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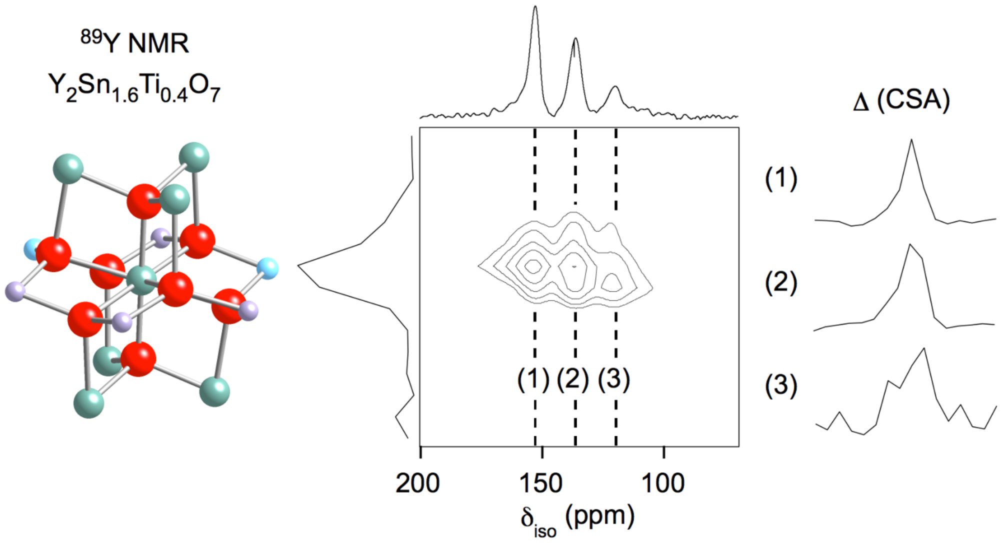
NMR Discussion Group



Postgraduate Meeting 2012

School of Chemistry
University of Bristol
14th June 2012

Dear Delegate,

Welcome to the fifth Postgraduate Symposium of the RSC NMR Discussion Group! This meeting has a broadly similar format to the previous meetings and brings together early career researchers, broadly defined as postgraduates, early career post doctorial workers, and young industrialists, who all have a strong research interest in magnetic resonance. The idea is that it provides a forum to showcase their work and networking opportunities within the NMR community.

This year we are continuing to have two overview lectures, given by leaders in their field, to highlight the power of magnetic resonance methods across a broad range of topics. Dr John Hollerton (GlaxoSmithKline) and Dr Melanie Britton (University of Birmingham) will present overviews of the use of NMR in drug discovery and applications of NMR and MRI to soft matter, emulsions and suspensions.

The programme is designed to be varied, with a wide range of talks. Posters allow delegates to discuss their work with other early career researchers and more established colleagues in a friendly and informal setting. There is also ample opportunity for further discussions over tea/coffee and lunch.

We hope that you will make the most of this opportunity and that you enjoy the meeting.

Iain Day	**Craig Butts**	**James Keeler**
University of Sussex Meeting Organiser	University of Bristol Local Organiser	University of Cambridge NMRDG Chairman

Local organisation and acknowledgements

Meeting coordinated by: Iain Day, University of Sussex
Local organisation coordinated by: Craig Butts, University of Bristol
Online registration coordinated by: John Parkinson, University of Strathclyde

The organisers would like to thank Stephen Byard (Covance) for significant help “behind the scenes”.

Thanks go to James Keeler (University of Cambridge), Iain Day (University of Sussex) and John Parkinson (University of Strathclyde) for acting as Judges for the prize giving.

The NMR Discussion Group gratefully acknowledges the following sponsorship for their generous support of this meeting:

Agilent Technologies UK Ltd

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Posters

Posters should be mounted on the poster boards during the arrival period prior to the formal welcome and start of the program and should be attached to the board for which the poster number has been designated. Posters should be removed after the close of the meeting.

Programme

1000 – 1025	Arrival, Registration, Poster mounting and Coffee
1025 – 1030	Welcome, James Keeler, NMRDG Chairman

Oral Presentation Session 1, session chair: Iain Day

1030 – 1110	**John Hollerton**, GlaxoSmithKline R&D *NMR in Drug Discovery*
1110 – 1130	**Anna-Winona Struck**, University of Manchester *Characterization of Nonribosomal Peptides Antibiotics with Non-Natural Amino Acids my MS-MS and NMR*
1130 – 1150	**Robert Kelly**, University of Warwick *Exploring the impact of Cu^{2+} ions on the aggregation of amyloid-beta (1-40) using Solid-State NMR*
1150 – 1210	**Stephen Day**, University of Warwick *Complimentary GIPAW DFT computational and ssNMR approaches to studying hydrogen bonding and disordered apatites systems*
1210 – 1230	**Smita Odedra**, University of Glasgow *Improved background suppression in ^{1}H MAS NMR using composite pulses*
1230 – 1250	**Antoine Vallatos**, University of Birmingham *Characterising stationary and translating vortex flow using magnetic resonance*

Lunch

1250 – 1330	Buffet lunch and mixing

Poster Session

1330 – 1400	Odd numbered posters manned
1400 – 1430	Even numbered posters manned

Oral Presentation Session 2, session chair: John Parkinson

1430 – 1510	**Melanie Britton**, University of Birmingham *Characterisation of reverse micelles in microemulsions using NMR*
1510 – 1530	**Godiraone Tatolo**, University of Bristol *SelEXSIDE – An incredibly fast, easy and reliable method for the measurement of long-range ^{13}C-^{1}H coupling constants.*
1530 – 1550	**John Moran**, Institute of Technology Tallaght *NMR Analysis of Urea-Based Molecular Clips that Display Rotameric Behaviour*
1550 – 1610	**Daniel Dawson**, University of St Andrews *Using Solid-State ^{13}C NMR Spectroscopy to Study Paramagnetic Metal-Organic Frameworks Loaded with Multiple Guests*

Close

1610	Tea and Coffee
1620	Award of Best Oral Presentation and Best Poster Presentation

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Abstracts of Talks

(Talk 001)

John Hollerton, GlaxoSmithKline R&D, john.c.hollerton@gsk.com

NMR in Drug Discovery

John Hollerton

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NMR is so versatile that it has huge application across Drug Discovery. This was not always the case and this presentation highlights some of the advances in NMR that have made this possible as well as touching on some of the diverse areas in which NMR has found a role.

