Final Report on GR/S47403/01 (First Grant Scheme)
A New Probe of Fundamental Weak Hydrogen Bonds: Solid-State NMR

Overview and Context of Research Programme

The experimental evidence for the classification of interactions such as CH…X (X = O,N) as hydrogen bonds comes largely from IR spectroscopy and crystallography. As early as 1963, it was shown that the formation of C-H…N bonds upon adding pyridine causes the C-H stretching frequency in the IR spectrum of 1,3,5-trichlorobenzene to be lowered by 35 cm^{-1}. Around the same time, Sutor presented the first systematic crystallographic investigation of C-H···O interactions for purine and pyrimidine systems. Her assertion that the observed short H···O contacts are indicative of hydrogen bonds was initially controversial, but its validity was proved by the study of Taylor and Kennard in 1982 who considered 113 organic crystal structures in the fledgling Cambridge Structural Database which were determined by neutron diffraction. Indeed, it is such statistical analyses of crystal structures in databases of both small-to-medium sized organic molecules[1] and also proteins[2] that constitute the primary source of evidence for the investigation of weak hydrogen bonds. In ^{1}H solution-state NMR, an investigation in 2000 of serine protease catalysis revealed that the Cε1-H proton chemical shift for the catalytic histidine is shifted ~0.6 to 0.8 ppm downfield because of C-H…O hydrogen bonding,[3] while Cordier et al. have in 2003 measured $^{h3}J_{C\alpha C'}$ couplings of 0.2 to 0.3 Hz across Cα-Hα…O=C hydrogen bonds in β-sheet regions of a small protein.[4] Considering solid-state NMR, the only previous study I am aware of is due to Scheffer *et al.*, who attributed the downfield shifts, relative to the solution-state values, of the ^{13}C solid-state NMR chemical shifts of the carbonyl carbons in crystalline quinines to C-H…O hydrogen bonding.[5]

In the final report form, the original objectives have been re-expressed as two objectives (note that the scientific content of the original six objectives has been maintained). The first revised objective refers to the evaluation, via experiment and calculation, of different solid-state NMR parameters as to their suitability as quantitative probes of weak hydrogen-bonding interactions, and summarises the first five specific original objectives. The second revised objective (based on the original sixth objective) refers to the optimisation of existing, and the development of, new solid-state NMR methodology necessary to achieve the first objective, with the original case for support stating that "50% of the applied for man hours will be devoted to this task".

Key Advances

(1) ^{1}H Chemical Shift: A Sensitive Indicator of Weak Hydrogen Bonding

As stated above, with the exception of one report looking at ^{13}C chemical shifts, at the start of the grant, there were no papers in the literature applying solid-state NMR to weak hydrogen bonding. As such, the original grant application presented various previously untested ideas for developing and applying solid-state NMR experiments as probes of weak hydrogen bonding. Of the suggested ideas, the focus turned out to be directed at a combined experimental and computational study of the ^{1}H chemical shift of protons at the centre of weak hydrogen bonds. In solid-state NMR, it is well established that conventional hydrogen bonding (i.e., XH…Y, where X,Y = N or O) leads to a marked downfield shift of the ^{1}H chemical shift, with the shift being correlated with the hydrogen bonding strength.[6] The major outcome of this research programme [SPB_1] 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 systems investigated so far) than that which I and indeed what most if not all researchers in the field would have expected*.

A difficulty of relying on statistical analyses of many crystal structures as a means of determining the extent of weak hydrogen bonding interactions manifests itself in the question: is a close approach of, say, a CH proton to an oxygen atom actually a bonding interaction or rather a "chance" occurrence caused by other interactions that determine the crystal packing? This question lies at the centre of the origin of the ongoing controversy concerning the importance of weak hydrogen-bonding interactions, for example, a 2004 quantum-chemical study in JACS concluded that a specific putative weak hydrogen bonding interaction did not constitute a stabilizing interaction.[7] Our research has shown that *the ^{1}H NMR chemical shift is a direct indicator of whether a close CH…O proximity is indeed a bonding interaction*.

