

Editorial

High Field Dynamic Nuclear Polarization – The Renaissance

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Sensitivity is a critical issue in NMR spectroscopy, microscopy and imaging and the factor that often limits the success of various applications. The origin of low sensitivity in NMR is well known and is due to the small magnetic moment of nuclear spins, which yields small nuclear spin polarizations and weak absorption signals. Historically, each advance in technology and methodology that has increased the signal-to-noise in NMR has shifted the boundary of what is achievable, often opening new areas of application and directions of research. The archetypal example of this phenomenon was the introduction of Fourier transform spectroscopy which led to increases of $\sim 10^2$ in signal-to-noise per unit time and revolutionized NMR and many other forms of spectroscopy. More recent technological developments of note include the continuing development of higher field superconducting magnets, and cryoprobes in which the excitation/detection coil is maintained at 20 K. In addition, innovations in NMR methodology have improved sensitivity, classic examples being Hartmann-Hahn cross polarization and INEPT transfer methods and the introduction of ^1H detection of $^{13}\text{C}/^{15}\text{N}$ resonances. Furthermore, techniques for non-inductive detection of resonance such as the AFM based technique of magnetic resonance force microscopy (MRFM) have recently allowed observation of a single electron spin and NMR signals from ~ 100 nuclear spins (per root Hz).

Another approach to enhance the sensitivity in NMR experiments is to couple the nuclear spins to a reservoir having much higher polarization, such as electrons. For example, laser-polarized noble gases, chemical induced dynamic nuclear polarization (CIDNP), para-hydrogen induced polarization (PHIP) as well as microwave driven dynamic nuclear polarization (DNP) all rely on this principle. In the cases of CIDNP and PHIP polarized states are generated by spin sensitive chemical reactions, and, while they are very successful, they are generally system specific. In contrast, in essentially all experimental situations electrons couple efficiently to the

lattice and permit some degree of sensitivity enhancement. For this reason microwave driven DNP experiments are evolving as a broadly applicable approach to increase signal strengths in solid state and solution NMR and imaging. Currently, DNP improves the sensitivity in NMR spectra by $\sim 10^2$ and/or in principle reduces the acquisition time in multidimensional experiments by $\sim 10^4$ thereby permitting studies of larger molecules, dynamics of reactions, or high throughput screening. In parallel, it can improve the information content by providing selectivity and contrast. For example, specific sections of a protein can be enhanced; metabolic cycles examined and contrast in MRI spectra increased. In structural studies of proteins additional distance and torsion angle constraints are in principle available from electron-nuclear dipolar or scalar coupling and paramagnetic shifts of sites in close proximity to spin labels or metal centers.

DNP is based on the transfer of the large electron spin polarization to nuclear spins ($\gamma_e/\gamma_n > 657$). This concept, originally proposed by Overhauser in 1953¹, was first experimentally demonstrated in metals² and later also observed in liquids^{3,4}, two classes of samples with mobile electrons. Thus, DNP is not a new area of scientific endeavor, but rather one undergoing a transition from low to high fields and frequencies, and thus the word “*renaissance*” is part of the title of this volume of PCCP. In the lead article of the issue, Charles Slichter describes the excitement of these early experiments performed in his group at the University of Illinois. Every scientist involved in DNP should read this paper as many of the challenges that we confront today were also of concern to Charlie and his colleagues.

During the 1960's and 70's, following the pioneering work of Overhauser, Carver and Slichter, DNP was used at low temperatures to produce highly polarized solid targets for nuclear scattering, and those experiments revealed that other polarization transfer mechanisms are present. In particular when the paramagnetic centers are localized the so-called solid-state effect⁵⁻⁷, cross-effect⁸⁻¹¹ and thermal mixing¹² dominate the polarization transfer, and involve the dipolar coupling of the nuclear spin to one, two or more electron spins, respectively. The theory for all three of these mechanisms predicts reduced transfer efficiencies at higher magnetic field values^{12, 13}. However, this feature of the polarization transfer mechanisms, in combination with the paucity of high frequency microwave sources to excite electron spins at magnetic field values above 1T, effectively relegated DNP to a position of an interesting scientific curiosity. Concurrently, during the 1970's and later, both solution and solid-state NMR moved briskly towards higher magnetic fields ($\sim 5-20$ T) yielding higher sensitivity and into multiple dimensions

to achieve higher spectral resolution. This latent phase for DNP persisted until the early 1990's when high field, solid state MAS DNP experiments directed at structural biology and utilizing gyrotron microwave sources were described by Griffin and coworkers^{14, 15}. Subsequently, in 2003 the Nycomed/Amersham group reported the possibility of polarizing samples at very low temperatures followed by fast dissolution, heating, and observation of the liquid state spectrum¹⁶. These two experimental approaches, and variations on these themes, received a good deal of attention in the magnetic resonance community and stimulated additional activities worldwide and initiatives in the fields of solid- and liquid state DNP and high-frequency microwave technology. Accordingly, a first international symposium on DNP was held in Nottingham in 2007 with 150 participants, resulting in a specialized issue on DNP in *Applied Magnetic Resonance*¹⁷. Two years later the 2th Symposium on DNP, held in Königstein and the EMAR Workshop on DNP in Eberbach highlighted the rapid pace of developments in this field. Therefore, this themed issue on high field DNP, presenting the newest results and innovations, is indeed timely.

