RSC NMRDG Postgraduate Meeting Programme

18th June 2021 (All times in BST)

9:30 Introduction and Welcome Prof Simon Duckett, University of York, York, UK

9:35 Invited Presentation *Magic-Angle Spinning Solid-State NMR of Organic Molecules*
Prof Steven Brown, University of Warwick, Coventry, UK

10:15 - 12:15 Posters Session A Prof Simon Duckett, York, UK (Chair)

Posters A1 – A6

- 10:15 – 10:30 1 min flash presentations
- 10:30 – 11:15 Poster breakout rooms

Posters A7 – A12

- 11:15 – 11:30 1 min flash presentations
- 11:30 – 12:15 Poster breakout rooms

12:15-13:30 Lunch

13:30 - 14:00 Careers Panel Discussion Dr Frédéric Blanc, University of Liverpool, Liverpool, UK (Chair)

13:30 - 13:35 Dr Vanessa Timmermann, SI Group, Manchester, UK

13:35 - 13:40 Dr Matthew Wallace, University of East Anglia, Norwich, UK

13:40 - 13:45 Dr Emily Corlett, Pfizer, Sandwich, UK

13:45 - 14:00 Careers panel discussion

14:00 - 16:00 Posters Session B Dr Frédéric Blanc, University of Liverpool, Liverpool, UK (Chair)

Posters B1 – B7

- 14:00 – 14:15 1 min flash presentations
- 14:15 – 15:00 Poster breakout rooms

Posters B8 – B13

- 15:00 – 15:15 1 min flash presentations
- 15:15 – 16:00 Poster breakout rooms

16:00 - 16.25 Publishing with the RSC Dr Meghan Halse, University of York, York, UK (Chair)

- Carri Cotton, Assistant Editor, Chemical Science
- Philippa Ross, Executive Editor, Analytical Chemistry journals

16:25 - 16:30 Closing Remarks and Poster Prizes Dr Frédéric Blanc, University of Liverpool, Liverpool, UK

RSC INTEREST GROUP
NMR DISCUSSION

Poster Session A

No.	Presenter Name		Title
A1	Jiafei	Mao	Room-temperature DNP NMR spectroscopy of small biological molecules in water
A2	Serena	Monaco	Multi-frequency STD NMR spectroscopy to assess protein-ligand pharmacophore
A3	George	Peat	2D DISPEL-TOCSY: Using 2D NMR to quantify 13C enrichment in metabolomics samples
A4	Tommy	Whewell	NMR Crystallography of Organic Anode Materials for Lithium- and Sodium-Ion Batteries
A5	Daniel	Morris	NMR Three Ways: Understanding The Causal Dynamics Of Ionic Liquid Solvent Effects On a SN2 Process
A6	Ben	Griffiths	Investigating the Nature of Zeolites in an Aqueous Environment
A7	Jonathan	Yong	On-the-fly, Sample-Tailored Optimisation of NMR Experiments
A8	Trey	Koev	Starch Hydrogels as Targeted Colonic Drug Delivery Vehicles
A9	Zachary	Davis	Solid-State NMR Investigation of Breathing Metal-Organic Framework MIL-53
A10	Bridget	Tang	Quantitative Interpretation of Protein Diffusion Coefficients
A11	Matheus	Rossetto	Exploring SABRE Polarisation Transfer using in situ Earth's field
A12	Nasima	Kanwal	Investigating ADOR mechanism through solid-state NMR

RSC INTEREST GROUP
NMR DISCUSSION

Poster Session B

No.	Presenter Name		Title
B1	Katarzyna	Malec	NMR spectroscopy as an aid in understanding elusive structure and transient interactions within pharmaceutical micelles
B2	Zahra	Al Aasmi	EXACT and Semi-Real Time acquisition methods to improve quantitative 13C spectra and chemical shift scaling experiments
B3	Mate Bonifac	Legrady	Multinuclear Solid-State NMR Studies of Si-γ-Al2O3 Materials
B4	Daniel	Cheney	Sample Volume Effects In Optically-Generated Overhauser Dynamic Nuclear Polarization
B5	Alastair	Robinson	Towards Photochemical Reaction Monitoring using Hyperpolarised Benchtop NMR Spectroscopy
B6	Jean-Paul	Heeb	Exploration of Dynamic Conformational Exchange using Variable Field NMR
B7	Yashwanth Kumar	D R	How the osmolyte TMAO affects the stability of the protein barnase
B8	Ran	Wei	Catch Me If You Can – New Stopped-flow NMR Methods
B9	Hao	Lan	Design, Synthesis and NMR Characterisation of Novel Polyether Chains under Conformational Control
B10	Cameron	Rice	Fast Room-temperature Lability of Zeolite Frameworks
B11	Andrea	Pugliese	Drug-Polymer interactions in Acetaminophen based Amorphous Pharmaceutical Solid Dispersions revealed by Multidimensional Multinuclear Solid-State NMR Spectroscopy
B12	Benjamin	Duff	Towards the Understanding of the Li Ion Migration Pathways in the Aluminium Sulfides Li 3 AlS 3 and Li 4.3 AlS 3.3 Cl 0.7 through 6,7 Li Solid-State NMR Spectroscopy
B13	Emma	Borthwick	Using Solid-State NMR Spectroscopy to Investigate Mixed-Metal MIL-53

Poster Abstract

Room-temperature DNP NMR spectroscopy of small biological molecules in water

Jiafei Mao[1], Danhua Dai[2], Vasyl Denysenkov[2],
Xianwei Wang[3,4], Yiwei Liu[3], Xiao He[3,5] and Thomas Prisner[2]

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[4] Zhejiang University of Technology, College of Science, Hangzhou, Zhejiang, China
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Nuclear magnetic resonance (NMR) spectroscopy is a powerful and popular technique for probing molecular structures, dynamics and chemical properties. However the conventional NMR spectroscopy is bottlenecked by its low sensitivity. Dynamic nuclear polarization (DNP) boosts NMR sensitivity by orders of magnitude and resolves this limitation. In liquid-state this revolutionizing technique is still restricted to a few specific model molecules in organic solvents. Here we present that, for the first time, a full scheme of small biological molecules, ranging from carbohydrates to amino acids, have been hyperpolarized efficiently in water directly at room temperature and at high-field. A trend between observed ODNP enhancement factor and paramagnetic shifts have been revealed, which instructs us to revisit paramagnetic NMR literatures and to discover new class of molecules (heterocyclics) that can be hyperpolarized by Overhauser DNP. The QM/MM MD simulation underscores the dynamic intermolecular hydrogen bonds as the driving force for Overhauser DNP. Our work reconciles DNP, paramagnetic NMR and computational chemistry, illuminates unexplored molecular space for modern liquid-state DNP NMR spectroscopy, and reveals new molecular and chemical mechanism of Overhauser DNP in liquids.

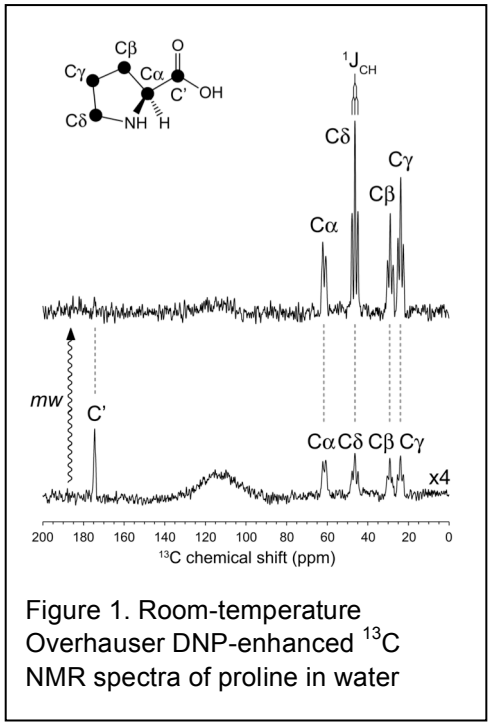

Figure 1. Room-temperature Overhauser DNP-enhanced ^{13}C NMR spectra of proline in water

Multi-frequency STD NMR to characterise weak protein-ligand interactions

Serena Monaco[1], Louise E. Tailford[2], Nathalie Juge[2], and Jesus Angulo[3]

1. School of Pharmacy, University of East Anglia, Norwich, UK
2. Institute of Food Research, Norwich Research Park, Norwich, UK
3. Departamento de Química Orgánica, Universidad de Sevilla, Sevilla, Spain

Saturation Transfer Difference (STD) NMR spectroscopy is extensively used to obtain epitope maps of ligands binding to protein receptors under fast exchange conditions [1], [2]. STD NMR reveals structural details of biomolecular recognition processes, which are fundamental to direct lead optimisation efforts in drug discovery.