Maltose, **1**, is a disaccharide that exists in two anomeric forms, α- and β-maltose. The solid-state structures adopted by anhydrous α-maltose and β-maltose monohydrate have been solved by single-crystal X-ray and neutron diffraction, respectively. It is to be noted that α-maltose crystallizes in the presence of approximately 20% of the β anomer – the latter corresponds to anhydrous β-maltose. The ^{1}H chemical shifts for the two forms were determined from ^{13}C-^{1}H MAS-*J*-HMQC spectra recorded by the PDRA employed on this grant (Dr. Tran N. Pham) and the PI for ~100 mg of sample at natural abundance in ^{13}C. *The 700 MHz spectrum of β-maltose monohydrate in Fig. 1 was featured on the front page of an advertising flyer from the MAS probe manufacturer, Doty Scientific (USA).*

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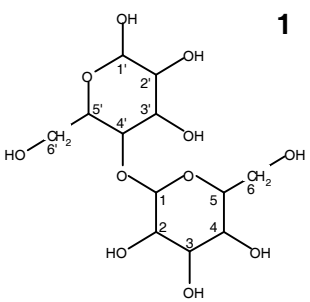

The investigation of CH…O weak hydrogen bonding interactions in the maltose anomers involved a combined experimental and computational approach – calculations were performed in the group of Dr. C. J. Pickard (then Cambridge, now St. Andrew's). Aware of existing collaborations between Pickard and Prof. R. K. Harris (Durham) as well as Prof. R. Dupree (Warwick), an important impetus for this collaboration (that was not envisaged at the time of the original application) was our meeting at an EPSRC Research Fellows conference at Nottingham in Summer 2003. The first-principles chemical shift calculations developed by Pickard and co-workers are well suited to solid-state NMR because of their consideration of the whole 3D crystal structure by virtue of the employed plane-wave pseudopotential approach. The accuracy of these calculations for maltose is ~±0.2 and ±2 ppm for ^{1}H and ^{13}C, respectively, and the calculations allowed the assignment of the resolved resonances in the ^{13}C-^{1}H correlation spectra (Fig. 1).

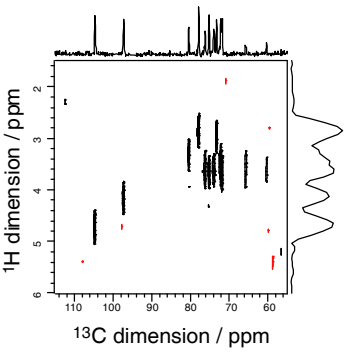

Fig. 1. ^{13}C-^{1}H MAS-*J*-HMQC spectrum of β-maltose.

The potential of a combined experimental and computational approach far exceeds a tool for assignment: At the experimentalists' suggestion, further calculations were performed whereby the chemical shifts were calculated for isolated single molecules extracted from the crystal structures. In this way, the difference 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, i.e., same bond lengths and bond angles, as in the full crystal), δ_{iso}(mol), can be determined for all distinct ^{1}H nuclei in anhydrous α-maltose, anhydrous β-maltose and β-maltose monohydrate. In the absence of any aromatic moieties that would give rise to ring current effects, a significant molecule to crystal chemical shift change, $\Delta\delta_{iso}$(^{1}H), can only arise as a consequence of intermolecular C-H…O hydrogen bonding. Fig. 2 presents, as a contour plot, the dependence of the calculated $\Delta\delta_{iso}$(^{1}H) values on the distance to the nearest oxygen of a different molecule, $r_{H...O}$, and the bond angle, ∠CHO. *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.* It is of much relevance in the context of the 2004 quantum-chemical study (involving energy calculations) referred to above[7] that Fig. 2 demonstrates that $\Delta\delta_{iso}$(^{1}H) is smaller (< 0.7 ppm) for cases where $r_{H...O}$ < 2.7 Å, but ∠CHO < 120º. In the 2004 study, the investigated interaction was for ∠CHO = 117º, and hence our identification that directionality is important is consistent with the study's conclusion that the specific investigated CHO close contact is not a stabilizing interaction. It is to be emphasised that database crystal structure studies are not suited to making statements about the directionality of CH…O hydrogen bonding.

