Final Report on GR/R75441/01 (Advanced Research Fellowship): Novel Very-High Resolution ^{1}H NMR as a Probe of Fundamental Non-Bonding Interactions in Solids

Background and Context In solid-state NMR, anisotropic interactions, notably dipolar couplings, chemical shift anisotropy (CSA) and (for spin $I \geq 1$) the quadrupolar interaction, cause spectral broadening that can prevent resonances due to chemically distinct nuclei being resolved. This is particularly true for ^{1}H solid-state NMR of organic solids, where broadening due to the strong dipolar couplings among the abundant ^{1}H nuclei is only partially removed by magic-angle spinning (MAS). At the start of the fellowship (2002), advances in hardware and methodology were leading to renewed interest in high-resolution ^{1}H solid-state NMR. MAS technology allowing rotation frequencies at 30+ kHz[1] had been shown to allow the resolution of resonances corresponding to hydrogen-bonded and aromatic protons, with structurally important proton-proton proximities being identified in two-dimensional ^{1}H double-quantum (DQ) MAS spectra.[SPB_1] Moreover, homonuclear decoupling pulse sequences suitable for application with moderate MAS frequencies in the so-called CRAMPS (combined rotation and multiple-pulse sequence) approach were being developed, e.g., the phase-modulated Lee-Goldburg (PMLG)[2] and DUMBO[3] methods. The anisotropic broadening in solid-state NMR spectra usually also obscures splittings due to through-bond *J* couplings; in spite of this, the late 1990s saw initial papers presenting solid-state NMR analogues of solution-state *J*-based experiments, e.g., ^{13}C-^{1}H MAS-*J*-HMQC[4] and ^{13}C-^{13}C refocused INADEQUATE[5] for application to organic solids. Building on advances in methodology and computing power, the early 2000s also saw initial publications of quantum-mechanics based methods for the accurate calculations of solid-state NMR chemical shifts.[6,SPB_2]

Executive Summary Research has focused on the development and application of solid-state NMR. Key methodological advances (objectives 3&4) have been: the demonstration of a high-resolution ^{1}H DQ CRAMPS experiment that delivered a resolution enhancement of a least a factor of 5 in the single-quantum (SQ) and DQ dimensions; the development of spin-echo based methods for measuring small *J* couplings (< 4 Hz) as well as off-MAS residual dipolar couplings; and the development of correlation experiments for half-integer quadrupolar nuclei, notably to probe oxygen-containing hydrogen bonds. In line with objective 1 of demonstrating the applicability of advanced solid-state NMR experiments to "real" systems, the ^{1}H DQ CRAMPS technique has been employed (in collaboration with Astra Zeneca) to identify the presence of a specific pseudo-polymorph in a tablet formulation and to determine the OH ^{1}H chemical shifts in a disaccharide, while the ^{1}H DQ MAS experiment has characterised self-assembly in supramolecular systems. Objective 2 concerned the probing of so-called "non-bonding" interactions, notably hydrogen bonding. Studies combining high-resolution ^{1}H experiments with first-principles calculations have shown that the ^{1}H chemical shift is a sensitive indicator of CH…X weak hydrogen bonding, while NH…N hydrogen bonds characteristic of specific modes of self assembly have been identified and quantified by means of hydrogen-bond mediated *J* couplings. Solid-state NMR has also been applied to biomolecules (objective 4), e.g., the quantitative determination of ^{13}C-^{13}C *J* couplings in cellulose and the rhodopsin chromophore. Collaboration with experts in first-principles calculations, synthetic chemists, biochemists and material scientists (objective 5) as well as other NMR spectroscopists has been central to most projects.