Standard procedures seek uniform saturation of the receptor to identify regions of the ligand contacting the protein binding pocket. However, in this way, the experiment does not provide information about the "nature" of the amino acids surrounding the ligand in the bound state. Besides, it is not possible to detect the geometrical orientation of adjacent ligands bound in neigbouring binding sub-sites.

Here we report two novel protocols (*DiffErential EPitope Mapping*-STD NMR or DEEP-STD NMR [3], and *Inter Ligand*-STD NMR or IL-STD NMR [4]) based on the multi-frequency irradiation of the protein and/or of the ligand. This allows:

- to identify the type of protein residues contacting the ligand,
- 2) to orient unknown ligands in the known binding site,
- 3) to finger print unknown binding ligands relative to known ones,
- 4) to detect specific interactions such as π-stacking, and
- 5) to orient ligands bound in adjacent binding sites relative to each other.

We demonstrate that the approaches constitutes a novel, versatile method to *orthogonally* explore the nature (aliphatic, aromatic, polar or hydrophobic) of the amino acid residues lining the surface of the binding pocket and their orientation relative to the ligand, allowing a whole new layer of information to be unveiled simply by ligand-based techniques.

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2D DISPEL-TOCSY: USING 2D NMR TO QUANTIFY ^{13}C ENRICHMENT IN METABOLOMICS SAMPLES

George Peat[a], Will Kew[b] and Dušan Uhrin[a].

[a]*School of Chemistry, University of Edinburgh, Edinburgh, UK*
[b]*Pacific Northwest National Laboratory, Richland, WA, USA*

DISPEL (Destruction of Interfering Satellites by Perfect Echo Low-pass filtration) is a NMR technique that supresses one-bond ^{13}C satellites in ^{1}H spectra [1]. While satellites normally appear at 0.54% intensity compared to the parent peaks and often have a negligible impact on the appearance of spectra, they can be much more intense in spectra of metabolites prepared using ^{13}C labelled feedstock for tracking metabolic pathways of microorganisms. [2]. This greatly increases the intensity of ^{13}C satellites in ^{1}H spectra causing them to overlap and obscure the ^{1}H-^{12}C signals. Simplification of the spectra achievable via DISPEL makes it a useful technique for identification of metabolites in such samples. For simple mixtures, the use of 1D DISPEL can also assist with quantification of the levels of ^{13}C incorporation. Nevertheless, in highly complex mixtures even this simplification is insufficient.

A further development of the DISPEL technique aimed to quantify site-specific ^{13}C enrichment of metabolites presented in complex mixtures, is described here. The combination of DISPEL with the commonly used 2D ^{1}H-^{1}H TOCSY sequence, shown in Figure 1b, can lead to selective suppression of signals arising from transfer between protons bonded to different carbon isotopes. This depends on where DISPEL is implemented in the TOCSY experiment. If the DISPEL sequence is included before the TOCSY mixing, transfer will only be observed from protons bonded to ^{12}C. Likewise, if DISPEL is included after the mixing time, the only transfer observed will be to protons bonded to ^{12}C. If DISPEL is implemented before and after the TOCSY mixing, the spectrum will only contain signals that started and ended up on ^{12}C bonded protons. By running all four combinations of DISPEL on/off and TOCSY in a single interleaved experiment, the resulting spectra can be manipulated to only show peaks arising from and ending up on specific sites, such as ^{12}CH $\rightarrow$ ^{12}CH, ^{12}CH $\rightarrow$ ^{13}CH, ^{13}CH $\rightarrow$ ^{12}CH and ^{13}CH $\rightarrow$ ^{13}CH. After correcting for differences in relaxation of ^{12}C- and ^{13}C-attached protons, the cross peaks in DISPEL-TOCSY spectra can be integrated to determine the levels of ^{13}C enrichment of individual metabolites in a site-specific manner.

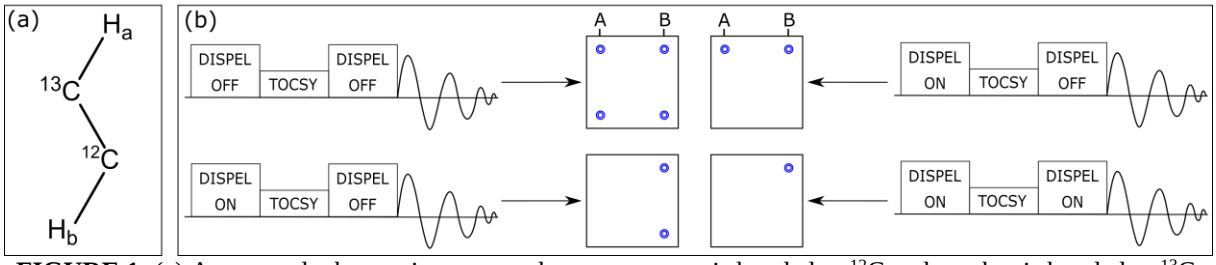

FIGURE 1. (a) An example three spin system where one proton is bonded to ^{12}C and another is bonded to ^{13}C. (b) Possible combinations of the DISPEL and TOCSY sequences showing the transfers that would be observed for the system in (a).

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NMR Crystallography of Organic Anode Materials for Lithium- and Sodium-ion Batteries

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With increasing demand for lithium and sodium-ion batteries comes increased demand for carbonaceous anode materials. These carbonaceous materials have associated environmental concerns associated with the mining and refinement of graphite and the high temperature synthesis of hard carbons. These issues could be addressed by switching to organic anode materials (OAMs) which have been proposed as sustainable alternatives to carbonaceous anode materials.[1,2] OAMs are metal dicarboxylate salts that still lack thorough understanding of the structural changes, such as lithiation and sodiation, occurring during battery cycling. Combining solid-state NMR spectroscopy, X-ray diffraction (XRD) and density functional theory (DFT) calculations we aim to gain a better understanding of these materials. Using a series of OAM structures and a range of DFT geometry optimisation strategies, we investigate the suitability of NMR crystallography for this class of compounds as well as the effects of changing the DFT optimisation approach on predicted NMR parameters. We show that DFT calculations based on XRD structures can predict ^{13}C NMR parameters with good accuracy provided that all atoms are geometry-optimised. NMR parameters of quadrupolar nuclei such as ^{7}Li and ^{23}Na can give further insight into the local coordination structure around metal sites. We show that reasonably good predictions of ^{7}Li and ^{23}Na NMR parameters are possible, apart from some exceptional cases, using DFT calculations. We also provide insight into a new phase of Na_2NDC for which the crystal structure was unknown.

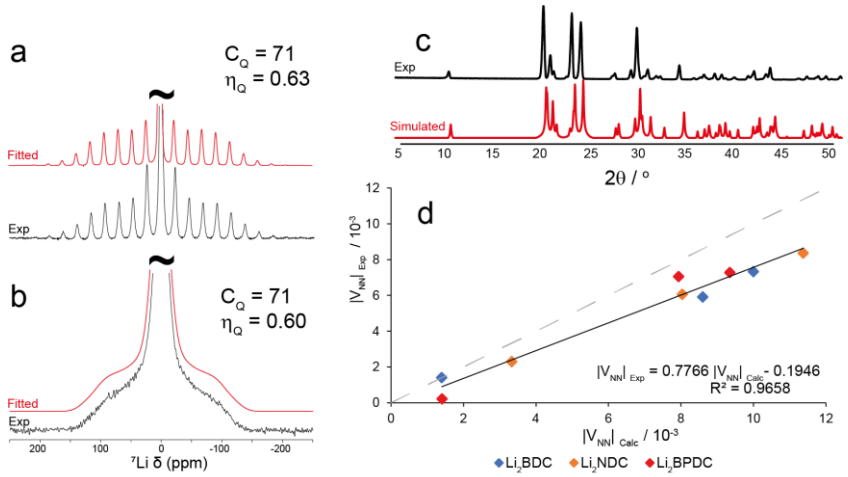

Figure 1 (a) MAS (5 kHz) and (b) static ^{7}Li NMR of lithium terephthalate (Li_2BDC) with fitted models shown in red. Spectra collected at 9.4 T. C_Q values given in kHz. (c) Experimental and simulated powder-XRD patterns of Li_2BDC. (d) Correlation plot of experimental ^{7}Li quadrupolar NMR parameters against calculated parameters based on an experimentally defined crystal structure.

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NMR THREE WAYS: UNDERSTANDING THE CAUSAL DYNAMICS OF IONIC LIQUID SOLVENT EFFECTS ON A S_N2 PROCESS

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Ionic liquids have been investigated as a potential replacement for molecular solvents due to their unique properties and customisability.[1] Despite this, common application remains inaccessible due to their often unpredictable effects on reaction outcome.[2]

The reaction between pyridine and benzyl bromide has been investigated via ^{1}H NMR in mixtures of acetonitrile and different ionic liquids in the 1-alkyl-3-methylimidazolium *bis*(trifluoromethanesulfonyl)imide ([$C_{2n+2}C_1$im][NTf_2], n = 0-5) homologous series. Unique behaviours as a function of mole fraction were seen in each ionic liquid, along with a consistent trend where longer alkyl chain substituents result in lower values of k_2.