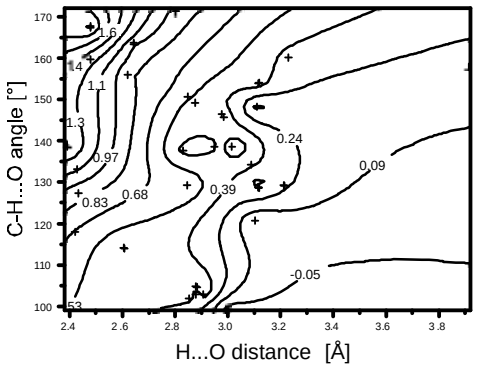

Fig. 2. Contour plot of the dependence of $\Delta\delta_{iso}$(^{1}H) for the 42 aliphatic ^{1}H resonances in the maltose crystal structures.

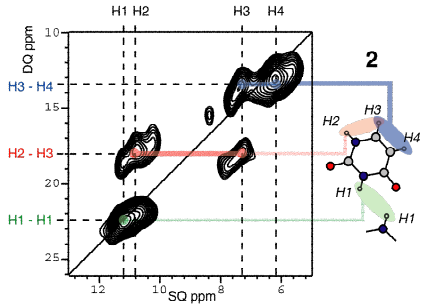

Fig. 3. ^{1}H (600 MHz) DQ MAS (40 kHz) spectrum of uracil.

We have extended our investigation of weak hydrogen-bonding to consider CH…O interactions in the nucleobase uracil, **2**, where the acceptor group is now a C=O carbonyl oxygen as opposed to an OH hydroxyl group. Fig. 3 presents a ^{1}H double-quantum (DQ) MAS (40 kHz using a Samoson 1.8 mm probe) spectrum of uracil, that was recorded by Brown's first PhD student, John Griffin (started September 2004), and the PDRA, with the PDRA having played a major role in training the PhD student in advanced solid-state NMR techniques. First-principles chemical shift calculations were performed by Dr. A.-C. Uldry, who is a PDRA employed in Pickard's group at St. Andrew's (since January 2006) on a joint EPSRC grant (EP/C007573/1) with Brown as a co-applicant. (Dr. Pham also received training in first-principles calculations in Cambridge (June 2004) and helped Dr. Uldry in implementing the CASTEP code on the Warwick high-performance computers.) For uracil, it is additionally necessary to consider the contribution of ring current effects to the molecule to crystal chemical shift changes, $\Delta\delta_{iso}$, because of the aromatic character of uracil. This can be achieved by calculating the chemical shifts for an isolated plane extracted from the crystal structure such that the effect of ring currents arising from uracil molecules in above and below layers is not considered. Table 1 shows that *the molecule to plane changes $\Delta\delta_{iso}$(^{1}H) for the CH…O weak hydrogen bonding interactions are 40 % of the changes associated with conventional NH…O hydrogen bonding.* While this observation is consistent with a previous quantum-chemical study where the association enthalpy of a CH…O bond was found to be roughly one half

of that of a NH…O bond,[8] it is a result that will be a surprise to most NMR spectroscopists (both solution and solid-state), who would not have expected that weak hydrogen bonds play such a large role in determining observed ^{1}H chemical shifts.