Key Advances: *(A) Development of Solid-State NMR Methodology*

(A1) High-resolution ^{1}H Methods A highlight of the research program was the development of a ^{1}H DQ CRAMPS pulse sequence,[SPB_3] as illustrated in Fig. 1, the resolution achieved using DUMBO ^{1}H homonuclear decoupling[3] is sufficient to resolve the two CH and two diastereotopic CH_2 ^{1}H resonances, allowing DQ peaks corresponding to all 22 close (< 3.5 Å) proton-proton proximities to be observed, with resolution enhancements of a factor of five and nine in the SQ and DQ dimensions, respectively, as compared to MAS alone at 30 kHz. This work led to the publication of an invited review article entitled "Probing proton-proton proximities in the solid state".[SPB_4] In further recent work, a two-dimensional ^{1}H-^{13}C correlation experiment has been developed whereby a high-resolution (DUMBO) ^{1}H DQ dimension is correlated with a ^{13}C dimension by means of an INEPT through-bond transfer.[SPB_5] Pulse sequences were developed with the group of Prof. L. Emsley (Lyon, France), with funding from a British Council UK-France exchange grant (2004-5) and the EU-NMR (FP6) program.

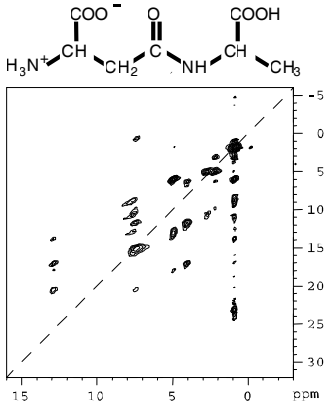

Fig. 1. ^{1}H DQ CRAMPS spectrum of a dipeptide.

Methodological development has been underpinned by work aimed at understanding the factors affecting ^{1}H solid-state NMR linewidths with Dr. P. Hodgkinson (Durham) (SPB was co-applicant on EPSRC grant GR/S56993/01, 2004-6) and Dr. C. Filip (Cluj, Romania, Royal Society Incoming Visit April – June 2005 and International Joint Project, 2007-2009). With Hodgkinson, 10-spin simulations of MAS spectra exploiting periodic symmetry confirmed that the intensity pattern of a spinning-sideband manifold can be well fit using a simple spin-pair model,[SPB_6] whereby the effective dipolar coupling, d_{rss}, tends towards the root sum square coupling, $\sqrt{(\Sigma d_{ij}^2)}$. d_{rss}^2 scales with the ^{1}H density in partially deuterated systems,[SPB_7] a

phenomenon that is being exploited in solid-state NMR studies of biomolecules. For model systems covering a wide range of different coupling strengths (ranging from 96 % deuterated adamantane to the rigid CH_2 group in malonic acid), the experimental spin-echo ^{1}H linewidth – referred to as the homogeneous component, i.e., that is not refocused by the spin echo – was found to be proportional to d_{rss}^2 / ν_r, where ν_r is the MAS frequency.[SPB_7] Moreover, efficient simulation approaches for homonuclear ^{1}H decoupling (that involves the combination of MAS and *rf* irradiation) have recently been employed to shed light on empirical experimental observations that have not been apparent from previous analytical studies, e.g., the effect of *rf* inhomogeneity or missetting in static and MAS experiments, and the effect of tilt pulses in acquisition windows.[SPB_8] With Filip, as well as developing low-load heteronuclear ^{1}H decoupling methods (see below), a focus of the ongoing collaboration is the development of a NMR simulation platform based on symbolic algebra, aiming to gain analytical insight into ^{1}H MAS and homonuclear decoupling experiments.