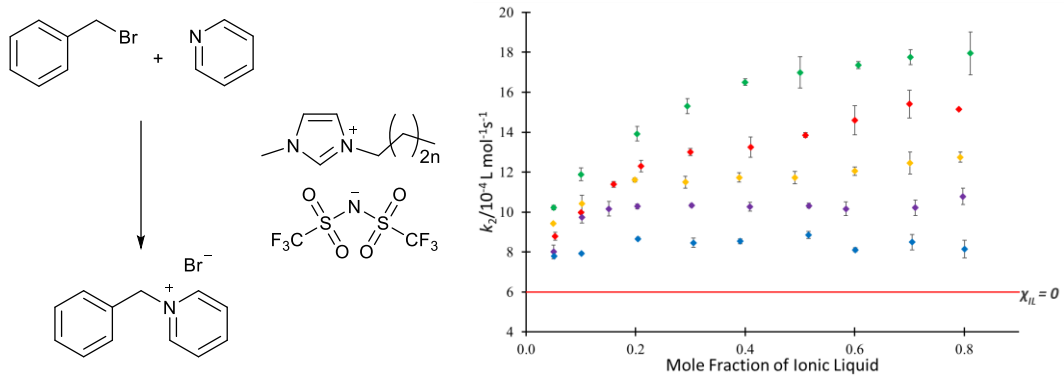

Figure 1. a) (left) the reaction of benzyl bromide and pyridine, performed in the presence of the [$C_{2n+2}C_1$im][NTf_2] homologous series of ionic liquids (n=0-5). b) (right) mole fraction dependence of the bimolecular rate coefficient (k_2) for the reaction of benzyl bromide and pyridine at 22.2°C in mixtures containing different proportions of either [C_2C_1im][NTf_2] (◆), [C_4C_1im][NTf_2] (◆),[3] [C_6C_1im][NTf_2] (◆), [C_8C_1im][NTf_2] (◆), or [$C_{12}C_1$im][NTf_2] (◆) with acetonitrile, and in acetonitrile (—). Errors are reported as the standard deviation of at least triplicate results.

Solvent relaxation NMR measurements are sensitive to both molecular motion and solvent structuring, with entropic differences such as increases in structuring having a large influence on the value of the spin-spin relaxation time (T_2). Since the observed increase in k_2 is entropically influenced, T_2 of the homologous series of ionic liquids was investigated via low field NMR. Correlation of T_2 and k_2 allows quantitative prediction of rate coefficients in various solvent mixtures. These data, along with associated activation parameters, indicate that solvent structuring plays an important part when understanding the microscopic origins of rate enhancement for these ionic liquid systems.[5] Further investigation of structuring behaviour via high field NMR diffusion experiments supports the existence of a step change in structuring behaviour upon moving to longer alkyl chain lengths for the ionic liquid cation.

References

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Investigating the Nature of Zeolites in an Aqueous Environment

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Aluminosilicate Zeolites are characterised by their unique array of topologies and are well known for their applications in various industrial processes[1-3]. Their applicability in industrial processes was thought to stem from the stability of the framework, resulting in zeolites acting as inert scaffolds. Owing to this perceived stability they were considered as candidates for further industrial processes, such as biomass refining, where catalytic reactions take place in an aqueous environment.

Recent studies[4][5] have shown that the zeolite framework is much more labile than expected when exposed to aqueous conditions. This has been evidenced by *in situ* NMR experiments reacting zeolites with $H_2{}^{17}O_{(l)}$ at room temperature, resulting in rapid incorporation of ^{17}O into the framework bonds (see Figure 1). It is clear that the framework remains intact confirming that the bond opening and closing is fully reversible.

Our current work is focused both on exploring the scope of this reactivity, and on understanding the mechanism by which this takes place a range of zeolites and different chemical linkages. The rate of enrichment and any preferential enrichment of different linkages or crystallographic sites is investigated using a joint experimental and computational ^{17}O NMR study. We investigate (i) the effect of different ratios of water and zeolite in the slurries, (ii) the rate and selectivity of enrichment of H- and ion-exchanged forms of MOR zeolite and (iii) the enrichment of CHA zeolites with different distributions of Al. The signals seen in the spectrum are assigned by comparison to DFT calculations, and these are also used to understand the dependence of the NMR parameters on local structure.

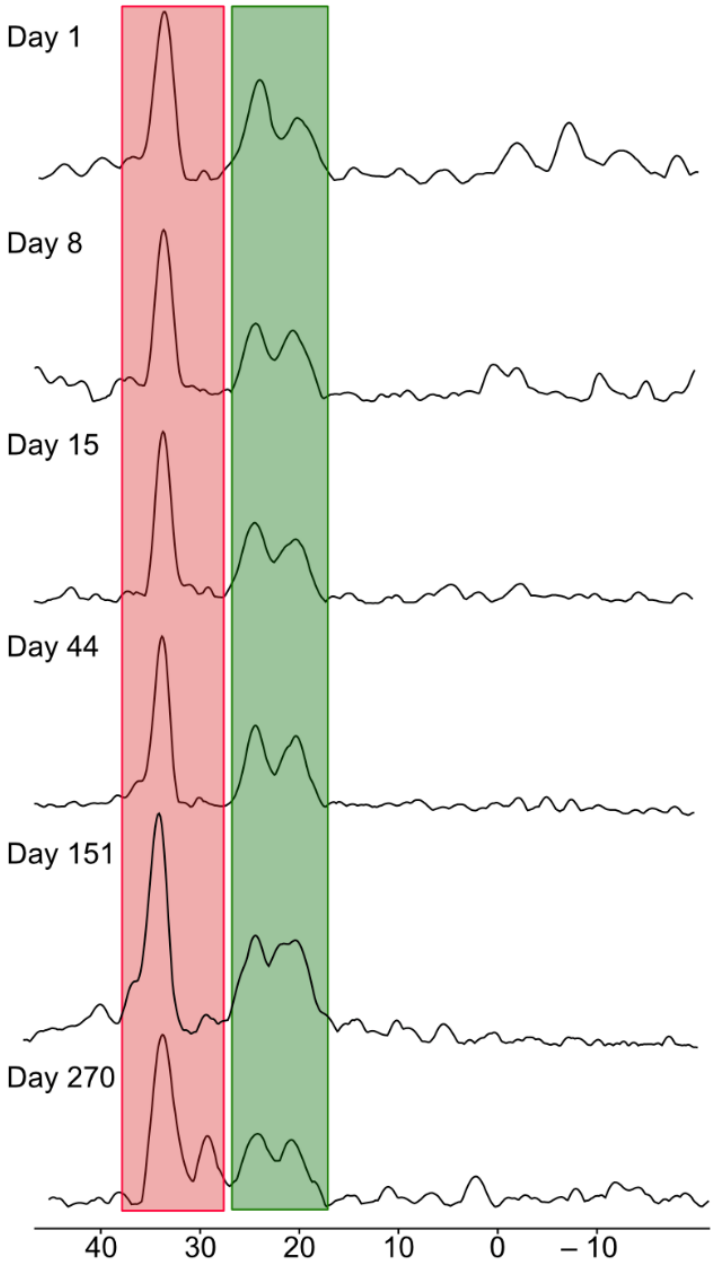

Figure 1. Projections from ^{17}O (14.1 T) MQMAS spectra taken over a 270 day period for a slurry of zeolite and $H_2{}^{17}O_{(l)}$, showing the ^{17}O enrichment of both Si-O-Si and Si-O-Al linkages in the framework.

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On-the-fly, Sample-Tailored Optimisation of NMR Experiments

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[1]Chemistry Research Laboratory, Department of Chemistry, University of Oxford

NMR experiments are often run with generic, suboptimal experimental parameters. This approach makes robust and automated acquisition on different samples and instruments extremely challenging; while the experiments will likely still work, they may not yield the best possible results either in terms of sensitivity or spectral purity.

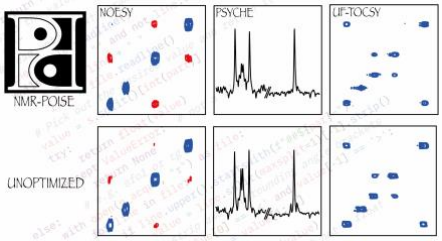

Figure 1. Comparison of unoptimised spectra (bottom row) with improved spectra acquired post-optimisation (top row).