Table 1: ^{1}H chemical shifts in uracil

Site	Experiment / ppm	First-Principles Calculation / ppm			
		δ_{iso}(crystal)	δ_{iso}(plane)	δ_{iso}(molecule)	δ_{iso}(pl)–δ_{iso}(mol)
H1 (NH)	11.2	11.7	12.5	7.4	5.1
H2 (NH)	10.8	11.2	11.6	6.5	5.1
H3 (CH)	7.5	7.2	7.9	6.1	1.9
H4 (CH)	6.0	5.5	6.1	4.1	2.0

Our investigations have also looked at molecule to crystal changes for other nuclei involved in weak hydrogen bonding. For the maltose anomers, changes in the ^{13}C chemical shift as well as the ^{17}O chemical shift and quadrupolar coupling constant cannot be readily correlated with weak hydrogen-bonding because of the involvement of the OH oxygens attached to the CH carbons in conventional OH…O hydrogen bonding, while for uracil the changes for the ^{13}C chemical shifts are also not clear cut, seemingly as a consequence of conjugation in the aromatic uracil ring. However, this remains an area of ongoing research with clear changes to be expected where weak hydrogen bonding interactions are better "isolated".

The project has also involved the synthesis of two selectively labelled compounds 4-Cyano-4'-trimethylsilylethynylbiphenyl, **3**, and 2,4,6-triethynyl-1,3,5-triazine, **4**, whose crystal structures indicate the existence of C≡CH…N interactions, where the acceptor group is either C≡N (**3**) or an aromatic N (**4**). The synthesis was carried out in the group of the project partner, Prof. R. M. Claramunt (UNED, Madrid) – please see Prof. Claramunt's separate report for an account of the synthesis, where it is noted that a publication is in preparation relating to a new synthetic procedure that had to be developed to introduce ^{15}N labels into **4**. First-principles calculations are currently running for these compounds, and it is expected that large ^{1}H chemical shift changes due to the C≡CH…N interactions will be observed, since the alkyne CH moiety is proposed to be one of the strongest type of CH weak hydrogen-bonding donor.[9]

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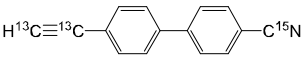

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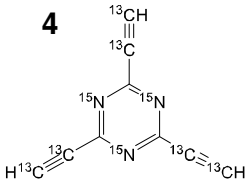
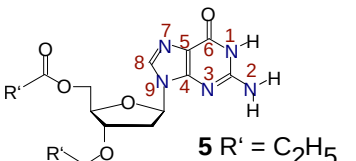


2. The Detection and Quantitative Determination of Small J Couplings

Direct evidence for the existence of a hydrogen bond can be obtained from the observation, first made in solution-state NMR of biomacromolecules in 1998, of a *J* coupling across a hydrogen bond, e.g., $^{2h}J_{NN}$ couplings of 7-10 Hz have been measured for the intermolecular N-H···N hydrogen bonds in RNA and DNA base pairs.[10] As a Marie Curie fellow in Prof. Emsley's group in Lyon, France, the PI and co-workers in Lyon and Madrid showed in 2002 that such hydrogen-bond mediated *J* couplings can also be detected in the solid state via the observation of a pair of cross peaks between two hydrogen-bonded nitrogens in a 2D INADEQUATE spectrum of a ^{15}N-labelled triazole derivative.[11] Moreover, we further showed that the $^{2h}J_{NN}$ couplings can be quantitatively determined to a high degree of accuracy using a simple spin-echo experiment, such that differences in hydrogen-bond strength were detected between closely related triazole and pyrrole derivatives as well as between the solid- and the solution-state.[12]