(Talk and Poster 002)

Anna-Winona Struck, University of Manchester,
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Characterization of Nonribosomal Peptides Antibiotics with Non-Natural Amino Acids my MS-MS and NMR

Anna-Winona Struck,[1] Matthew Styles,[1] Jenny Thirlway,[1] Richard Lewis,[2] Laura Nunns,[1] Majid Al Nakeeb,[1] Colin P. Smith, [2] Jason Micklefield[1]

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Nonribosomal peptides are a group of structurally diverse secondary metabolites, which are synthesised by nonriobosomal peptide synthetases (NRPS). We engineered the biosynthesis of calcium-dependent antibiotics (CDA) to incorporate a synthetic non-natural amino acid into the decapeptide lactone core of CDA. Our strategy focused on altering the specificity of the Module 10 A-domain, of CdaPS3, so that it preferentially incorporates (2*S*,3*R*)-3-methyl glutamine (mGln) and Gln over the natural substrates (2*S*,3*R*)-3-methyl glutamic acid (mGlu) and Glu. The new product was subsequently purified by HPLC and subjected to high-resolution MS, confirming the proposed molecular formula. The sequence of the CDAs was obtained by tandem MS and confirmed by 2D ^{1}H NMR spectroscopy.

Reference:

J. Thirlway, R. Lewis, L. Nunns, M. Al Nakeeb, M. Styles, A.-W. Struck, C. P. Smith and J. Micklefield, Angew. Chem. Int. Ed. 2012, in press.

(Talk and Poster 003)

Robert Kelly, University of Warwick, r.t.kelly@warwick.ac.uk

Exploring the impact of Cu^{2+} ions on the aggregation of amyloid-beta (1-40) using Solid-State NMR

Robert T. Kelly,[a] Ray Dupree,[a] Józef R. Lewandowski,[a] Steven P. Brown,[a] Oleg N. Antzutkin [a,b]

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Aggregation of amyloid-beta$_{1\text{-}40}$ (A$\beta_{1\text{-}40}$) is linked to the pathology of Alzheimer's disease with current ssNMR research focusing on the interaction of oligomers of Aβ with membranes.[1] In this work, 2D and 3D solid-state NMR (ssNMR) spectra, chemical shift values and electron microscopy images of A$\beta_{1\text{-}40}$ aggregates formed in the presence of Cu^{2+} are presented. Short (20 ms) and long (200 ms) mixing time ^{13}C-^{13}C MAS DARR experiments were performed on Bruker Avance II+ 600 MHz and Bruker Avance III 850 MHz spectrometers so as to separate inter- and intra-residue cross peaks. ^{13}C chemical shift values are compared to those obtained for other Aβ fibrils [2-4] and Aβ1-40 fibrils which, after formation, had Cu^{2+} ions introduced,[5] noting that carbon chemical shifts are sensitive to the secondary structure.

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[2] Petkova, A., Yau, W. M. and Tycko, R. "Experimental constraints on quaternary structure in Alzheimer's beta-amyloid fibrils" *Biochemistry* **45**, 498-512 (2006)
[3] Paravastu, A. K. et al "Molecular structural basis for polymorphism in Alzheimer's beta- amyloid fibrils" *Proc. Natl. Acad. Sci. USA*. **105**, 18349-18354 (2008)
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(Talk and Poster 004)

Stephen Day, University of Warwick, s.p.day@warwick.ac.uk

Complimentary GIPAW DFT computational and solid state NMR approaches to studying hydrogen bonding and disordered apatites systems

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The combination of GIPAW DFT computation and solid state NMR (SSNMR) has been shown to be a powerful combination when dealing with many different types of chemical and materials systems. Solid organic structures which are strongly influenced by hydrogen bonding, and materials systems characterised by structural and positional disorder are very amenable to this type of analytical approach. This investigation into hydrogen bonded structure uses the benzoic acid motif as a starting model to investigate more complex Group I hemobenzoate systems, where the effect of the alkali metal ion on the hydrogen bonded network will be reported. This project has used SSNMR techniques such as fast MAS, MQMAS and DOR in combination with GIPAW DFT calculations facilitated with the CASTEP code.

In contrast, rare earth apatites ($A_{10-x}(Si/Ge)_6O_{26+y}$ (A = rare earth)) are potential oxide-ion electrolytes for solid oxide fuel cells which exhibit positional and structural disorder, and these pose very different computational issues. Recent ^{17}O MAS NMR, DFT and MD studies[4] on $La_8Y_2Ge_6O_{27}$ have shown that the oxide-ion excess(y) is preferentially incorporated as an interstitial species between two GeO_4 tetrahedra. These complex systems require a systematic and efficient strategy to handle large DFT computational load needed to accurately describe these structures and thus predict the NMR parameters characterising the relevant species. We have statistically addressed the computed results by constraining them within Boltzmann distributions to identify structurally probable realisations based on their final energy, and weighted the average NMR parameters over these configurations according to their respective probabilities.

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[4] Panchmatia, P. M., Orera, A., Rees, G. J., Smith, M. E., Hanna, J. V., Slater P. R. and Islam M. S. ,*Angew. Chem.*, 50 (**2011**) 9328–9333

(Talk and Poster 005)

Smita Odedra, University of Glasgow, smoded@chem.glas.ac.uk

Improved background suppression in ^{1}H MAS NMR using composite pulses

Smita Odedra and Stephen Wimperis

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A well known feature of ^{1}H MAS NMR spectroscopy, particularly of solids where the concentration of ^{1}H nuclei is low, is the presence in the spectrum of a significant broad "background" signal arising from ^{1}H nuclei that are outside the MAS rotor and radiofrequency coil, probably located on the surfaces of the static components of the probehead. A popular method of suppressing this unwanted signal is the "depth pulse" experiment,[1,2] consisting of a 90° pulse followed by two 180° pulses that are phase cycled according to the "Exorcycle" scheme,[3] which removes signal associated with imperfect 180° pulses. Consequently, only spins in the centre of the radiofrequency coil contribute to the ^{1}H MAS spectrum, while those experiencing a low B_1 field outside the coil are suppressed. Although very effective at removing background signal from the spectrum, one drawback with this approach is that significant loss of the desired signal from the sample also occurs owing to the spatial inhomogeneity of the B_1 field produced by the coil.

By using novel antisymmetric passband composite pulses[4,5] to replace the simple pulses in the "depth pulse" experiment, we achieve improved intensity of the ^{1}H signals of interest while still maintaining effective background suppression. We expect that our results will be relevant to ^{1}H MAS NMR studies of, for example, nominally perdeuterated biological samples or nominally anhydrous inorganic materials.