Here NMR-POISE (Parameter Optimisation by Iterative Spectral Evaluation) is introduced, which allows rapid on-the-fly optimisation of a wide range of NMR experiments. This allows NMR acquisition parameters to be tailored to specific samples and instruments, without requiring manual adjustment by expert users. POISE uses grid-free optimisation algorithms to find optimal parameter values quickly, which makes it much faster than traditional grid-based methods or trial-and-error; thus, optimisations may typically be completed in a matter of seconds to minutes.

POISE is implemented as a Python 3 package, including a “front-end” script which can be called directly from the TopSpin command line. Detailed installation and usage guidance is available online at https://foroozandehgroup.github.io/nmrpoise/.

In this presentation, we illustrate how POISE maximises spectral sensitivity and quality with a diverse set of examples, including pulse width calibration, NOE experiments, the ASAP-HSQC experiment[1], ultrafast NMR[2], and PSYCHE pure shift spectroscopy[3].

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Starch Hydrogels as Targeted Colonic Drug Delivery Vehicles

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Hydrogels have a complex and heterogeneous structure and organisation, making them promising candidates for applications in the biomedical and pharmaceutical industry. Starch is a particularly attractive material for producing hydrogels due to its low cost and biocompatibility, but the structural dynamics of polymer chains within starch hydrogels are not well understood, which has limited their development and utilisation. [1]

Physiologically, starch hydrolysis by a-amylase occurs in several places in the human body and involves host's salivary and pancreatic a-amylase enzymes, as well as amylolytic enzymes of bacterial origin. [2] There has been some research on the impact of starch on the gut microbiota[3], but not much is known about the structure-function relationships governing starch hydrogels' interaction and impact on the full extent of the gastrointestinal tract (GIT).

In this study, we integrate two widely accepted models of *in vitro* digestion[4] and colonic fermentation[5] in order to probe the viability of starch hydrogels as orally administrable drug delivery vehicles for targeted release of small drug molecules in the colon. We demonstrate a quick and easy method for the preparation of pharmaceutical excipients from easily accessible materials, and their ability to provide targeted release of orally administrable physiologically relevant small molecules in the colon, with minimal to no release in the upper GIT. Our work aims at providing important insights into the role and function of starch hydrogel structure on its drug delivery properties, elucidating its impact and interaction with the GIT, and the role of individual components of the digestive system. Furthermore, we show how structure governs interactions of starch gel systems with host's commensal bacteria, and their ability to utilise the hydrogel excipient as a substrate for the production of important physiologically relevant microbial metabolites, such as SCFAs.[6,7] These insights provide important knowledge for the development of superior orally administrable targeted drug delivery systems with auxiliary physiologically relevant properties. [2,8]

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Poster Abstract

Solid-State NMR Investigation of Breathing Metal-Organic Framework MIL-53

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Metal-organic frameworks (MOFs) are a class of compounds that belong to the family of microporous solids, known for their range of applications (gas storage, catalysis, drug delivery *etc.*), arising from their characteristic molecular-scale pores.[1–3] There is an increasing need to understand in greater detail the structures of MOFs which, in general, consist of nodes, *i.e.,* a single or a cluster of metal cations, connected by linkers, which are typically polytopic organic ligands, forming a 3D structure.[4] One known framework, MIL-53, is known as a "breathing MOF"[5] because of the significant variation in pore size it displays upon interaction with guest molecules and the type of metal present in the framework.

The bridging nature of the oxygen atoms present in MOFs, connecting nodes and linkers, makes ^{17}O NMR spectroscopy a potentially useful technique for investigating small changes in their structures. However, ^{17}O NMR is not routine, owing to its quadrupolar nature (I = 5/2), extremely low natural abundance (0.037%) and only moderate gyromagnetic ratio. For these reasons pathways for cost-effective ^{17}O enrichment have been investigated using either a direct synthetic approach, such as dry gel conversion (DGC), or a post-synthetic exchange, such as hydrothermal steaming or slurrying.[6,7]

In this work, the effects of metal cation composition on the breathing behaviour of a mixed-metal (Al,Ga)-MIL-53 have been explored by analysing the structural variations in the various pore forms using multinuclear NMR spectroscopy. Additionally, investigations have been undertaken to understand the metal cation distribution in these important materials through comparison of frameworks prepared using a DGC and a hydrothermal steaming approach. Finally, work on the lability of these frameworks has been looked at with investigation into ^{17}O enrichment *via* a slurry method at room temperature alongside the process of post synthetically exchanging the metal present in the framework.

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ACKNOWLEDGEMENTS: ERC, EPSRC, BBSRC, UKRI

Quantitative Interpretation of Protein Diffusion Coefficients

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Pulsed field gradient nuclear magnetic resonance spectroscopy has become a routine technique for the measurement of self-diffusion coefficients of molecules.[1] Diffusion coefficients are a starting point for understanding the chemistry of a system and can yield information such as molecular size and the presence of any aggregation or association.

The diffusion behaviour of molecules in mixed solutions, such as deuterated/protiated aqueous solvents which are often used in the study of proteins, is still poorly understood. Proteins themselves further complicate matters as they can exhibit a range of structures from the highly structured to the intrinsically disordered.[2] By combining the Stokes-Einstein equation with both the well-established Gierer-Wirtz modification (SEGWE)[3] and also a composition-dependent viscosity, we propose a model that can predict the diffusion coefficients of proteins based on their molecular weight, solvent composition and sample temperature.

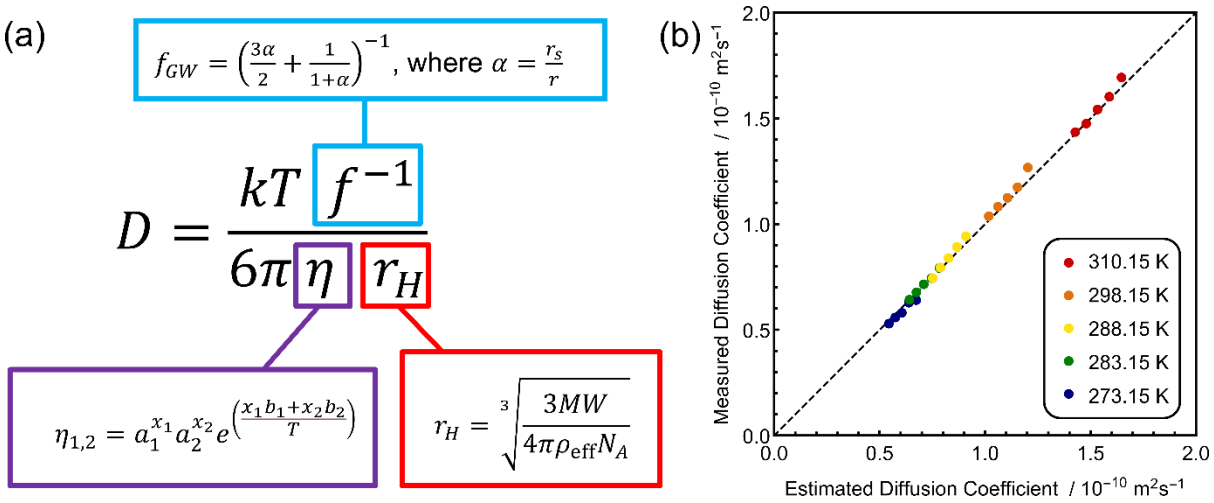

Figure. 1 (a) SEGWE equation adapted for mixed aqueous solvents. (b) Measured diffusion coefficients plotted against those estimated using the mixed-viscosity-modified-SEGWE equation for 1 mM lysozyme at temperatures ranging from 273.15 to 310.15 K and a range of compositions between 90:10 and 10:90 H_2O:D_2O.

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Exploring SABRE Polarisation Transfer using *in situ* Earth's field NMR

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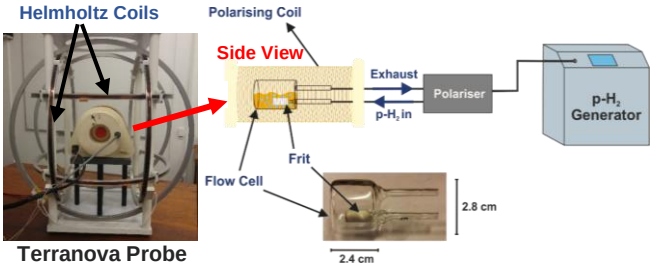

Figure 1. In-situ EFNMR SABRE setup consisting of a p-H_2 generator attached to a glass flow cell that lives within a Magritek Terranova probe. The setup makes use of a built-in polarising coil and a set of triaxial

Various techniques have been developed to improve the sensitivity of NMR via hyperpolarisation of the spin system. Of particular interest to this work is the *para*-hydrogen (*p*-H_2) based technique, Signal Amplification by Reversible Exchange (SABRE) [1] in which a metal catalyst is used to transfer polarisation from *p*-H_2 to a target analyte that subsequently dissociates allowing high levels of analyte polarisation to build up in free solution over a period of seconds.