(A2) The detection and quantitative determination of J couplings Although *J* couplings are usually at least 2-3 orders of magnitude smaller than the anisotropic interactions encountered in solid-state NMR, they can be detected and determined by the use of spin echoes whereby all interactions that behave like an offset are refocused leaving only the *J* modulation. Specifically, in collaboration with Profs. M. H. Levitt (Southampton) and Emsley, considering isolated homonuclear spin pairs, a combined theoretical, numerical simulation and experimental study has shown (provided rotational resonance conditions are avoided) that the dominant spin-echo modulation frequency is indeed exactly equal to the *J* coupling,[SPB_9] with the CSA and dipolar couplings actually tending to stabilise and not obscure the *J* modulation. In follow-on work (with Levitt, Emsley and Prof. D. Massiot (Orléans, France) & Dr. J. J. Titman (Nottingham)), a study combining theory, experiment and computer simulation has demonstrated that DQ correlation peaks in a refocused INADEQUATE spectrum are indicative of a *J* coupling,[SPB_10] provided that the isotropic chemical shifts of the 2 nuclei are different and far from rotational resonance. Through the British Council funded UK-France exchange program with Emsley's group (also with Prof. Baltisberger, Berea, USA), the observation of distorted peaks and unexpected correlation peaks in refocused INADEQUATE spectra of multispin systems, e.g., uniformly labelled ^{13}C solids, and the use of a additional *z* filter to improve the observed lineshapes has been explained by means of product-operator analysis, numerical simulations and experiment.[SPB_11] A study describing the use of the refocused INADEQUATE experiment to obtain high-resolution correlation spectra of disordered solids (with Emsley and Prof. A. Pines (Berkeley, USA)) has been published[SPB_12] (featured in Am. Chem. Soc. C. & E. News highlights of the year, Vol. 81, issue 51, p.39).

The reliable determination of a *J* coupling requires the observation of the $\cos(\pi J\tau)$ modulation beyond the first zero crossing that occurs at $\tau = 1/2J$ for a $\tau/2 - \pi - \tau/2$ spin echo.[SPB_13] The determination of a small *J* coupling (< 5 Hz) hence requires the recording of experiments with a spin-echo duration, τ, out to at least 200 ms. For organic solids, the spin-echo dephasing time, T_2', for a heteronucleus, e.g., ^{13}C or ^{15}N, depends critically on the efficiency of ^{1}H decoupling.[7] Commonly used ^{1}H decoupling methods, e.g., TPPM[8] or XiX[9,10] employ continuously applied (though with changing phase) high-power ^{1}H *rf* nutation, with the decoupling times for such schemes being limited to ~50 ms so as to minimise the risk of damage to the *rf* electronics. With the motivation of enabling the measurement of small *J* couplings in organic solids, recent work has considered the use of low-load ^{1}H decoupling approaches, specifically the rotor-synchronised Hahn-echo pulse train (RS-HEPT) sequence. For the model compound ^{13}CH-labelled *L*-alanine, the measured RS-HEPT T_2' value at 30 kHz MAS was found to be ~50% of that for XiX. Experimental trends were reproduced in 10-spin simulations (collaboration with Filip): notably, T_2' was found to increase at faster MAS frequencies, with the RS-HEPT value at 55 kHz MAS (experiments performed in the group of Prof. A. Samoson, Tallinn, Estonia) being double that at 30 kHz MAS.[SPB_14] Using RS-HEPT ^{1}H decoupling at 22.5 kHz MAS, a $^2J_{NN}$ coupling as small as 3.8 Hz has been measured (τ_{max} = 200 ms).[SPB_13]

(A3) Residual dipolar couplings Measuring *J* couplings by the spin-echo MAS experiment requires the precise setting of the magic angle (to 54.74°). With Levitt, we have recently shown that off-magic-angle spinning leads to an additional dipolar-coupling dependent modulation, i.e., corresponding to the solid-state analogue of the important solution-state NMR residual dipolar couplings (RDC) effect.[SPB_15] Specifically, for $^{13}C_2$-glycine, an angle misset as small as 0.26° is sufficient to observe a RDC modulation allowing the quantitative determination of the dipolar coupling provided that the angle misset is known. (Experiments were performed by Dr. Ying Guo, funded by a Royal Society 1-year China Incoming Fellowship, 2006-2007) As compared to existing recoupling methods for determining dipolar couplings, the new method has the advantage of being a simple pulse sequence. Moreover, the weak coupling approximation isn't broken, thus frequency-selective *rf* pulses can be used to isolate individual homonuclear couplings in a multi-spin coupled network.[SPB_16] Reliable methods for measuring many homonuclear distances for a single multiply-labelled sample are currently lacking, and the further development of this novel approach offers much potential for use in molecular structure determination.