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(Talk and Poster 006)

Antoine Vallatos, University of Birmingham, axv982@bham.ac.uk

Characterising stationary and translating vortex flow using magnetic resonance

Antoine Vallatos[1], Marc C.T. Wilson[2], Annette F. Taylor[3], Melanie M. Britton[1]

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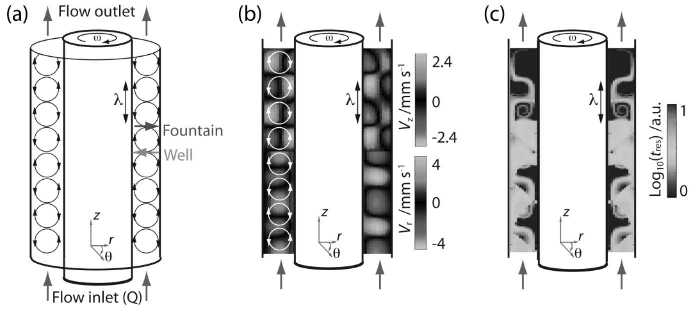
Understanding molecular displacements within complex flows is of great importance in fluid mechanics, engineering, biology and chemistry, and there is an increasing interest in oscillating and time periodic vortical flows. High-resolution, three-dimensional velocity mapping, which can characterise the transport properties in these systems, remains a challenge. Also, where mechanical instabilities generate dispersion and anomalous diffusion it has been found that enhanced molecular displacements are produced, which are not predicted from velocity maps alone. This is especially the case for vortical and periodic flows.

In this work[1], we report magnetic resonance (MR) velocity and diffusion maps in three directions for stationary vortices (Taylor Vortex Flow) and velocity maps (fig. b) for translating vortices (Vortex Flow Reactor) produced in a Couette cell (fig. a). Imaging translating vortices is difficult due to the artefacts produced by unsteady flow. However, these motion artefacts were removed by synchronising data acquisition with the translation period of the vortices. MR propagator experiments, which measure the conditional probability density for displacement, were performed to characterise molecular displacements in these systems. Simulations were performed using the experimental velocity and diffusion maps to aid interpretation of experimentally measured propagators and enable characterisation of the macro-mixing properties. These simulations enabled molecular transport to be assessed over longer-time scales than are accessible experimentally (fig. c), allowing plug-flow, by-pass flow and inter-vortex mixing to be quantified.



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(Talk 007)

Melanie Britton, University of Birmingham, m.m.britton@bham.ac.uk

Characterisation of reverse micelles in microemulsions using NMR

Melanie M. Britton

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Water-in-oil reverse micelles (RMs), in a microemulsion, are composed of nanosized water droplets surrounded by surfactant molecules in a continuous organic phase. These self-assembled structures form thermodynamically stable droplets of water ranging in intramicellar diameter from approximately 1 to 20 nm, depending on the molar water-to-surfactant ratio (ω). The aqueous core of reverse micelles provides a highly adaptable environment for a variety of chemical and biochemical reactions, protein extraction, synthesis of nanoparticles, as well as providing a model for biological systems. For all of these applications, an understanding of the chemistry, dynamics and structure within the interior of the droplets is important, and typically a variety of molecular probes and spectroscopic techniques have been used to probe intramicellar parameters such as pH, ionic strength, microviscosity and micropolarity. However, the use of probe molecules has a number of limitations. The first is associated with the location of the probe molecule and difficulties in the getting the probe molecule to reside in the region of interest. The other problem is that the probe molecule may adversely affect the size, stability or environment of the reverse micelle. In this talk, I will discuss these issues and present methods[1, 2] for probing the chemistry of reverse micelles using NMR spectroscopy, without the need for a probe molecule.

In addition to characterising the chemistry and physical environment within reverse micelles, knowledge of their structure, size and polydispersity is also extremely important. Typically, methods such as dynamic light scattering (DLS) or small-angle x-ray scattering (SAXS) have been used to determine these properties. However, these techniques also have a number of limitations. Recent developments[3] for measuring size distributions using the inverse Laplace transformation of NMR measurements of diffusion will be presented.

[1] Halliday, N. A.; Peet, A. C.; Britton, M. M., "Detection of pH in Microemulsions, without a Probe Molecule, Using Magnetic Resonance." *J. Phys. Chem. B* **2010**, 114, 13745–13751.

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[3] Law, S. J.; Britton, M. M., "Determination of Droplet Size Distributions in Microemulsions using NMR Measurements of Diffusion." *Langmuir* **2012**, submitted.

(Talk and Poster 008)

Godiraone Tatola, University of Bristol, chxgt@bristol.ac.uk

SelEXSIDE – An incredibly fast, easy and reliable method for the measurement of long-range ^{13}C-^{1}H coupling constants.

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The application of 3-bond ^{13}C-^{1}H scalar coupling constants has seen a tremendous growth in elucidation of 3-dimensional structures of organic molecules. Unfortunately, in practical terms $^{3}J_{CH}$ values are difficult to extract – they are relatively small and of same magnitude as $^{3}J_{HH}$ coupling constants but also made more complicated by the low sensitivity of the ^{13}C nucleus. Many new experiments for simplifying the measurement of $^{3}J_{CH}$ have been reported in literature(1) and their main setbacks are that the interpretation of the resulting spectra is not straightforward, long selective pulse sequences lead to the loss of signal due to t2 relaxation and high-resolution 2-dimensional methods typically require extended experiment times. Of these methods, the most straightforward in our experience is the EXSIDE,(2) which gives rise to simple in-phase doublets in the F1 (^{13}C) dimension from which the $^{n}J_{CH}$ value can be read directly from the spectrum, however the extremely high F1 resolution required, means typical experiments take around 7 hours.

A new, fast, easy to interpret approach is reported for determination of long-range ^{13}C-^{1}H coupling constant where EXSIDE is converted to be doubly-selective in both the ^{13}C and ^{1}H domains. This sequence termed SelEXSIDE, is easy to interpret and reduces a multi-hour (> 6 hrs) experiment to a matter of minutes (as short as 4 mins) for each coupling constant measured.