Typically, SABRE is carried out with NMR detection in the high-field regime where polarisation transfer occurs *ex-situ* of the detection field because the polarisation transfer step requires ultra-low magnetic fields (ca. 0 – 10 mT). With the Earth's Field NMR (EFNMR) setup shown in Figure 1, SABRE polarisation transfer can be carried out *in-situ* of the detection field due to the polarising and Helmholtz coils that allow control of the applied magnetic field during the different stages of the SABRE experiment.[2] This provides a route towards directly interrogating SABRE polarisation transfer over the full range of polarisation transfer fields from below the Earth's field to the mT range.

In this work, a range of fluorinated N-heterocycles were polarized via SABRE with *in-situ* EFNMR detection. ^{19}F is our heteronucleus of choice due to its 100% natural abundance as well as the very small difference in Larmor frequency between ^{1}H and ^{19}F (~120 Hz) at the Earth's magnetic field, allowing for simultaneous observation of ^{1}H and ^{19}F in a single spectrum. Control of the applied magnetic field during SABRE hyperpolarisation and NMR acquisition provides insight into the magnetic states that are enhanced under different polarisation transfer conditions through analysis of the resultant *J*-coupled EFNMR spectra. Analysis is facilitated using spin dynamics simulations. Going forward, these insights can be exploited to optimize the SABRE polarisation transfer process from *p*-H_2 to heteronuclei.

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Investigating ADOR mechanism through solid-state NMR

Zeolites are inorganic microporous framework solids that generally contain corner-sharing silicate or aluminate tetrahedron crosslinked into a 3D framework. The ADOR (Assembly Disassembly Organisation Rearrangement) is a recent synthesis technique that utilises chemical weaknesses in the zeolites to make new zeolites with different structures than a starting zeolite. [1] The ADOR process has 4 steps: Synthesis of the parent zeolite (Assembly), controllable disassembly of the starting parent zeolite into layered units (Disassembly), the arrangement of the layers into suitable orientation (Organisation) and finally condensation into new zeolite structure (Reassembly). The key feature of the ADOR process is the presence of a hydrolytically unstable dopant element connecting the silica layers. The importance of the ADOR method is that it is the first technique that can used to manipulate pre-formed zeolites to form new, predictable frameworks opening up the potential to prepare many new zeolites that were previously thought not possible.

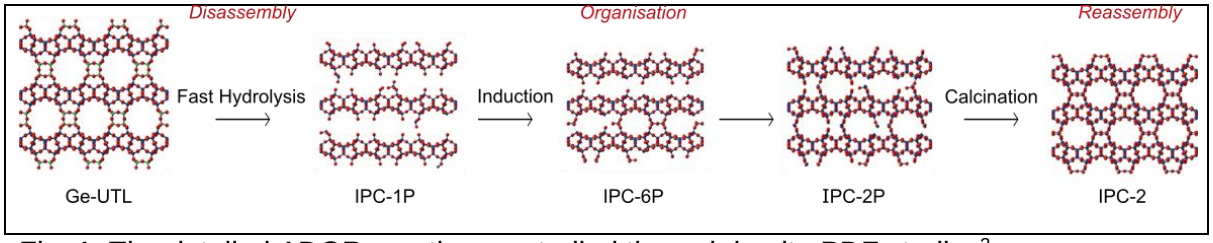

Fig. 1. The detailed ADOR reaction as studied through in-situ PDF studies[2]

In this work, we have attempted to investigate different steps of the ADOR process through solid-state NMR.

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NMR spectroscopy as an aid in understanding elusive structure and transient interactions within pharmaceutical micelles

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Micelles are characterized by continuous exchanges between dissolved monomers and micellar aggregates. In those nanosize drug delivery systems transient interactions between surfactant and drug do not occur at particular binding site.(1, 2) This dynamic exchange poses a significant analytical challenge to complete understanding of the structure and interactions within those supramolecular assemblies. DEEP-STD NMR (DiffErential EPitope mapping by Saturation Transfer Difference NMR spectroscopy) is a method that has been used to evaluate preferable ligand conformation within binding pocket in proteins.(3) Regarding drug as ligand and surfactant molecule as macromolecular receptor DEEP-STD NMR protocol allows to establish the preferential localization of drug within model micelles.

The aim of the study was to investigate drug-surfactant interactions in micellar systems composed of structurally different surfactants (Pluronic® F-127, Tween 20, Tween 80 or sodium lauryl sulphate) and two model drugs of significantly different water solubility (fluconazole or indomethacin). The investigated systems were analysed using DEEP-STD NMR protocol within a wide range of surfactant concentrations and temperatures. Complementary analytical methods (1D and 2D NMR spectroscopy, dynamic light scattering, transmission electron microscope, spectrofluorimetry, surface tension measurements, high-performance liquid chromatography) were used to explain differences in the obtained DEEP-STD NMR factors.

The results provided the insight into possible localization of the drug within micellar systems. Among properties of the materials that affect application of the DEEP STD NMR protocol water solubility of the drug, concentration and solubilisation ability of the surfactant as well as its size and structure were identified. Mapping drug-surfactant interactions using DEEP-STD NMR in combination with complementary analytical techniques enables molecular level understanding of transient host-guest interactions in these complex colloidal materials.

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EXACT and Semi-Real Time acquisition methods to improve quantitative ^{13}C spectra and chemical shift scaling experiments

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We demonstrate here two applications of the related EXACT[1] (EXtended ACquisition Time) and SRT[2] (Semi-Real Time) acquisition methods to explore improvements in existing NMR methods.

Firstly: $^{13}C\{1H\}$ NMR spectra are made less quantitative by the Nuclear Overhauser Effect (NOE) which arises from the heteronuclear spin decoupling. We use here EXACT NMR (Figure 1) to obtain quantitative ^{13}C NMR spectra with reduced NOEs and thus reduced experimental times

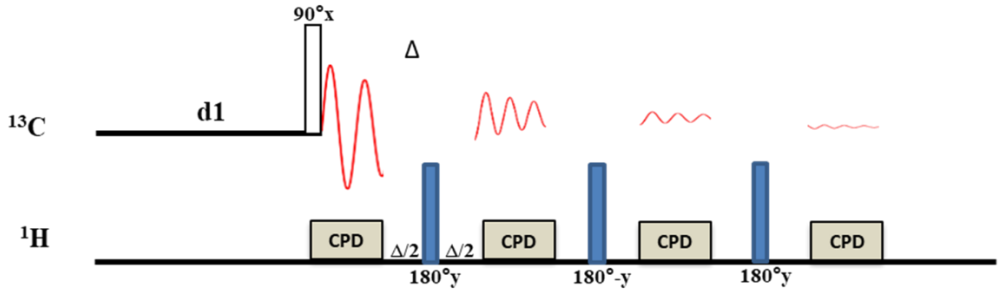

Figure1: EXACT acquisition on ^{13}C channel (WALTZ ^{1}H decoupling during the chunk acquisition and a single 180° refocusing pulse during the gaps).

Secondly: Real-Time chemical shift scaling experiments use high radiofrequency power as many 180° refocusing pulses are applied between every datapoint.[3] Here we use the SRT acquisition approach to reduce this RF power by skipping the acquisition of every second datapoint and thus spread the RF pulses over a longer period.

We showed that both techniques work and provide high quality NMR spectra in less experiment time as with quantitative ^{13}C or with lower RF power as with chemical shift scaling.

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Multinuclear Solid-State NMR Studies of Si-γ-Al_2O_3 Materials

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Silicated aluminas are commonly employed as solid acid catalysts finding application in numerous industrial processes. The presence of both Si and Al at the surface of these materials generates the mild acidity that is essential to catalytic behavior, yet a general consensus on the structure of acidic environments has still to be reached. The difficulty lies primarily in the diverse range of possible surface structures, not only of the silicate derivatives but of the γ-Al_2O_3 support, and also in the disordered character of these materials.

Preparation of ^{29}Si-enriched Si-γ-Al_2O_3 has facilitated the acquisition of ^{29}Si NMR spectra *via* single-pulse excitation and cross-polarisation. At the lowest Si loading studied (1.5% Si), five different types of Si environments have been distinguished and tentatively assigned. Cross-polarisation studies indicated the presence of silanol and siloxane functionalities, while homonuclear single quantum - double quantum correlation experiments revealed clustering of Si species, which is also supported by ^{29}Si-^{27}Al dipolar coupling measurements. The Si environments present are found to be different to the most often presumed zeolitic sites. ^{17}O NMR spectroscopy is an attractive technique for the study of materials where oxygen is an integral component of the chemical structure. Si-γ-Al_2O_3 materials (0-6% Si) have been enriched post-synthetically by exchange with 70% $^{17}O_2$ gas. Two dominant ^{17}O resonances have been observed in the bulk structure of γ-Al_2O_3 experimentally and assigned to three different oxygen environments. The assignments are supported by periodic DFT calculations, which also provide insight into the nature of disorder accounting for the large distribution of chemical shifts observed in high resolution ^{17}O NMR spectra. Calculations also highlight the importance of surface effects on the appearance of experimental ^{17}O NMR spectra. Two additional surface sites can be distinguished in high-field (20.0 T) ^{17}O NMR spectra, which could be assigned to strongly bound water molecules and certain types of aluminol species. In the silicated materials, Si-O-Si and Si-O-Al species were identified and the effects of increasing Si loading as well as the ^{17}O enrichment conditions have been examined.