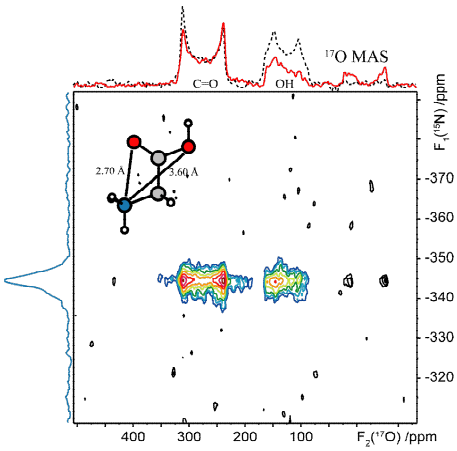

Fig. 2. ^{15}N-^{17}O correlation spectrum of ^{17}O,^{15}N-labelled glycine.HCl.

(A4) Half-Integer Quadrupolar Nuclei While oxygen is a key constituent of important hydrogen-bonding interactions, it is challenging to study by NMR since the only NMR-active isotope is the spin I = 5/2 ^{17}O nucleus. ^{17}O solid-state NMR methodology development is the primary focus of Dr. Ivan Hung, a Leverhulme-Trust (2005-2008) funded PDRA. By simultaneous sample spinning around two axes corresponding to the roots of the P_2 and P_4 Legendre polynominals, the double-rotation (DOR) technique removes the second-order quadrupolar broadening to yield high-resolution ^{17}O spectra. Using a density-matrix simulation program written using the GAMMA[11] libraries, it has been shown that CSA components as well as the relative orientation of the CSA and quadrupolar tensors can be determined from fits of ^{17}O DOR spectra of ^{17}O-labelled *L*-alanine and glycine.HCl.[SPB_17,18] In ongoing work, ^{15}N-^{17}O MAS experiments are being developed (no previous ^{15}N-^{17}O experiments in the literature), e.g., Fig. 2 presents ^{15}N-^{17}O correlation spectra of ^{15}N,^{17}O-labelled glycine.HCl, while ^{15}N-^{17}O REAPDOR and TRAPDOR experiments have been used to quantitatively probe ^{15}N-^{17}O dipolar couplings.[SPB_19]

Experiments to establish homonuclear correlations between half-integer quadrupolar nuclei have also been developed, e.g., ^{27}Al DOR 2D exchange spectra unambiguously assign the Al sites in $9Al_2O_3.2B_2O_3$.[SPB_20] The development of such experiments and their application to borate glasses (relevant potential long-term radioactive waste storage) are the subject of a current EPSRC (EP/D080355/1) project-student (Nathan Barrow) grant (with Dr. S. E. Ashbrook, St Andrews, Dr. D. Holland, Warwick and BNFL).

(B) Applications of Solid-State NMR Methodology

(B1) High-Resolution ^{1}H DQ Experiments ^{1}H NMR has high inherent sensitivity (proportional to γ^3) and is applicable to as-prepared samples, i.e., no requirement for isotopic labelling. The development of new high-resolution ^{1}H methodologies, thus, have much potential for wide application. Recently, we have shown that high-resolution ^{1}H DQ CRAMPS spectra of an active pharmaceutical ingredient (API) in its anhydrate and hydrate forms (referred to as pseudo-polymorphs) and in a tablet formulation (in the presence of other excipients) can be recorded in under 2 hours for each spectrum.[SPB_21] Importantly, the 2D DQ CRAMPS spectra constitute "fingerprints" for the 2 pseudo-polymorphs, showing that it is only the anhydrate form that is present in the tablet (see Fig. 3). The work was carried out in collaboration with Astra Zeneca, who have provided funding for 2 of my PhD students, John Griffin (2004-7, CNA scheme) and Jonathan Bradley (2007-). This first application of the ^{1}H DQ CRAMPS experiment to pharmaceuticals has generated much interest including reports in Chemistry World (December 2007, p. 27), www.labtechnologist.com and www.spectroscopynow.com. High-resolution ^{1}H DQ experiments have also been applied to supramolecular structures formed by synthetic derivatives of DNA and RNA bases (in collaboration with Dr. A. Marsh (Warwick) and Prof. G. Gottarelli (Bologna, Italy)), polymorphs of paracetamol, in particular form III, for which no crystal structure currently exists (in collaboration with Dr. M. Duer (Cambridge)), and the disaccharide maltose, so as to determine the OH ^{1}H chemical shifts (publications in preparation). Studies using ^{1}H DQ MAS and ^{1}H-^{13}C correlation spectra to probe π-π interactions in dendritic polymers (with Prof. H. W. Spiess (Mainz, Germany) & Prof. V. Percec (Philadelphia, USA))[SPB_22] and molecular tweezer complexes (with Spiess, Prof. F.-G. Klärner (Essen, Germany) & Prof. C. Ochsenfeld (Tübingen, Germany)[SPB_23] have been published.