In order to introduce the PDRA to solid-state NMR *J* coupling experiments, he implemented the refocused INADEQUATE experiment on the Warwick spectrometers and recorded ^{15}N refocused INADEQUATE spectra for the ^{15}N-labelled deoxyguanosine derivatives, **5** and **6**. These compounds were synthesised in the group of Prof. Gottarelli (Bologna) as part of an ongoing programme to gain insight into the self assembly of these nucleosides, which have promising molecular electronic properties, namely **6** can be introduced into the gap between nano-contacts so as to produce nano-devices that are photoconductive or act as rectifiers. In Ref. [SPB_2], we have presented the ^{15}N refocused INADEQUATE spectra shown in Fig. 4. In addition to peaks corresponding to intramolecular two-bond *J* couplings (N1-N2, N2-N3, N3-N9), peaks corresponding to different intermolecular hydrogen-bond mediated *J* couplings are observed in Fig. 4. X-ray single-crystal diffraction has revealed that **5** adopts a ribbon-like polymeric structure via the formation of N1H…N7 intermolecular hydrogen bonds corresponding to the N1-N7 peaks in Fig. 4a. For the polymorph of **6** that forms more readily under recrystallisation from ethanol (for which it has not been possible to obtain a diffraction crystal structure), Fig. 4b *unambiguously demonstrates a different intermolecular hydrogen bonding arrangement*, namely



5 R' = C_2H_5

6 R' = C_9H_{19}

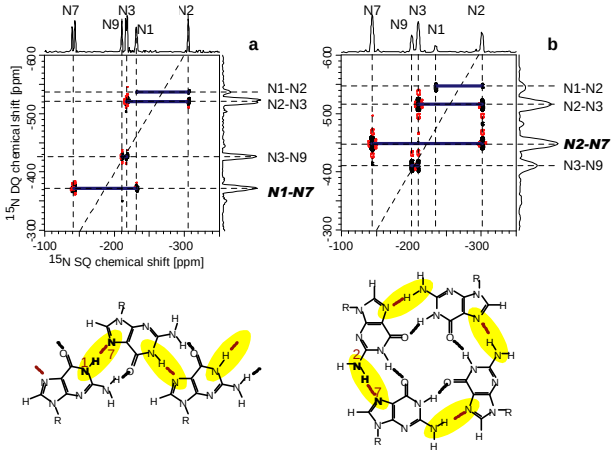


Fig. 4. ^{15}N refocused INADEQUATE spectra of (a) **5** and (b) **6** demonstrate ribbon and quartet formation.

N2H…N7 hydrogen bonding that is indicative of a quartet arrangement. This observation is chemically most interesting since it has occurred in the absence of metal ions. *This is one of very few experimental observations that challenge the accepted dogma that guanosine quartet formation requires metal ions.*

J couplings can be quantitatively determined from spin-echo experiments. However, for a reliable fitting procedure, it is necessary to observe at least the first zero-crossing point which occurs at $\tau = (1/2J)$, i.e., corresponding to $\tau = 100$ ms for $J = 5$ Hz. For the usual approach of high-power continuous ^{1}H decoupling such a long spin-echo duration exceeds a standard MAS probe's specifications and risks serious damage to the *rf* electronics. With the problem in mind of how can we measure the small *J* couplings associated with weak hydrogen bonding, we developed (in collaboration with Dr. C. Filip, Cluj, Romania, who visited the PI's group for 3 months in 2005 on a Royal Society visiting fellowship) a new low duty-cycle ^{1}H decoupling spin-echo experiment applicable under fast MAS, whereby a rotor-synchronized Hahn-echo pulse-train (RS-HEPT)[13] consisting of a ^{1}H π pulse every $2\tau_r$ is applied during the spin-echo evolution periods. The applicability of this method at 22.5 kHz MAS has been demonstrated for the ^{15}N-labelled guanosine derivatives **5** and **6** [SPB_3]. Specifically, Fig. 5(a,b) shows spin-echo curves for the two distinct N7 resonances observed for **5**. *The extracted J couplings of 6.2 ± 0.4 and 7.4 ± 0.4 Hz are in agreement with different N…N distances of 2.91 Å and 2.83 Å for the two distinct molecules in the crystal structure of **5**.* Moreover, Fig. 5c presents a spin-echo curve for the N9 resonance of **6** from which the *intramolecular* $^2J_{N9,N3}$ *coupling of only 3.8 ±0.1 Hz was determined.*