Poster Abstract

Sample Volume Effects In Optically-Generated Overhauser Dynamic Nuclear Polarization

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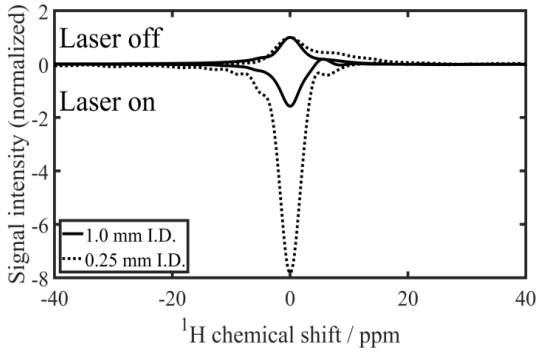

Figure 1. Proton NMR spectra of water in the presence of TEMPO and Rose bengal, with and without laser illumination in 1.0 and 0.25 mm tube inner diameters.

Overhauser Dynamic Nuclear Polarization (DNP) is a widely-used method for transferring spin polarization from electron spins of a free radical to nearby nuclear spins, thereby improving upon the intrinsically limited signal-to-noise ratio of NMR spectroscopy[1]. DNP is usually carried out by irradiating the EPR transitions of the radical with microwaves, but in recent years, a novel optical approach has been demonstrated. This has the potential to overcome the theoretical limit of DNP, where the electronic saturation factor can typically have a maximum value of 1.[2] Visible light is used to photoexcite a dye to its triplet state, which is subsequently quenched by the radical, generating electron spin polarization in the latter due to the Radical-Triplet Pair Mechanism (RTPM).[3] This polarization can be transferred to nuclear spins via cross-relaxation. In the original proof-of-concept study, enhancements of −4 were achieved for water protons using the radical TEMPO and the dye rose bengal. We have recently carried out an extensive theoretical investigation into the effects of changing various experimental parameters on the DNP enhancements.[4] One particularly interesting result from this was the prediction that enhancements should increase significantly when the sample volume is reduced, due to the greater photon density. Here, we present the first experimental verification that this is indeed the case. The optical DNP approach therefore has the potential to significantly boost the sensitivity in the study of volume-limited samples in microcoil NMR.

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Poster Abstract

Towards Photochemical Reaction Monitoring using Hyperpolarised Benchtop NMR Spectroscopy

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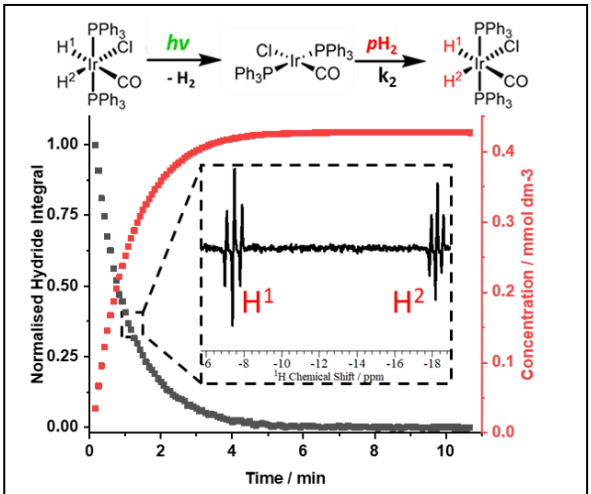

Figure 1. Reaction monitoring for the oxidative addition of pH_2 to $[IrCl(CO)(PPh_3)]_2$ after photoinitiation, highlighting hyperpolarised hydride signal decay (grey) and reaction product growth (red).

Benchtop NMR spectrometers offer unique capabilities for reaction monitoring compared to their high-field alternatives. The increased portability, protio solvent tolerance and higher accessibility of these spectrometers make them well suited for mixture analysis and allow for facile incorporation of additional features such as photochemical initiation or flow systems.[1]

One drawback of the lower operational magnetic field strength of benchtop NMR (1 – 2 T) is a reduction in sensitivity. This is problematic for reaction monitoring where detecting low concentration, transient species is desirable for mechanistic insights. To overcome this limitation, hyperpolarisation techniques can be employed. One method, known as PHIP (*Para*Hydrogen Induced Polarisation), utilises *para*hydrogen (pH_2) to chemically modify an analyte. The hydrogenation process breaks the symmetry of pH_2, unlocking its latent polarisation, which enhances the signals observed for the product molecule.[2] This approach has been seen to be effective for thermal reaction monitoring at low-field[3] and experiments performed within this project have verified this method to be valid and robust.

The work presented focuses on the expansion of this technique to investigate photochemical reactions through the integration and optimisation of a low-cost, *in situ* photoinitiation step. This advancement dramatically increases the range of chemical reactions that can be explored (Figure 1) and opens a route to observe millisecond timescale processes. Within this regime, there is potential to detect the initial magnetic evolution of the chemical system post-irradiation, which encodes additional diagnostic information into the spectra recorded. This interesting spin physics phenomenon has been previously observed at high-field[4] and is now potentially viable at low-field for the first time using photochemical pump – NMR probe experiments.

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Poster Abstract

Exploration of Dynamic Conformational Exchange using Variable Field NMR

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[1]Department of Chemistry, University of Bristol

Chemical shift scaling[1-3] (CSS) is a powerful method capable of obtaining lower field strength spectra from a higher field strength spectrometer. As the apparent frequency is reduced, second-order effects increase (as in the equivalent "real" spectra) and, in exchanging systems, coalescence may eventually be observed due to the linear relationship between the rate of exchange at the coalescence temperature and the peak separation in Hertz.[4,5] Whilst this method shows the potential to provide complementary information to variable temperature NMR (VTNMR) in this regard, very little has been published in this particular area.[3]

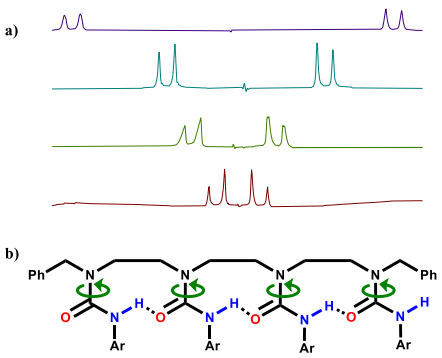

Figure 1. a) CSS spectra of N-acetyl cytosine (200, 100, 50 & 25 MHz respectively). b) An example dynamic foldamer based on a polyethyleneurea backbone. Rotation around the green arrows can invert the H-bond chain.

Our groups are interested in the development of CSS for the study of dynamic systems such as figure 1b.[6] VTNMR is often hindered by both temperature range incompatibilities as well as enthalpic and entropic complications. CSS may prove advantageous, therefore, in being able to obtain similar or supplementary data without these inherent limitations.

We have been able to study several simple (non-)exchanging systems over a range of 500 MHz to 5 MHz (a 100-fold decrease in apparent field strength). Artefacts can be seen at the extremes of the pulse sequence, however in most cases the observed spectra accurately match simulations. Further work is required for reliable comparison to VTNMR results and line shape calculations for exchange rate determination.

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ACKNOWLEDGEMENTS: We would like to thank the EPSRC for project funding.

Catch Me If You Can – New Stopped-flow NMR Methods

Ran Wei[1] and Guy C. Lloyd-Jones[1]

1. Department of Chemistry, University of Edinburgh

NMR spectroscopic analysis of chemical reactions has become an essential tool, as it offers a wealth of quantitative structural information and a high degree of spectral resolution. Nevertheless, *in-situ* monitoring of rapid irreversible reactions that are initiated by mixing, poses challenges to traditional NMR experiments, therefore requires specialised techniques.

A new stopped-flow apparatus[1] was constructed to capture the fleeting information from irreversible reactions at the millisecond timescale. Its adaption to standard NMR probes; the pre-magnetisation equilibration; mixing efficiency; heat-transfer versus reaction enthalpy; and optimal NMR parameters in obtaining qualitative and quantitatve kinetic data are discussed. With the aid of this technique, we are able to study short-lived intermediates, and evolving reactions that occur beyond the measurement deadtime of traditional NMR experiments. Here an example ($t_{1/2}$ = 45 ms) was used to demonstrate the monitoring of rapid irreversible reactions by interleaved ^{19}F stopped-flow NMR spectroscopy.