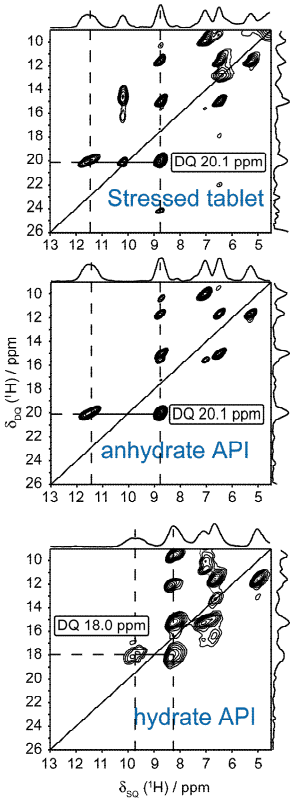

Fig. 3. ^{1}H DQ CRAMPS spectra of tablet and API.

(B2) Weak Hydrogen Bonding While it is well established that the ^{1}H chemical shift depends on the strength of conventional hydrogen bonding (i.e., XH…Y, where X,Y = N or O), there are very few accounts of using NMR to probe so-called CH…X (X = O,N) weak hydrogen bonds, most evidence for the existence of which comes from statistical analyses of crystal structures that however cannot reveal whether a close contact is indeed a bonding interaction or a chance occurrence due to other structure-directing interactions. Our approach was a combined experimental and computational study of the ^{1}H chemical shift of protons at the centre of weak hydrogen bonds for sp^3, sp^2 and sp hybridised CH donors in maltose anomers (prepared by Drs. Amado & Gil, Coimbra & Aveiro, Portugal), uracil and 4-cyano-4'-ethynylbiphenyl (synthesised in the group of Prof. R. M. Claramunt, Madrid, Spain), respectively. First-principles chemical shift calculations considering the whole 3D crystal structure by virtue of the employed

plane-wave pseudopotential approach were performed in the group of Dr. C. J. Pickard (St. Andrews, formerly Cambridge). The major outcome of this research programme (supported by EPSRC First-Grant scheme award GR/S47403/01, overall assessment: Outstanding; PDRA: Dr. Tran Pham, 2004-6) was the surprising but key observation that the determined changes in the ^{1}H chemical shift due to weak hydrogen-bonding interactions are much larger (up to 2 ppm for the investigated systems) than that which I and indeed what most if not all researchers in the field would have expected. The initial work considered the anomeric forms, α- and β- of the disaccharide maltose, with the CH ^{1}H chemical shifts being determined from ^{13}C-^{1}H MAS-*J*-HMQC spectra. The 700 MHz spectrum of β-maltose monohydrate in Fig. 4 is featured on the website and an advertising flyer from the MAS probe manufacturer, Doty Scientific (USA). In calculations, the effect of intermolecular C-H…O hydrogen bonding was determined as the difference $\Delta\delta_{iso}(^{1}H)$ between the calculated isotropic chemical shift for the full periodic crystal structure, δ_{iso}(cry), and that for an isolated molecule (maintaining the same geometry as in the full crystal), δ_{iso}(mol), for all distinct ^{1}H nuclei. Importantly, a clear correlation between a large chemical shift change (up to 2 ppm) and both a short H···O distance (< 2.7 Å) and a CHO bond angle greater than 130º is observed, thus showing that directionality is important in C-H…O hydrogen bonding.[SPB_24] For uracil, it has been found that $\Delta\delta_{iso}(^{1}H)$ for the CH protons involved in CH…O weak hydrogen bonding are ~40 % of $\Delta\delta_{iso}(^{1}H)$ for the NH protons involved in conventional NH…O hydrogen bonding, while for the well isolated CH…N intermolecular interactions in 4-cyano-4'-ethynylbiphenyl, clear changes have been determined for the ^{1}H, ^{13}C and ^{15}N nuclei.[SPB_25]

