-density kinetic data collection with minimal sample disruption, offering deeper mechanistic insights and facilitating process optimisation for liquid-liquid biphasic reactions.

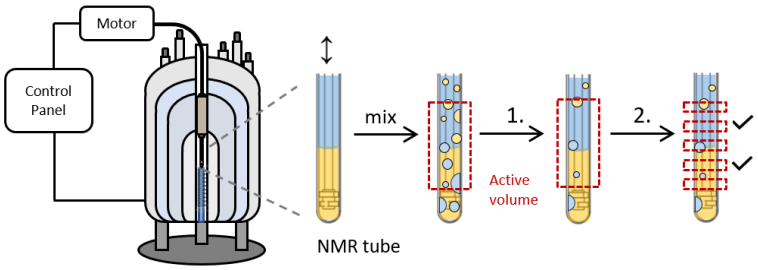

Figure 6: A schematic of the NMR-based in-situ mixing device with a liquid-liquid biphasic sample (immiscible phases are indicated in different colours). Mixing of liquid-liquid biphasic system leads to formation of immiscible droplets. 1. Optimisation of the reaction conditions and mixing system 2. Incorporation of slice-selective NMR.

1. S. Kar, H. Sanderson, K. Roy, E. Benfenati and J. Leszczynski, (2021), Chem. Rev., 122, 3637–3710.
2. Y. Gao, A. M. R. Hall, N. A. Fohn, E. J. King, L. A. L. Mitchell, G. A. Steedman and G. C. Lloyd-Jones, (2024), Eur. J. Org Chem., 27, e2024400095.
3. K. D. Catlin, J. Simmons and S. Bai, (2022), Phys. Chem. Chem. Phys., 24, 17961–17965.

Poster 15:

Real-Time Monitoring of Glycosyl Fluoride Interconversion Using High-Resolution FlowNMR

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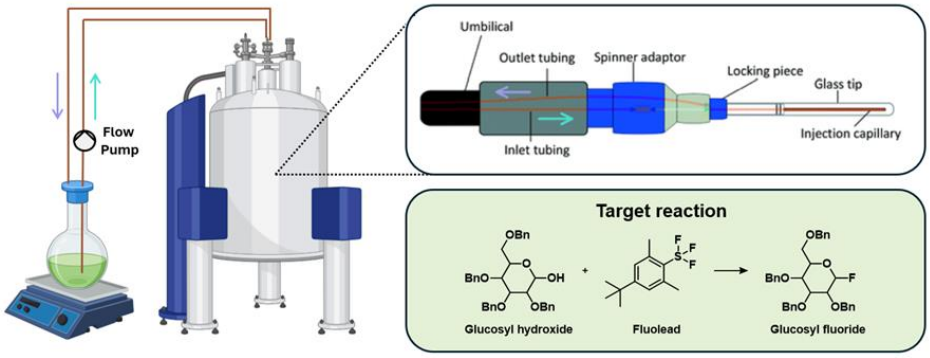
Glycosyl fluorides are well-established as important, stable, and versatile glycosyl donors in synthetic carbohydrate chemistry, making their efficient and stereoselective synthesis a critical area of research. However, unlike other types of glycosyl donors with different leaving groups, methods for the stereoselective synthesis of glycosyl fluorides remain underexplored. In this study, FlowNMR was utilised to monitor the real-time stereoselective formation of α/β-glycosyl fluorides, providing dynamic insights into their reaction mechanisms. Glycosyl fluorides were stereoselectively synthesised using Fluolead (4-tert-Butyl-2,6-dimethylphenylsulfur trifluoride) as a deoxofluorinating agent, enabling the efficient introduction of fluorine into the carbon 1 position of the glycosyl pyranose ring (C1).

By combining FlowNMR with rapid-scan 1D NMR technology, fast reaction kinetics, such as glycosidic bond (C1-F) formation, were tracked with high temporal resolution. This approach offered valuable insights into reaction dynamics, aiding in the optimisation of reaction conditions and the improvement of stereoselectivity in glycan assembly. FlowNMR demonstrated its versatility as a tool for refining synthetic methodologies and advancing carbohydrate chemistry.



1. Saib, A., et al. (2021) *React. Chem. Eng.,* **6,** 1548-1573.
2. Crawford, C. J., & Seeberger, P. H. (2023) *Chem. Soc. Rev.,* **52,** 7773-7801.