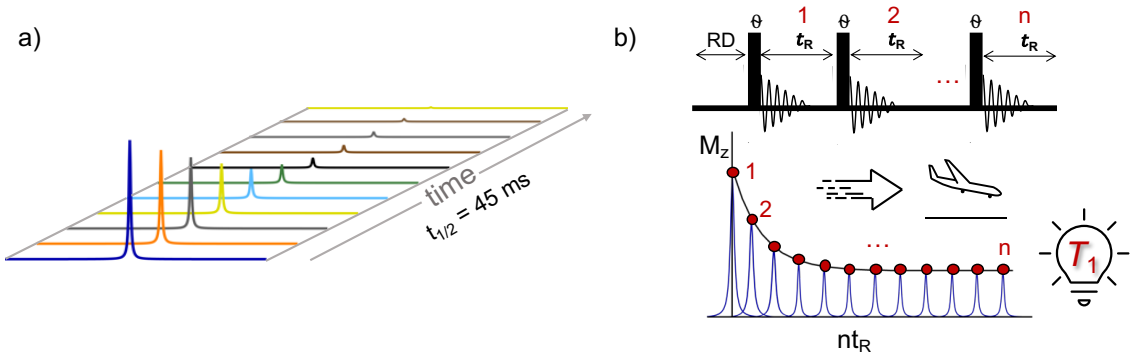

Figure 1. a) Stacked interleaved ^{19}F stopped-flow spectra to monitor the protodeboronation of penta-fluorophenyl boronic acid. b) FLIPS method for rapid T_1 measurement.

At the same time, we have also developed a rapid T_1 estimation method, termed FLIPS (Fast Longitudinal relaxation Investigated by Progressive Saturation)[2], which has been routinely applied prior to quantitative NMR experiments. It offers a 10-fold reduction in experimental time comparing to the conventional inversion recovery method. Therefore it is expected to facilitate the general chemistry community to obtain knowledge of the T_1 constants within a shorter spectrometer time.

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Design, Synthesis and NMR Characterisation of Novel Polyether Chains under Conformational Control

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Molecular conformation is important in material science and drug discovery. Our group has realised the conformational control on several hydrocarbon scaffolds in linear/helical shapes through computational modelling, asymmetric synthesis and solution-state NMR analysis.[1,2] This project aims to expand the toolbox from hydrocarbon scaffold to polyether --- common conjugation motif in chemical biology. We have designed a novel semi-rigid polyether chain without using any rings. Based on feasible synthesis and steric effect of quaternary carbon centres, the library of chains with different length and end-group was established. Their torsional rigidities were elucidated with DFT-calculated Karplus relation and experimental $^{3}J_{CH}$ scalar couplings together.

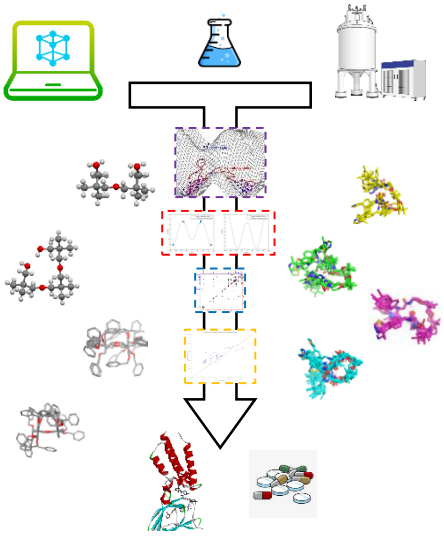

Figure 1. Synergy of computation, synthesis and NMR for linker design and conformational elucidation of PROTAC folding in solution.

The chain is to be applied as a linker for Proteolysis Targeting Chimera (PROTAC), a heterobifunctional drug conjugate capable of selective protein removal utilising ubiquitin-proteasome system.[3] Traditional flexible PEG linkers in PROTAC have shown poor membrane permeability as well as self-aggregation problem in water, which may hinder cooperative binding with both target protein and E3-ubiquitin-ligase in cell.[4] Our linker showed unique property that may overcome these issues. For example, NOE/ROE-refined computational ensembles of the PROTAC system under rigidification demonstrated turn mimetic with internal hydrogen bonding in non-polar solution as well as extended conformation in polar solution… More biological assay for such PROTAC chameleon is on the way. Our research is expected to expand the chemical space for more potent and selective degradation of protein with therapeutic benefit.

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Fast Room-Temperature Lability of Zeolite Frameworks

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Zeolites are microporous materials comprising corner-sharing TO_4 (T = Si, Al) tetrahedra, connected through bridging oxygen linkages. Their perceived stability under a range of operating conditions, particularly in the presence of nucleophiles like water, have made their use as inorganic supports in commercial processes widespread.[1] However, the interaction of zeolites and water is complex and can, under certain conditions, result in catalyst deactivation or framework degradation.[1-3]

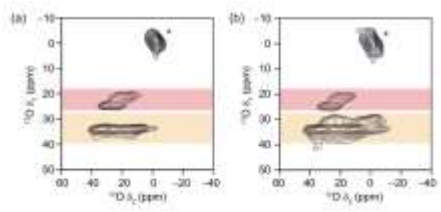

Figure 1. (14.1 T, 14 kHz) ^{17}O MQMAS NMR spectra of protonated **CHA** exposed to 40% $H_2{}^{17}O$ for (a) 0 and (b) 7 days. *(key gold = Si-O-Si linkages, red = Si-O-Al linkages, asterisk (*) denotes water).*

Our recent work using ^{17}O NMR spectroscopy has extended the understanding of zeolite instability in the presence of water, showing widespread bond lability and flexibility at room temperature.[4,5] A sensitive probe of local structure, NMR shows changes to the local geometry and bonding in zeolites under aqueous conditions. ^{17}O, the NMR-active isotope of oxygen is chosen as the nucleus of study in spite of its extremely low natural abundance (0.037%), moderate gyromagnetic ratio and quadrupolar (I = 5/2) spin.

Through exposure of a commercially relevant aluminosilicate chabazite (**CHA**) zeolite catalyst, and related heteroatomic **CHA** zeolite materials, to small amounts of $H_2{}^{17}O_{(l)}$, *in-situ* NMR studies reveal enrichment of Si-O-X bonds (X = Si, Al) on rapid timescales (< 1 hour) (Figure 1). This room-temperature framework enrichment is reversible, proceeding without degradation of the material. Molecular dynamics calculations have revealed that bond lability in a protonated **CHA** is likely to proceed *via* a mechanism involving a hydrogen-bonded chain of water molecules, with energetic barriers to bond cleavage as low as ~30 kJ mol^{-1}.[4] The present work explores and extends the applicability of this mechanism, using ^{17}O NMR to investigate the effects of cation substitution, silicon to aluminium ratio and incorporation of heteroatoms (X = Ti, Zn, B) on the rate and extent of this surprising oxygen exchange.

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ACKNOWLEDGEMENTS: PhD studentship *via* EPSRC DTG (grant code EP/N509759/1).

Drug-Polymer interactions in Acetaminophen based Amorphous Pharmaceutical Solid Dispersions revealed by Multidimensional Multinuclear Solid-State NMR Spectroscopy

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Solid state NMR spectroscopy has been successfully developed into powerful toolkit in the pharmaceutical science,[1,2] leading to the understanding of complex systems. This work probes the stability of the acetaminophen active pharmaceutical ingredients (API)-hydroxypropylmethylcellulose acetyl succinate (polymer) amorphous solid dispersions (ASDs)[4] using multidimensional multinuclear NMR spectroscopy approaches. ^{1}H-^{13}C HETCOR and ^{14}N-^{1}H synchronised HMQC experiments recorded on the 20% wt API ASD identified spatial API-polymer proximities, demonstrating the stability of this system, while for the 40% wt API ASD no acetaminophen-polymer interaction is observed which correlates well with the partial recrystallisation of acetaminophen detected by both ^{13}C CP and XRD. In conclusion, it has been demonstrated that important structural information on the stability of ASDs can be access by multidimensional multinuclear NMR experiments opening up ways to further understand these systems and yielding to the development of more stable ASDs.