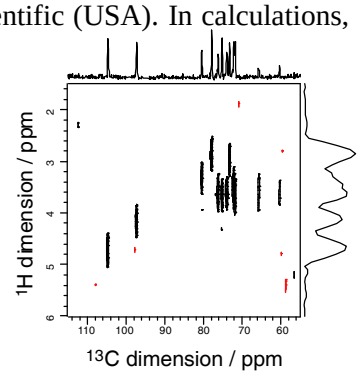

Fig. 4. ^{13}C-^{1}H MAS-*J*-HMQC spectrum of β-maltose.

(B3) Hydrogen-bond Mediated J Couplings

Intermolecular NH…N bonds in two ^{15}N-labelled deoxyguanosine derivatives (Gottarelli (Bologna)) with promising molecular electronic properties, e.g., in photoconductive or rectifying nano-devices, have been characterised via $^{2h}J_{NN}$ couplings. Specifically, in ^{15}N refocused INADEQUATE spectra (Fig. 5), in addition to peaks due to intramolecular two-bond *J* couplings (N1-N2, N2-N3, N3-N9), peaks corresponding to different intermolecular hydrogen-bond mediated *J* couplings are observed, namely N1H…N7 intermolecular hydrogen bonds characteristic of a ribbon-like polymeric structure, or N2H…N7 hydrogen bonding that is indicative of a quartet-like arrangement.[SPB_26] A crystal structure was not available in the latter case, and the observation is chemically most interesting since it has occurred in the absence of metal ions, with this being one of very few experimental observations that challenge the accepted dogma that guanosine quartet formation requires metal ions. In ^{15}N MAS spin-echo experiments using low-load RS-HEPT ^{1}H decoupling, the $^{2h}J_{NN}$ couplings have been measured. For the ribbon-like arrangement, *J* couplings of 6.2 ± 0.4 and 7.4 ± 0.4 Hz were determined for the two distinct molecules in the asymmetric unit cell, with different N…N distances of 2.91 Å and 2.83 Å.[SPB_13] In collaboration with Dr. S. Joyce (Cork, Ireland) and Pickard (SPB is co-applicant on EPSRC grant EP/C007573/1, 2005-8), the *J* couplings have subsequently been calculated as 6.5 and 7.7 Hz.[SPB_27]

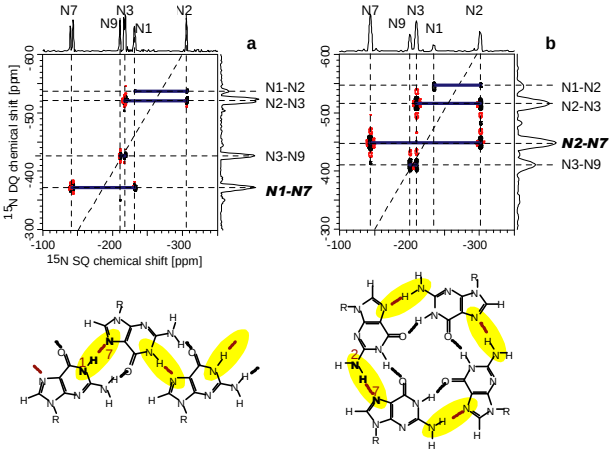

Fig. 5. ^{15}N refocused INADEQUATE spectra demonstrate ribbon and quartet formation.