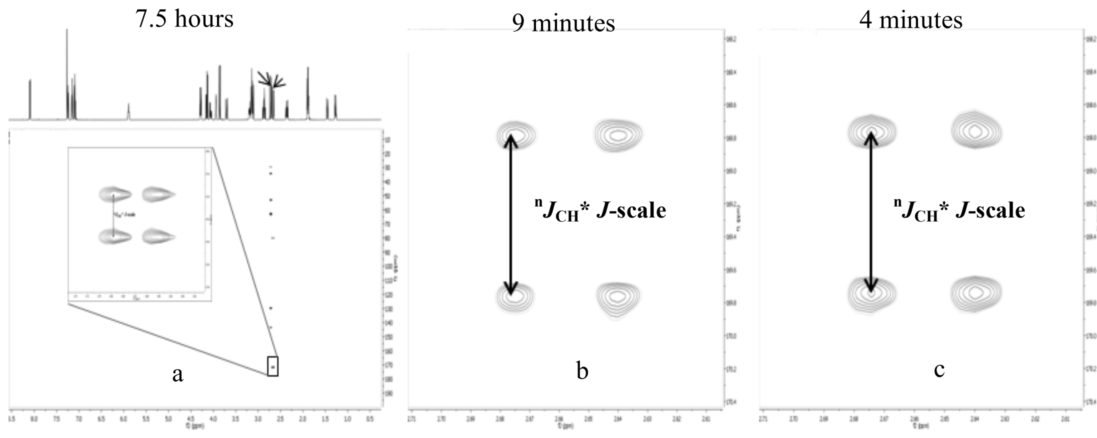

Figure 1: (a) EXSIDE spectrum (~7.5 hours) for H11b-C10 of strychnine with 200 ppm (spectral width, 1675 t1 increments, 4 scans/inc. (b) SelEXSIDE spectrum (9

mins) for H11b-C10 of strychnine with 4 ppm (500 Hz) ^{13}C spectral width, 32 t1 increments, 4 scans/inc. (c) SelEXSIDE spectrum (4 mins) for H11b-C10 of strychnine with 4 ppm (500 Hz) ^{13}C spectral width, 32 t1 increments, 2 scans/inc.

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[2] Krishnamurthy V.V., *J. Magn. Reson*. **1996**, Series A 121, 33-41.

(Talk and Poster 009)

John Moran, Institute of Technology Tallaght, johnmoran@ittd.ie

NMR Analysis of Urea-Based Molecular Clips that Display Rotameric Behaviour

John Moran[1], John McGinley[2], Brian A, Murray[1]

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Urea-based molecular clips mimic natural receptors, with a pre-organised upper organic-cavity that binds to dihydroxybenzene (DHB) molecules, which are the subunits of many neurotransmitters. The lower aromatic rings of the clip hold it in an X-shaped conformation.[1]

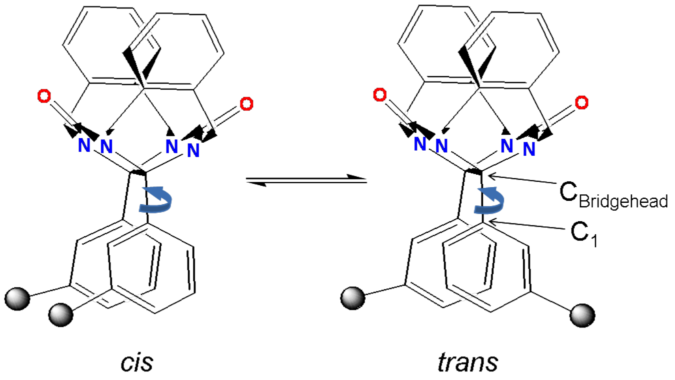

Figure 1: Cis and trans rotameric forms of a 3,3’-Disubstituted Molecular Clip

Molecular clips with substituents at the 2,2’- and 3,3’-positions of the lower phenyl rings of the clips display rotameric activity. These rotamers are generated due to hindered rotation around the $C_{Bridgehead}$-C_1 bonds of the urea backbone (Figure 1). Work has concentrated on substitution at the 3,3’-positions. ^{1}H NMR can be used to determine the cis/trans ratio of the molecular clips and variable temperature NMR can be used to determine the barrier of interconversion between the two forms.[2]

NMR titrations can be employed to determine the binding strength between DHB molecules and the organic cavity of the clip.

References

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(Talk and Poster 010)

Daniel Dawson, University of St Andrews, dmd7@st-andrews.ac.uk

Using Solid-State 13C NMR Spectroscopy to Study Paramagnetic Metal-Organic Frameworks Loaded with Multiple Guests

Daniel M. Dawson,[1] Lauren E. Jamieson,[1] Alistair C. McKinaly,[1] M. Infas H, Mohideen,[1] Siobhan Day,[1] Romain Cadou,[1] Neil S. Keddie,[1] Iain A. Smellie,[1] Russell E. Morris,[1] and Sharon E. Ashbrook[1]

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Metal-organic frameworks (MOFs) are an important class of microporous materials consisting of metal or metal oxide centres connected in an infinite network by organic "linker" species. MOFs have applications such as gas separation and storage, drug delivery, catalysis and sensing. HKUST-1 is a copper-based MOF showing promise in applications including storage of fuel and medicinal gases and drug delivery.[1] STAM-1 is a new MOF containing the same copper dimers as HKUST-1, showing promise in gas storage and separation, as well as being an unusual "protecting group" in the synthesis of monomethyl trimesate.[2] As these MOFs are both paramagnetic, acquiring and assigning their ^{1}H and ^{13}C NMR spectra is challenging, although partial spectra have been reported.[2,3] By combining fast magic-angle spinning, rapid repeat rate, extensive signal averaging and frequency-stepped acquisition, complete ^{13}C NMR spectra have been acquired, with a total experimental time of 5 h, despite using only a few milligrams of natural-abundance sample. Selective ^{2}H- and ^{13}C-labeling and signal-editing by cross-polarisation enabled assignment of all resonances. The experimental approach adopted here allows rapid determination of the location of guest molecules in the pores of HKUST-1, here demonstrated by dual-loading HKUST-1 with a series of medically-relevant guest species.