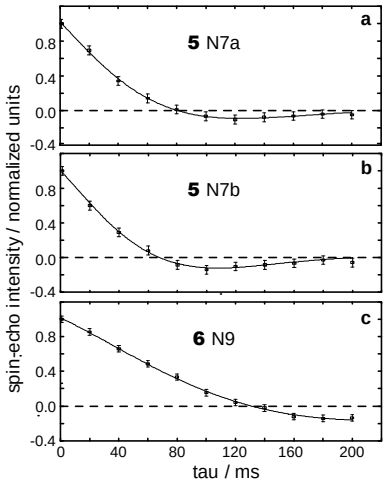


Fig. 5. ^{15}N spin-echo data for **5** and **6**, together with best-fit curves.

The same RS-HEPT decoupling method can be straightforwardly incorporated into heteronuclear spin-echo experiments, and we shall apply this approach to the determination of ^{13}C-^{15}N heteronuclear *J* couplings across the C≡CH…N weak hydrogen bonds in **3** and **4** as soon as we take delivery of a fast MAS triple-resonance probe for our 600 MHz spectrometer (expected November 2006). The detection and quantitative determination of *J* couplings across weak hydrogen bonds will be aided by the ongoing development of first-principles methods for their accurate calculation by Dr. Uldry, the PDRA working with Dr. Pickard on the joint EPSRC grant with a primary focus of developing such methods for determining *J* couplings, as well as the original project partner Prof. C. Ochsenfeld (Tübingen, Germany).

3. Developing High-Resolution Methods for Determining and Assigning ^{1}H Chemical Shifts

An important element of this project has been the development and implementation of high-resolution ^{1}H solid-state NMR methodology, for example the ^{13}C-^{1}H MAS-*J*-HMQC experiment incorporating PMLG homonuclear ^{1}H decoupling was used to record the maltose spectra in Fig. 1 by which the ^{1}H chemical shifts of the specific CH resonances involved in weak hydrogen bonding could be experimentally determined. This aspect of the project has benefited from interaction with Dr. P. Hodgkinson (Durham) and a PDRA, Dr. V. Zorin, employed at Durham on a concurrent EPSRC grant (GR/S56993/01), where Brown is a co-applicant, that has been looking at the fundamental factors determining resolution in ^{1}H solid-state NMR, with Dr. Pham visiting Durham twice during the project. Dr. Pham received further training in high-resolution ^{1}H methodology during two visits funded by a British Council exchange program to the Emsley group in Lyon, where the DUMBO homonuclear ^{1}H decoupling methods were developed.

Dr. Pham invested considerable time in implementing the ^{1}H DQ CRAMPS experiment utilising ^{1}H DUMBO decoupling in both dimensions on the Varian Infinity+ spectrometers available to the Warwick group – this experiment was first performed[14] on a Bruker spectrometer in the Emsley group at Lyon by the PI during a British Council funded visit in March 2004 just before the start of this project. The resolution achieved with this experiment at 300 MHz and moderate MAS (< 15 KHz) matches and often exceeds that achievable at 600 MHz and 40 kHz MAS. We look forward to the improved resolution that will be achievable at 600 MHz when this experiment is implemented on our soon to be delivered new console (expected November 2006) – it had not been possible to achieve good performance on our 1997 Infinity console. This experiment has applicability beyond this specific project looking at weak hydrogen bonds. As

an example, Fig. 6a presents a ^{1}H DQ CRAMPS spectrum of β-maltose monohydrate recorded in Lyon as part of the British-Council funded exchange program: such a disaccharide represents a challenge for high resolution ^{1}H solid-state NMR with resonances corresponding to 14 CH_2 and 8 OH protons between 3 and 7 ppm. Yet with a much better resolution than the "blob" achieved with MAS at 30 KHz (see Fig. 6b), it is possible to assign all the resolved resonances to the close proton-proton proximities of the crystal structure, such that the OH ^{1}H resonances can be experimentally determined and assigned for the first time. As further applications of the methodology, the PhD student, John Griffin, after training from Dr. Pham, has applied the experiment to pharmaceutical compounds from AstraZeneca (CASE PhD), while this Summer, Dr. J. Titman (Nottingham) with one of his PhD students and a PhD student of Dr. M. Duer (Cambridge) have visited Warwick in order to apply the ^{1}H DQ CRAMPS experiment to their systems, namely a synthetic nucleotide with a vinyl phosphate group used in solid-phase oligonucleotide synthesis and polymorphs of paracetamol, respectively.