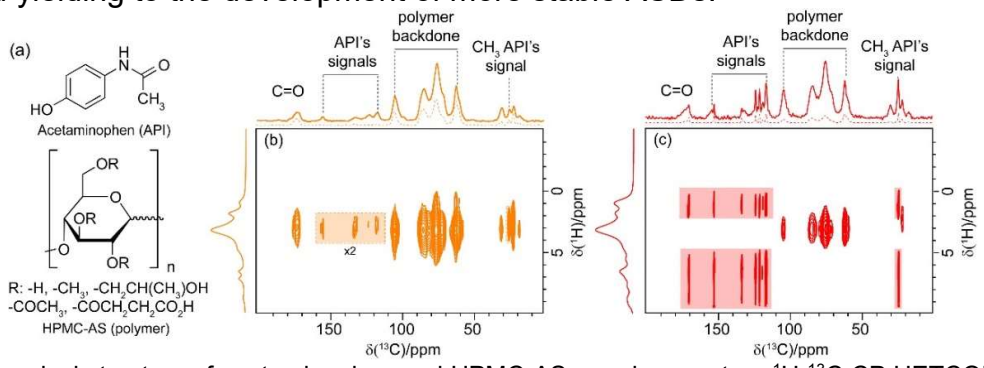

Figure 1. (a) Chemical structure of acetaminophen and HPMC-AS are given on top. ^{1}H-^{13}C CP HETCOR spectra of (b) 20% and (c) 40% wt. acetaminophen—HPMC-AS obtained at 9.4 T and 12.5 kHz MAS frequency. The ^{1}H-^{13}C CP and ^{1}H spectra recorded at 9.4 T and 12.5 kHz MAS frequency are shown on the top and left side of each HETCOR, respectively. The shaded section in (b) indicates the presence of API-interaction while in panel (c) illustrates signals corresponding to crystalline API interacting with itself. The proposed ^{13}C signal assignment is based on the previous literature[5,6] and results obtained in this work

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Towards the Understanding of the Li Ion Migration Pathways in the Aluminium Sulfides Li_3AlS_3 and $Li_{4.3}AlS_{3.3}Cl_{0.7}$ through $^{6,7}Li$ Solid-State NMR Spectroscopy

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All solid-state batteries (ASSBs) are being intensively investigated as a next-generation energy storage solution to overcome the limitations of current battery technology mainly to enable increased energy and power density while improving safety.[1] Solid-state electrolytes (SSEs) offer advantages over liquid electrolytes, such as large electrochemical stability windows and better thermal stability.[2]

Solid-state nuclear magnetic resonance spectroscopy (NMR) is a powerful technique to tackle the structure of disordered materials and assess the dynamics behaviours of the charge carriers, *i.e.*, Li+ ion. NMR was used here to elucidate the structure of newly synthesised materials Li_3AlS_3[3] (Figure 1) and $Li_{4.3}AlS_{3.3}Cl_{0.7}$[4] through ^6Li Magic Angle Spinning (MAS) and ^{27}Al multiple quantum MAS NMR. Insights into the microscopic and macroscopic Li ion migration were obtained from $^{6,7}Li$ NMR lineshape, relaxometry and exchange spectroscopy experiments. These experiments allowed for quantification of ionic conductivity for both materials as well as determination of Li migration pathways and identification of the limiting factor for ion mobility in the parent Li_3AlS_3 which is absent in $Li_{4.3}AlS_{3.3}Cl_{0.7}$ leading to increased ion mobility in the later phase.

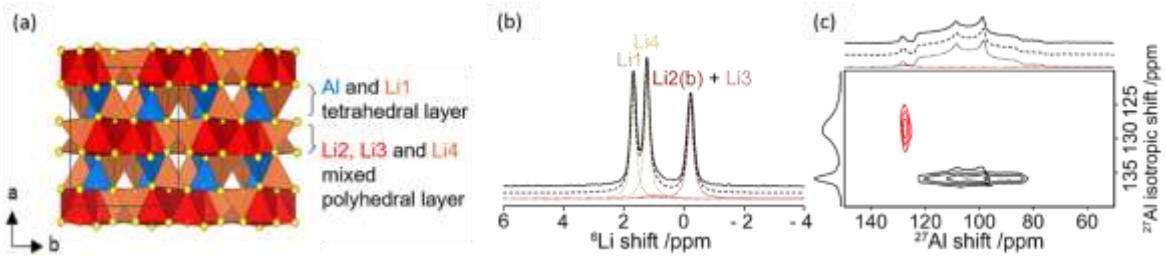

Figure 1. (a) Crystal structure of Li_3AlS_3 showing the tetrahedral layers containing AlS_4 and LiS_4 tetrahedra and the mixed polyhedral layers containing Li-only polyhedra. (b) ^6Li MAS spectrum of Li_3AlS_3, the experimental spectrum (full line), total fit (dashed line) spectral deconvolution (dotted lines) and Li_5AlS_4 impurity (red dotted lines) are shown. (c) ^{27}Al MQMAS NMR spectrum of Li_3AlS_3, the black dotted lines and the red dotted lines represent the spectral deconvolution of Li_3AlS_3 and the Li_5AlS_4 impurity, respectively. The dashed lines show the total fit for the sample, and the solid lines show the anisotropic one-dimensional ^{27}Al spectrum, while the vertical spectrum shows the non-quantitative isotropic ^{27}Al spectrum.

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Using Solid-State NMR Spectroscopy to Investigate Mixed-Metal MIL-53

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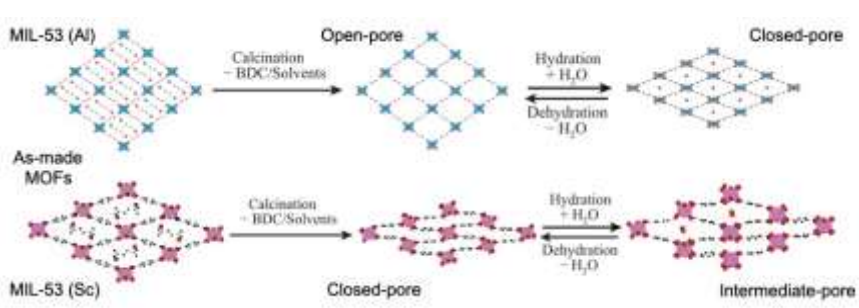
Metal-organic frameworks (MOFs) are a class of microporous solids that have a continuous network structure. They are made up of metal nodes and organic linkers, and have a range of applications including catalysis and gas storage.[1,2]



In this work, solid-state NMR is used to investigate the metal cation disorder and breathing behaviour in a number of Sc, Al and mixed-metal MIL-53 samples. As the linker in MIL-53 is a carboxylate based compound, benzene-1,4-dicarboxylic acid (BDC), it is important to look at ^{17}O when utilising solid-state NMR spectroscopy.

A range of post-synthetic ^{17}O enrichment techniques (e.g., steaming, *ex situ* and *in situ* enrichment) have been explored for a range of end-member and mixed-metal MIL-53 (Sc, Al) materials. This allows the metal cation disorder and subsequent effects on the breathing behaviour in the materials to be investigated. The various methods are compared to determine the level and selectivity of enrichment. Experimental results are compared to parameters from first-principles DFT calculations (using a suite of potential structural models) and to aid spectral assignment and interpretation.

During the steaming enrichment process it was seen that scandium-rich MIL-53 is less thermodynamically stable than aluminium-rich MIL-53, and the framework transforms into the non-breathable denser scandium MOF, Sc_2BDC_3. However, using ^{17}O MAS and MQMAS experiments it was seen that aluminium-rich MIL-53 showed good levels of enrichment, approximately 7.5-10%, of all the possible oxygen sites, Sc and Al carboxylate environments, and three bridging hydroxyls sites, Al–O(H)–Al, Sc–O(H)–Al and Sc–O(H)–Sc.

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How the osmolyte TMAO affects the stability of the protein barnase

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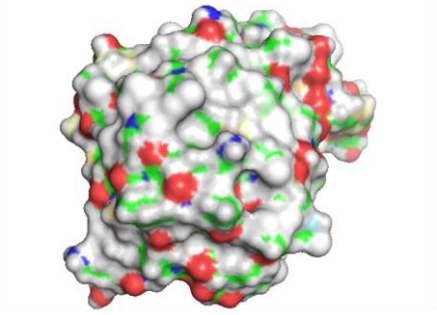

Figure 1. Proton gradients on barnase surface observed using pymol

The Hofmeister series has been known for over 100 years and describes how different salts affect the stability and solubility of proteins[1]. However, it is still unclear what the physical basis is. We have previously studied the effects of salts on the NMR spectrum of the protein barnase and concluded that the main effect of the salts is that they alter the properties of bulk water, by changing its chemical potential and the freedom of water molecules to solvate the protein surface[2]. Here, we present results on trimethylamine N-oxide (TMAO). This is an osmolyte, widely produced by marine organisms as an intracellular solute, to counteract the destabilizing effects of osmotic stress, denaturants such as urea, and high pressure. DSC results suggest that TMAO may not strongly stabilize the protein by itself but can counteract the destabilizing effects of urea. NMR Data show that the effects of TMAO on NMR spectra of the protein barnase are smaller than those of typical Hofmeister ions such as sulphate and thiocyanate. NMR Data also shows that TMAO binds very weakly on protein surface and data from mixed osmolyte solutions suggest that TMAO does not bind to urea either. This implies that direct binding to the protein is not required and TMAO affects the protein stability by its ability to withdraw water from the protein surface – it therefore counteracts the perturbations induced by other solvents.

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