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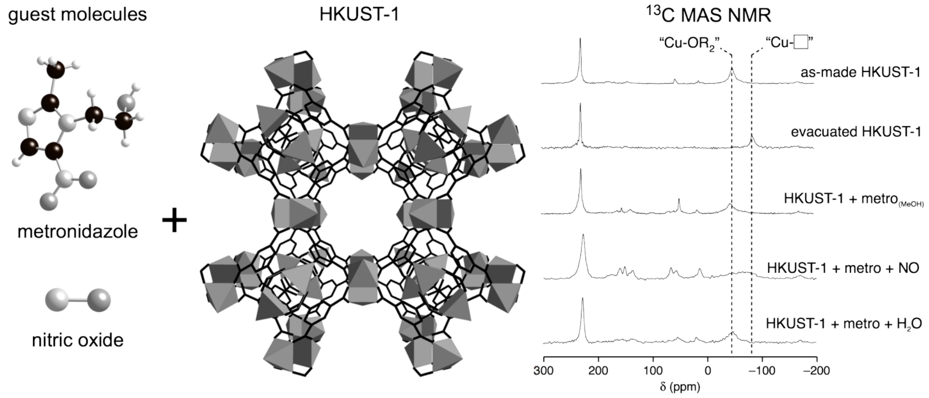

Abstracts of Posters

Poster 011

Catharine Jones, University of Bristol, chcrj@bris.ac.uk

Accurate NOE-Derived Interproton Distances – Fact or Fiction?

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Establishing an Initial Level of Accuracy
We present a simple method to derive accurate interproton distances from within rigid and flexible systems using NOE data. Strychnine is used as a rigid model system to test the validity of this method. A comparison of the 1D NOE-derived distances and the computed structure of strychnine[1] (right) gives an average error of only 2.3% (0.07Å).[2]

Low Level Conformer Identification
A second low-level conformer of strychnine is identified using NOE data and confirmed computationally, showing the potential of accurate NOE measurements to determine minute contributions to structure ensembles in solution.[3]

Modelling Populations in Flexible Compounds
NOE data is further applied to the small flexible molecule, 4-propylaniline, to confirm and predict the relative populations of the multiple possible conformers.[4] It is suggested that with the highly accurate interproton distances determined using this method, there is less need for reliance on the large numbers of loose restraints, such as scalar couplings, typically used in the dynamical analysis of flexible molecules.

Monitoring Changes in Conformer Populations with Temperature
NOE-distance relationships are also shown to be sufficiently accurate to monitor very small changes in conformer populations in solution (<0.5%/10 °C) – in response to temperature – in good agreement with Boltzmann-predictions, illustrating the effectiveness of accurate NOE-distance measurements in obtaining high quality dynamical, as well as structural, information for small molecules.

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Poster 012

Rebecca Joyce, University of Sussex, r.joyce@sussex.ac.uk

Monitoring Membrane Permeation using a Phosphorous-31 NMR and a Paramagnetic Shift Reagent

Rebecca Joyce, Louise C. Serpell and Iain J. Day.

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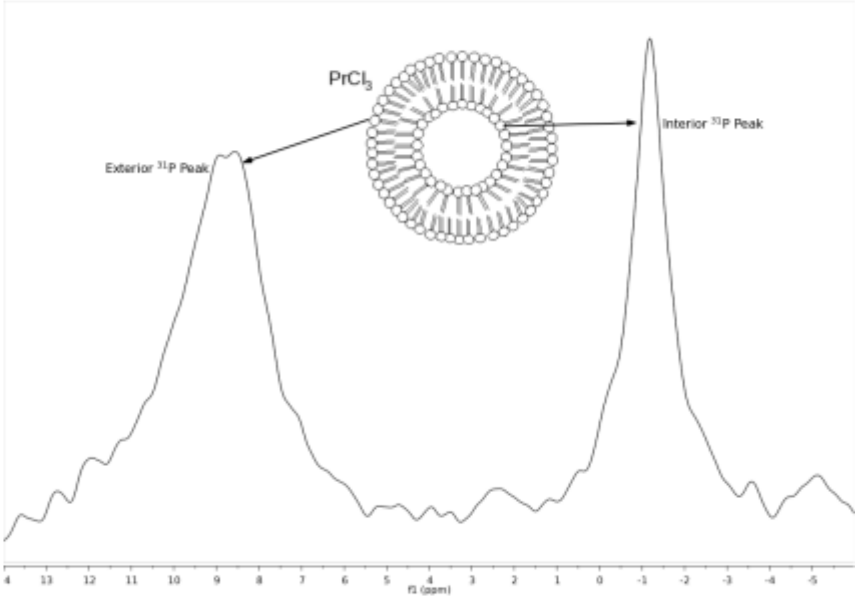
Aggregation of amyloidogenic peptides has been found to be a cause of several diseases; for instance, Aβ plaques have been found in the brains of Alzheimer's patients[1] and αSynuclein in those patients with Parkinson's disease[2]. The mechanism of toxicity of these peptides is not confirmed, however, many studies suggest that it is the small soluble oligomeric species in the aggregation pathway which are cytotoxic.[3] In this work NMR has been applied to assist in the elucidation of the mechanism of membrane permeation. Small unilamellar phospholipid vesicles have been used as biomimetic membranes. The ^{31}P peaks of the interior and exterior leaflets are separated by addition of $PrCl_3$, a paramagnetic shift reagent, to the exterior solution of the vesicles only. Changes to the lipid distribution in the vesicles, caused by membrane permeation or instability, leads to changes in the ratio of peak areas. Monitoring the peak distributions over time with and without the addition of aβ illustrates the membrane permeation ability of the amyloidogenic protein.



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A Multinuclear Solid State NMR Investigation into the Speciation and Structure of Aluminium Doped Phosphate Bioactive Glasses

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Calcium phosphate glasses exhibit interesting properties and compatibility for use as bioactive materials; in particular, they provide bone support and also demonstrate a tendency to stimulate bone regeneration. Aluminium doping of these glass systems induces more favourable properties, due to the strengthening of the structure and through subsequent greater control of dissolution rates from the glass network. A multinuclear solid state MAS NMR study of a glass series with the nominal stoichiometry $x(Al_2O_3)\ (11\text{-}x)(Na_2O)_{44.5}(CaO)_{44.5}(P_2O_5)$ (with $x = 0, 3, 5, 8$) has been undertaken in order to construct a picture of the glass network, and to determine how the structure may influence the bioactive properties. ^{23}Na and ^{27}Al MAS NMR provide insight on the coordination and disorder within the glass network. Information on the phosphorus Q speciation present within the glasses is evidenced by ^{31}P MAS NMR, which shows both chain like Q^2 species and less polymerised Q^1 units. Further information is obtained, however, by the implementation of the newly developed ^{31}P refocused INADEQUATE Spin Echo (REINE) technique that reveal 2D correlations of the $^2J_{PP}$ couplings with the ^{31}P chemical shifts of the coupled nuclei. These measurements have been performed for the first time on a coherent suite of samples thus enabling the evolving speciation and polymerisation of the phosphate network to be mapped out throughout the entire series. The structural information obtained from this study provides a much greater insight to support their development as bioactive materials.