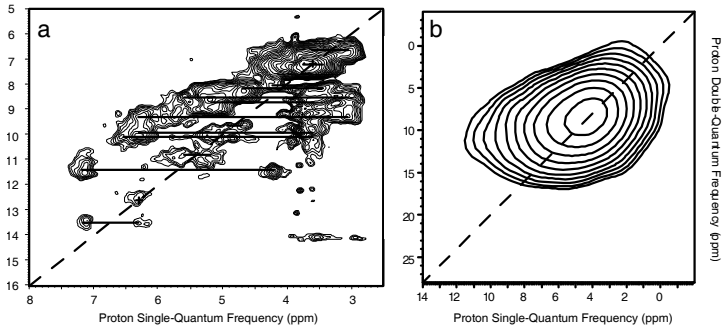


Fig. 6. ^{1}H (a) DQ CRAMPS and (b) DQ MAS spectra of β-maltose.

Project Plan Review, Training and Explanation of Expenditure

While there was some evolution of ideas and methodology that was not envisaged at the time of the original application, the project proceeded essentially along the lines originally laid out. Since the project involved applying solid-state NMR to an essentially new area, I am pleased that the project, firstly, has demonstrated the ^{1}H chemical shift as a sensitive indicator of weak hydrogen bonding, and, secondly, made much progress in developing the new methodology that will be required to detect and quantitatively determine the small *J* couplings expected to be observable across weak hydrogen bonds.

The work carried out by the PDRA employed for 27 months on this First Grant project, Dr. T. N. Pham, in implementing, developing and applying new solid-state NMR methodology was of much benefit, on the one hand, to Pham's career development, and, on the other hand, in assisting Brown in building up an independent research program. Pham's background was in solution-state NMR, and the training he received in solid-state NMR together with the publications in a top chemistry journal resulting from this project made him an attractive candidate for future employment, as is demonstrated by his appointment in August 2006 as a NMR spectroscopist at GlaxoSmithKline – his new employer is encouraging him, in particular, to make known within the company the considerable potential for structural and dynamic insight offered by state-of-the-art solid-state NMR techniques. Dr. Pham was the first scientific co-worker with Brown and was very helpful as Brown's group grew from two to five (PI + 3 PDRAs + 1 PhD) at the end of the project. Moreover, his work in implementing various pulse sequences forms the basis for many ongoing projects.

There were two named project partners on the original application. The collaboration with Prof. Claramunt (Madrid, Spain) to produce the labelled compounds **3** and **4** ran as envisaged, although the synthetic work was carried out later in the project than originally planned due to the synthetic chemist taking maternity leave. A significant development not envisaged in the original application was the fruitful collaboration with Dr. Pickard, in whose group the first-principles calculation element of the combined experimental and computational approach was performed. This UK-based collaboration that has been formalised in a subsequent joint EPSRC project (EP/C007573/1, start January 2006) reduced the involvement of the original project partner, Prof. Ochsenfeld (Tübingen, Germany) – Brown, nevertheless, continues to interact with Ochsenfeld since his group's development of new quantum-chemical methodology is enabling NMR parameters to be calculated for ever larger numbers of atoms. This change led to an underspend on travel, which was, however, swallowed up by extra salary costs that were not covered by the original award even though the PDRA was paid at the initial spine point indicated in the original application – this anomaly presumably arose due to delayed start of the project (April 2004) that was a consequence of a combination of the EPSRC 6 month appointment moratorium in force at the time and the originally appointed PDRA pulling out days before his proposed start date.