(B4) Biological and Materials Science Applications $^{1}J_{CC}$ couplings have been determined (with Emsley, Levitt et al.) by the spin-echo MAS experiment for a partially ^{13}C labelled cellulose sample extracted from wood[SPB_28] and the rhodopsin retinylidene chromophore.[SPB_29] Doubly-labelled retinylidene samples were used, with DQ filtration being employed to remove the background natural abundant ^{13}C signal; the measured couplings are direct measures of bond order, giving insight into structural mechanism of how rhodopsin is responsible dim light vision. In collaboration with Dr. A. Dixon (Warwick), a research program is being developed (funded by a Warwick Research Development Fund award and involving SPB's PhD student Amy Webber) to apply advanced solid-state NMR methodology (in particular methods for measuring multiple distances in labelled samples) to membrane proteins. In initial work (by a Systems Biology Doctoral Training Centre project student), a ^{13}C DQ-filtered spectrum has been recorded for the labelled Ala and Val residues of a 30 amino acid Glycophorin A membrane protein in a hydrated lipid environment.

Applications to materials science: ^{11}B DOR 2D exchange spectra quantified the bond-angle distribution in vitreous B_2O_3;[SPB_30] A ^{31}P refocused INADEQUATE spectrum (in the EPSRC funded Warwick-Kent-UCL sol-gel partnership) identified the different crystalline phases present in a ternary

sodium calcium phosphate of composition $(CaO)_{0.4}(Na_2O)_{0.1}(P_2O_5)_{0.5}$;[SPB_31] ^{13}C CP MAS characterised tertiary amine oxide derivatized surfaces that resist non-specific protein adsorption.[SPB_32]

Research Impact and Benefits to Society The availability of advanced analytical techniques for probing structure at the atomic level is a pre-requisite for establishing key structure-property relations across science. While solid-state NMR already has a demonstrated track record of providing unique insight in chemistry, materials science, biology and beyond, there is much potential to increase the applicability of the technique. The above account of the research program during my fellowship illustrates an approximate 50:50 split between the development and application of solid-state NMR. Important applications have already been demonstrated for some of the methodology, notably: the identification from ^1H DQ CRAMPS spectra of the presence of a specific pseudo polymorph of an active pharmaceutical ingredient in a tablet formulation; the elucidation of the mode of self assembly from a ^{15}N refocused INADEQUATE spectrum for a synthetic guanosine derivative with promising molecular electronic properties; the probing of bond order in the rhodopsin chromophore by DQ-filtered ^{13}C spin-echo experiments. The development of solid-state NMR in combination with first-principles calculations as a new probe of weak hydrogen-bonding interactions has clear application to supramolecular chemistry, pharmaceuticals and polymorphism, as well as protein science. Other recently developed new methodologies are likely to be widely applied in the future, e.g., low-load ^1H decoupling methods for measuring small *J* couplings, using residual dipolar couplings, and ^{15}N-^{17}O correlation experiments. Direct future societal benefits can be identified, e.g., the development of new materials with enhanced energy efficiency or for radioactive waste storage exploiting a better understanding of structure-property relations, or improved medical treatments through better insight into biological structures and pharmaceuticals.

Research Plan Review and Explanation of Expenditure The original research objectives have been largely met (although clearly much scope exists for further development building on progress made), and the research program proceeded largely as originally planned, notably establishing key collaborations, with pharmaceutical industry, experts in first-principles calculations and supramolecular, materials and biological chemists. The support fund financed equipment (contributions to MAS probes and IT), research expenses (e.g., MAS rotors, cryogens, chemicals, probe repairs), conference attendance and visits to collaborators. EPSRC events attended: fellows' conferences (June 2003 & Sept. 2004 – met key collaborator, Pickard), Exploitation of Intellectual Property (Nov. 2003), Chemistry programme meetings (Exciting Areas in Chemistry Workshop, Jan. 2003, Regional Meeting to shape the programme's strategy and direction, March 2005), a research equipment review (July 2003), and a peer review college launch event (March 2006).