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Dynamics and Structure of Novel Polymer Electrolyte Membranes Investigated using Multinuclear Solid-State NMR

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Fuel cells have the potential to revolutionise power generation due to their high energy efficiency and low Greenhouse emissions footprint. A key component of any fuel cell is the electrolyte membrane separating the electrodes which must exhibit excellent proton or oxide ion conduction characteristics depending on the material and nature of the fuel cell. The most commonly used proton conducting electrolytes are water-based which limits their use to low temperatures yet temperatures above 130°C are desirable to limit CO poisoning of the Pt catalyst [1].

The dynamics and structure of novel polymer electrolyte membranes based on naphthalene sulfonate formaldehyde (NSF) resin inserted into mesopourous metal oxides creating a metal-organic framework (MOF) have been investigated using ^{1}H pulsed field gradient (PFG) NMR and ^{1}H, ^{17}O and ^{13}C MAS NMR techniques. The ^{1}H PFG data from pure NSF shows that this material is characterised by high proton diffusion behaviour which are only two orders of magnitude smaller than that of H_2O ($2.0 \mathrm{x} 10^{-11}$ m^2 s^{-1} vs. $5.6 \mathrm{x} 10^{-9}$ m^2 s^{-1} at 70°C [2]). In a mesoporous TiO_2/H_2O assisted inclusion of NSF system clear two component diffusional behaviour is observed with the faster ^{1}H diffusional process being characterised by D values which are higher than that of H2O ($8.7 \mathrm{x} 10^{-9}$ m^2 s^{-1}, 70°C), and a second slower diffusional process characterised by a much smaller D value ($1.4 \mathrm{x} 10^{-10}$ m^2 s^{-1}). This second slower process is ascribed to areas of the MOF with reduced NSF concentrations or less efficient NSF contact near the pore structure to assist in the proton conduction process. These results will be correlated with structural findings obtained from ^{1}H, ^{17}O and ^{13}C MAS NMR measurements.

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Poster 015

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Conformational Analysis of New Rotameric Molecular Clips Using Variable Temperature NMR Study

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Key words: molecular clips, rotamers, energy barrier, interconversion, VT-NMR.

Molecular clips are well-known artificial receptors for dihydroxyaromatics, e.g. resorcinol, catechol and other biomolecules bearing a dihydroxyaromatic unit. Two xylylene walls and two carbonyl groups, making a pre-organized cavity, are the key features which bind the substrate via two aryl-stacking & two hydrogen-bonding interactions[1] (Figure 1).

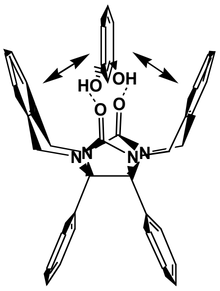

Figure 1: a molecular clip binds resorcinol

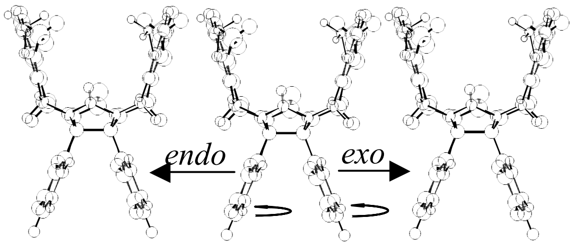

Figure 2: interconversion from *cis* (middle) to *trans* (left and right)

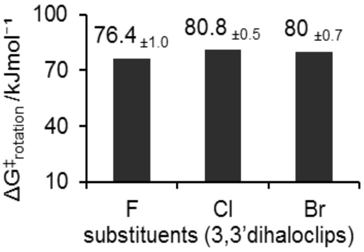

Figure 3: the free energy was found to be same

Figure 1: a molecular clip binds resorcinol Figure 2: interconversion from cis (middle) to trans (left and right) Figure 3: the free energy was found to be same

Recently we have prepared[2] new clips which exist as "rotamers" (isomers interconverted by rotation about a single bond; Figure 2). A VT-NMR study shows that the barrier for the interconversion of these rotamers, together with free energy calculations, is almost the same for any substituents at 3,3-positions of the locking phenyl (Figure 3). The energy barrier was found to be too high to access by VT for 2,2-disubstituted clip.

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Poster 016

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Investigating the ^{31}P CSA of Aluminophosphates by First-Principles Calculations and 2D CSA-Amplified PASS

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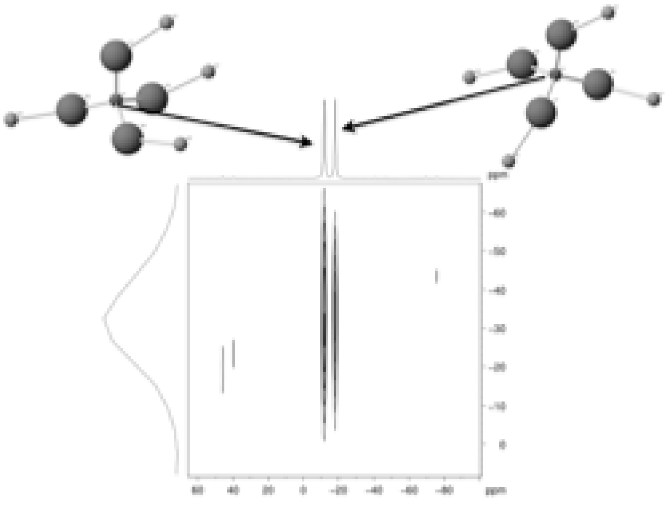
Aluminophosphates (AlPOs) are an important class of microporous materials that were first reported in 1982 by Wilson et al. [1] and consist of alternating corner-sharing AlO4 and PO4 tetrahedra. Solid-state NMR can be used to probe the local structure and order of AlPOs, since the basic components are all NMR active (^{27}Al, ^{31}P, ^{17}O), as are many of the nuclei in the templates (for example ^{13}C, ^{1}H and ^{15}N). The ability to quantify both the isotropic and anisotropic shielding parameters, in experimental work and using first- principles calculations, would ease the challenge of spectral assignment in solid-state NMR.