Research Impact and Benefits to Society

The demonstration that CH…O weak hydrogen bonding can lead to a significant change in the ^{1}H chemical shift that depends on the geometrical bonding arrangement is a key result, which while of immediate relevance to NMR spectroscopists interpreting spectra of organic molecules has significance that extends to understanding the chemical interactions that direct the adoption of a specific three-dimensional structure, with clear application to supramolecular chemistry, pharmaceuticals and polymorphism, as well as

protein science. The international significance is evident from the publication of the initial maltose study in a top chemistry journal, JACS; the follow-up work on uracil and the labelled compounds **3** and **4** will be shortly submitted to a leading journal. The use of small *J* couplings to identify specific intermolecular hydrogen bonding interaction (again published in JACS) and the subsequent development of a new low-load decoupling method to allow their quantitative determination, as well as the research into high-resolution ^{1}H methodologies will enable new applications of solid-state NMR, e.g., to DNA & RNA nucleosides in molecular biology and supramolecular chemistry. The research carried out during this First Grant project has opened up new avenues for application, whose exploitation will ultimately lead to societal benefits such as new materials developed via a better understanding of structure-property relations as well as improved medical treatments through better insight into biological structures and pharmaceuticals.

Further Research and Dissemination Activities

To date, two papers have been published, with an additional paper submitted. Dr. Pham gave oral presentations at two national conferences (IOP BRSG NMR meeting, December 2004 & RSC Biophysical Chemistry meeting, June 2006) and attended three international conferences (EENC, Lille, 2004, Alpine Solid-State NMR conference, Chamonix 2005, EUROMAR, York 2006) giving poster presentations. The results obtained during the project enabled Brown to give contributed talks at conferences in Chamonix, France 2005 (promoted to full length plenary presentation) and EUROMAR 2006, with a further talk to be given at the Materials Research Society Fall Meeting at Boston, USA in November 2006. In addition, Brown gave an invited talk at a 1-day NMR symposium at St. Andrew's (2005), as well as seminars in Cambridge (2004), Tübingen, Germany (2005) and Durham (2006). Papers on the following projects are expected to be submitted in the next three months: (i) A combined experimental and computational study of ^{1}H chemical shifts in uracil and **3** and **4**; (ii) ^{1}H DQCRAMPS of β-maltose; (iii) refocused INADEQUATE of multispin (e.g., U-^{13}C labelled) systems (Dr. Pham took a particular interest in this experiment during British-Council Warwick-Lyon exchange visits, working closely with a Lyon PhD student, S. Cadars); (iv) lineshape distortions in ^{1}H homonuclear-decoupled solid-state NMR experiments (with Durham group).

The research avenues that have opened up during this project are continuing to be pursued within Brown's group at Warwick by the PhD students, John Griffin and Amy Webber (starting 2006). Short-term projects are (i) A systematic experimental and computer simulation investigation of low-load decoupling fast MAS methods; (ii) ^{13}C-^{15}N spin-echo experiments to measure *J* couplings in ^{13}CH…^{15}N compounds. In the longer term, there are other ideas for probing weak hydrogen bonding; e.g., the PI has recently discussed with Dr. S. Wimperis (Glasgow) the possibility of using the phenomenon of NOE enhancements observed in his group[15] to quantify restricted dynamics for CD_3 groups involved in weak hydrogen bonding. The work by Pham in implementing advanced solid-state NMR experiments will underpin ongoing and future applications of, e.g., ^{1}H DQ CRAMPS (collaborations with Dr. Titman (Nottingham), Dr. Duer (Cambridge), and with industry (AstraZeneca)) and ^{31}P refocused INADEQUATE to disordered materials with medical applications in dentistry and tissue replacement (Dr. Y. Guo is a 1-year Royal Society Chinese visiting fellow working on this topic with the Warwick PhD student, P. Guerry (supervisor Prof. M. E. Smith)).

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