Dissemination and Public Awareness Activities The research activities outlined above have resulted in 23 publications to date, including 9 (6 as lead author) in JACS or Angew. Chem. Oral presentations by fellow: invited talks at EU-NMR conference (Florence, Italy, 2007) and the RSC NMRDG meeting (London, 2007), with future invitations for Joint Pharmaceutical Analysis Group (London) and ACS Spring (New Orleans, USA) meetings in 2008; contributed talks at RSC international conference (Cambridge, 2003), Alpine conference (Chamonix, France, 2005 (promoted to full length plenary presentation) & 2007), EUROMAR (York, 2006 & Tarragona, Spain, 2007), Materials Research Society Fall Meeting (Boston, USA 2006); seminars Durham (2003 & 2006), Southampton (2003 & 2007), Bologna, Italy (2004 & 2007), Cambridge (2004), St. Andrew's (2005, 1-day NMR symposium), Tübingen, Germany (2005), Astra Zeneca (2007), Bruker users meeting (2007). Oral presentations by research group: Pham: IOP BRSG meeting (London, 2004) & RSC Biophysical Chemistry meeting (June 2006); Hung: IOP BRSG meeting (Nottingham, 2006 & London, 2007); Griffin: seminars at Cluj, Romania (2006), Lyon, France (2006), Bruker users meeting (2006), Astra Zeneca (2007, won best student presentation). Poster presentations by fellow and group at Alpine conference (2003, 2005, 2007), EENC (Lille, France 2004), EUROMAR (2006, 2007). The fellow (with PhD student, Barrow) is responsible for the Warwick solid-state NMR group; this is regularly updated with news items (57 since Sept. 2006) and latest publications. With assistance from the university press officer, the fellow has publicised important research developments (^1H DQ CRAMPS of tablet, see above) and the funding of a 850 MHz UK solid-state NMR facility (news item in Coventry Evening Telegraph and on various websites). The fellow regularly gives tours of the NMR labs during university open days to prospective students and their families. I am willing to assist EPSRC in relevant future promotional activity.

Outcomes: Fellow, Further Research, Host Organisation Support and Scheme Effectiveness At the end of the fellowship, I have built up a research group of 4 PhD students (Griffin successfully defended his thesis in January 2008, and will take up a PDRA position at St. Andrews) and 1 PDRA (2 former PDRAs have remained in research with Pham a solid-state NMR spectroscopist at GlaxoSmithKline and Guo a PDRA at Lehigh University, USA). The above research description has identified a number of active current research projects that build upon work carried out during the fellowship. I have benefitted from the strong support of working within the solid-state NMR group (with Profs. R. Dupree & M. E. Smith and experimental officer,

Dr. A. P. Howes) at the Department of Physics, University of Warwick. Importantly, I have been given equal access to the group's suite of 5 solid-state NMR spectrometers (200-600) – note that I was PI on a £451k EPSRC grant (EP/D051908/1, 2006-8) to purchase a new *rf* console and probes for the 600 MHz system. The department and university have also supported my career development; my reduced teaching duties have included the supervision of undergraduate project students and the 3rd-year Magnetic Resonance lecture course – this contact has been central to the recruitment of PhD students. I successfully completed the modules required to obtain the Warwick Teaching Certificate. I have been involved in the interdisciplinary Molecular Organisation and Assembly of Cells (MOAC) DTC at Warwick, teaching NMR in a MSc module, supervising 8-week project students and as a member of the scientific steering committee. I was promoted to Associate Professor from October 2006, on an indefinite contract from the end of the fellowship. The effectiveness of the fellowship in enabling me to establish a strong independent research career is evident from the increasing number of conference invites and a steep upward trend in research outputs, with 9 publications in 2007. I currently serve in the combined role of BRSG (Institute of Physics NMR society) secretary/ treasurer, and have been an external PhD examiner in Southampton, Nottingham and Lyon, France. I am also chair of the national management committee of the recently funded UK 850 MHz solid-state NMR facility (PI on £3.7M EPSRC grant EP/F017901/1).

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