This work focuses on the ^{31}P chemical shift anisotropy (CSA) of as-prepared and calcined AlPOs. By using the 2D CSA-amplified PASS experiments of Orr et al. [2], the CSA can be reintroduced in the indirect dimension with an effective MAS rate of ωr/NT, where NT is the total scaling factor. The CSA can be extracted and compared with values obtained from first-principles DFT calculations. It is hoped that a deeper understanding of ^{31}P CSA in AlPOs, will afford greater insight into the local structure and interactions in these industrially-relevant materials.



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Poster 017

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Simultaneous Acquisition of Homonuclear and Heteronuclear Long-Distance Contacts with Time-Shared Third Spin Assisted Recoupling

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It is well known that low inherent sensitivity is a major limiting factor of NMR and its application to the study of large biomolecules, often leading to acquisition timescales on the order of days or weeks for 2D and higher dimensionality spectra. In solution-state NMR, so-called time-shared experiments have been shown to cut experimental times by effectively multiplying the amount of information gained per experiment[1-3], but their use is uncommon in the solid state. We present a time-shared Third Spin Assisted Recoupling (TSTSAR) experiment that allows for simultaneous acquisition of long-distance homonuclear (^{13}C-^{13}C) and heteronuclear (^{15}N-^{13}C) contacts in biomolecular solids under magic angle spinning, with a view to gaining complementary distance constraints for biological systems. TSTSAR is demonstrated to lead to substantial time savings and to increase the information content of 2D correlation spectra, without or with very little loss of peak intensity compared to each experiment performed separately.

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Poster 018

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Probing Small Molecule Aggregation Phenomena using NMR Spectroscopy and Small Molecule Probes

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Aggregation, one form of which is the grouping of large planar aromatic molecules through a $\pi - \pi$ non-covalent interaction, is known to occur in systems such as dyes and pigments[1,2], and various drug molecules[3,4]. Increasingly larger aggregates present with slower rates of diffusion and amplified magnetic shielding due to an enhancement of the ring shielding affect in neighbouring molecules. Nuclear Magnetic Resonance can be employed as an effective tool in the investigation of such changes. Using a pulsed field gradient echo experiment to monitor diffusion coefficients[5] or tracking concentration dependent changes in chemical shifts[6] it becomes possible to quantify the size and degree of aggregation. These approaches however, can fall victim to complications such as spectral crowding and extensive line broadening, making detailed analysis difficult or impossible.

Here we aim to apply the already accepted NMR toolbox in a new way. By introducing a reporter probe molecule with a unique magnetically active nucleus such as ^{19}F or ^{31}P into a self-aggregating system it becomes possible to ameliorate those spectral complications and hence provide a new means of monitoring these changes. With the introduction of Fluorophenol (1 mol%) into a range of samples with varying Sunset Yellow concentrations, we will show that it becomes possible to uncover information about the aggregates via the monitoring of the new unique fluorine marker.

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Poster 019

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Size Distributions of Reverse Micelles using NMR Diffusion Measurements.

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This work reports a novel method for evaluating the size distributions of water-in-oil (w/o) reverse micelles (RMs) using NMR diffusion measurements.[1] Reverse micelles (w/o) are nano-sized water droplets surrounded by surfactant molecules in an organic continuous phase. They are of great interest, as they provide adaptable environments for chemical reactions, as well as providing a model for biological systems.[2] Knowing the RM size distribution is crucial in understanding the chemistry, properties and reaction kinetics of RMs. Traditionally, Dynamic Light Scattering (DLS) has been used to characterise the size distributions of RMs, however, this technique has a number of limitations, which include a need for samples to be dust-free and transparent. Frequently errors can also be introduced into size distributions by the analysis used. In this poster, we show an alternative method for droplet sizing using NMR. This technique is not affected by many of the problems which affect DLS, but also has several advantages.

Diffusion coefficients (D) of RMs were determined by measuring D for surfactant molecules contained in the RMs, acquired using pulsed gradient stimulated echo (PGSTE) experiments. Diffusion coefficient distributions, $G(D)$, were produced using the inverse Laplace transform (a constrained regularization method)[3]. Size distributions were produced from the $G(D)$ data using the Stokes-Einstein relation. AOT/n-octane/H2O and CTAB/hexanol/H2O microemulsions were studied and the effect of ω (ω = [H2O]/[surfactant]) and the presence of additives were investigated.[4,5] Our method produced distributions in good agreement with the literature values produced by DLS, and was able to detect monomodal and bimodal distributions.

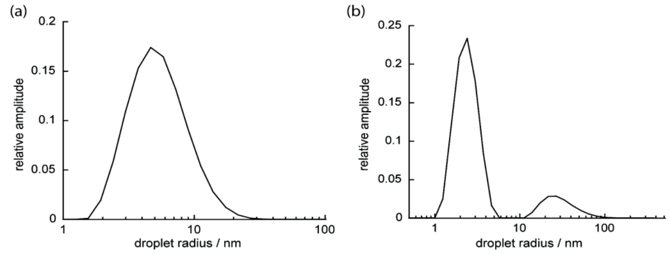

Figure 1. Droplet size distributions for RMs in AOT/n-octane/H2O microemulsions at (a) $\omega = 15$, droplet fraction = 0.15 and (b) at $\omega = 12$ and droplet fraction = 0.5, loaded with [H2SO4] = 0.25M ,[NaBrO3] = 0.16 M and [malonic acid] = 0.25 M .

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Poster 020

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Magnetic Resonance Imaging of Hydrodynamic Instabilities in Porous Media

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Viscous fingering is a hydrodynamic instability formed when there is an interface between two solutions of different viscosity. At such an interface flow becomes non-linear and the interface deforms producing finger-like tendrils. Such instabilities are of interest in a variety of applications, such as extraction of oil from pipes[1], instabilities in combustion[2] and growth of microorganism colonies[3].

In recent years, there is an increasing interest in systems that involve chemical reactions at the interface. The products of these reactions effect the formation of the fingers, either through changing the viscosity or altering the composition of the porous media. Both experimental[4, 5] and theoretical[6] studies have been conducted on these systems. However, experimental work has typically relied on investigating systems optically using Hele-Shaw cells[4, 5]. This pseudo-2D experiment provides limited information on the formation of instabilities in a 3D system.

We have used magnetic resonance imaging (MRI) to visualise the formation of viscous fingers at various reactive interfaces. The production of both worm-like micelles and precipitate at the interface has been investigated. MRI's ability to probe opaque systems makes it uniquely amenable to directly investigate flow instabilities in these systems in 'real' porous media, such as a packed bed. 3D imaging was used to monitor the development of these instabilities and characterise their growth.

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Poster 021

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Aggregation behaviour of lipid and MALDI matrices in methanol using NMR

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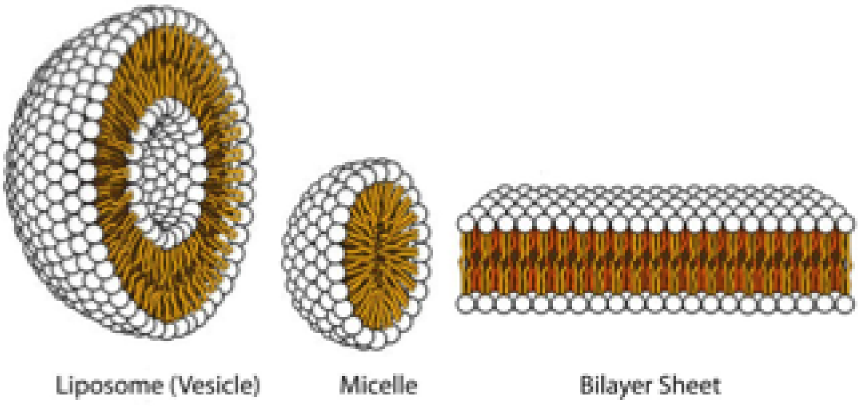
NMR diffusion experiments are reported which have been used to probe possible aggregation of MALDI matrix compounds with lipids at various concentrations. Matrix Assisted Laser Desorption Mass Spectrometry (MALDI-MS) is a soft ionisation technique employed for the analysis of biomolecules and large organic molecules like lipids[1]. MALDI uses a matrix compound to promote ionisation of the analyte[1] e.g. lipid, and the matrix and analyte are solvated using methanol. Investigations of lipids show that some matrix compounds produce more abundant lipid peaks than others. This was thought to be due to interactions between lipid and matrix compounds through self-aggregation. As lipids possess both hydrophobic and hydrophilic regions, they are expected to form self-aggregated assemblies in solution. Possible assemblies include lipid bilayers, micelles and liposomes (vesicles) in methanol.

The formation of these aggregated structures was tested using pulsed field gradient stimulated echo (PGSTE)experiments which measure the translational diffusion of the lipid, matrix and solvent[2]. The diffusion coefficient of the solvent methanol was found to decrease on increasing concentration, suggesting the formation of aggregated structures. No change in the diffusion coefficient of the lipid or matrix molecules was observed. The behaviour of the methanol can be explained by the formation of a liposome (vesicle) aggregation assembly, where some of the methanol molecules can reside both inside and outside the liposome.



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Poster 022

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Using NMR to Probe the Characteristics of a Gadolinium Binding Coiled-Coil

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Herein we report the development of MRI contrast agents based on gadolinium binding peptides using the common coiled-coil (CC) motif (Figure 1). Magnetic resonance measurements of relaxation were used to characterise these contrast agents using Carr-Purcell-Meiboom-Gill (CPMG) and Inversion Recovery experiments. Diffusion measurements were performed using the Pulsed Gradient Stimulated Tanner Echoe (PGSTE) experiment to assess the oligiomeric state. The toxic lanthanide, Gadolinium, is widely used as a contrast agent in Magnetic Resonance Imaging. It has been proposed that in order to increase the relaxivity and sensitivity of contrast agents the number of coordinated water molecules and the water exchange rate must be increased, as well as decreasing the correlation time. CC motifs have the potential to suit these requirements due to their larger size compared to previous contrast agents, and their potential ability to control the water environment through their hydrophobic core.[1]

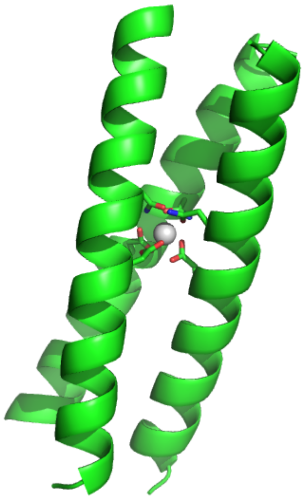

Figure 1. Pymol model of gadolinium binding coiled-coil based on PDB crystal structure 3H5F.

CC proteins are common structural motifs, occurring in over 10% of eukaryotic cells. They are made up of two or more α-helices consisting of seven residue repeats, known as heptads. Under appropriate pH conditions, the α-helices begin to aggregate and super coil.[2,3] By modifying the heptad repeating units, proposed by Harbury et al. it has been possible to incorporate a binding site within the hydrophobic core. [4]

These peptide structures can exist in a variety of states, such as dimers, trimers and tetramers, depending on the sequence and number of modifications. The diffusion coefficients of the well understood TRI coiled-coil, found by PGSTE experiments, were compared with that of the binding peptide to help characterise its structure and assess the effects of the sequence modifications.

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Poster 023

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Predicting the Physical Stability of Polymer-Stabilised Amorphous Dispersions for Oral Drug Delivery: Part I - Indomethacin studies

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Poor physical stability is a huge limiting factor in the development and use of amorphous drugs within the pharmaceutical industry. Amorphous drugs are attractive due to increased solubility and bioavailability; however they unpredictably revert to the thermodynamically stable insoluble crystalline form [1]. Accurate prediction of physical stability on a molecular level would be a great advantage – polymers can be used to stabilise amorphous systems but we need a firm understanding of the mechanism of stabilisation on a molecular level. Indomethacin was systematically chosen as the initial investigative compound as it has been widely formulated and studied both as an amorphous drug and dispersion [1- 3]. There is a wealth of information available, however only a handful of studies have utilised solid-state NMR [1, 3, 4]. This technique has the ability to provide molecular level information on structure and dynamics and could therefore be a powerful tool to predict the physical stability of polymer-stabilised amorphous systems.

Indomethacin was successfully formulated as a pure amorphous drug [2] and as multiple solid dispersions (varying drug:polymer ratios) with PVP-VA [2]. Initial characterisation with PXRD, DSC and solid-state NMR confirmed amorphous behaviour and determined T_g values and spectral peak assignments. Variable temperature solid-state NMR studies highlighted a possible recrystallisation of amorphous indomethacin to the α-polymorph. VT ^{1}H-^{13}C CP/MAS NMR, ^{13}C {^{1}H} and relaxation studies highlighted a change in mobility of the drug when formulated with different levels of polymer, indicating the possible formation of drug-rich domains within the higher loaded dispersions. CP kinetics studies also showed a difference in relaxation behaviour between pure amorphous indomethacin, solid dispersions and pure PVP-VA.

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