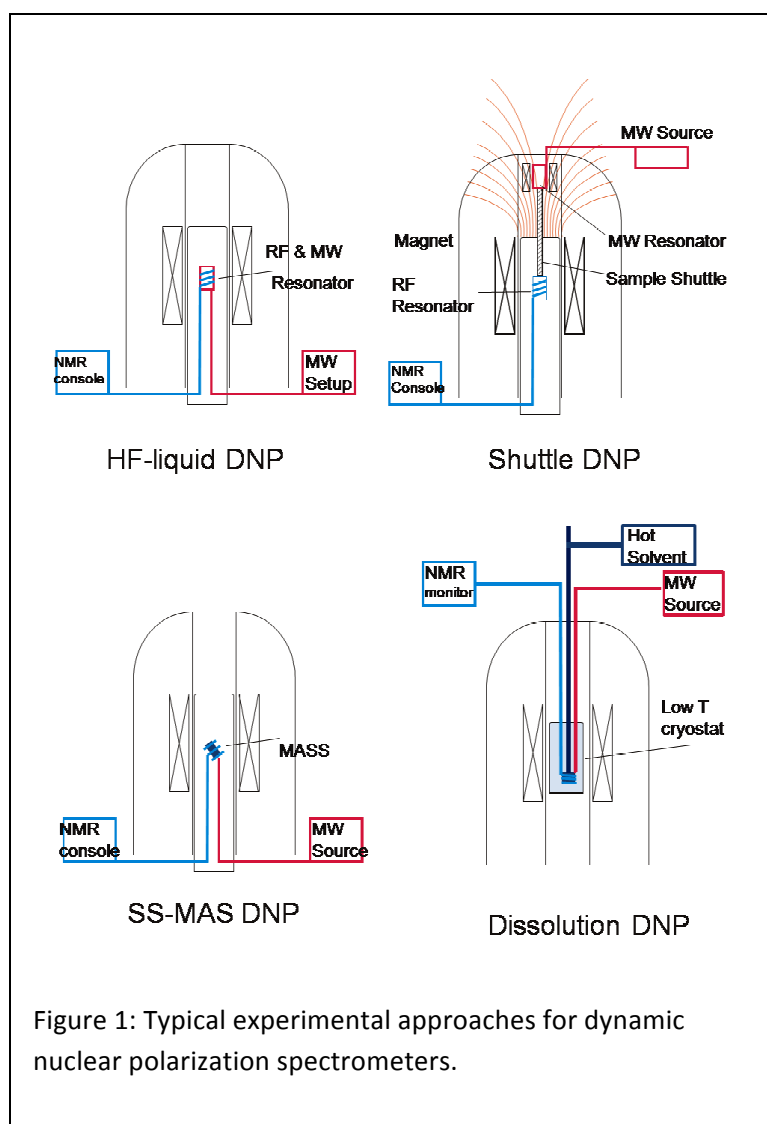
A key barrier to the dissemination of high field DNP experiments to many laboratories remains the development of the required instrumentation. In particular, high frequency microwave technology is an area that generally remains outside the expertise of the primary consumers of enhanced signal intensities available from DNP, namely the practitioners of solid state or solution NMR and MRI. This instrumentation includes high frequency microwave sources, efficient waveguides to transmit the microwaves from the source to the probe, and the probe itself, that must provide for irradiation of the polarizing electrons and NMR detection at multiple resonance frequencies – ¹H, ¹³C, ¹⁵N, -- often at cryogenic temperatures. Finally, there must be a suitable polarizing agent which requires expertise (or colleagues with expertise) in organic synthesis.

Currently, semiconductor diodes and vacuum electron devices are the microwave sources of choice in all DNP spectrometers. Semiconductor technology (Gunn and IMPATT diodes) reaches its limit at frequencies of ~100 GHz, corresponding to a magnetic field of 3.5 T (150 MHz ¹H NMR). Higher frequencies can be attained most conveniently by generating higher harmonics and combining outputs from multiple sources, but with significant losses in power. Despite this limitation, several labs are successfully using diodes for high field DNP experiments, and some of their results appear in this issue. Alternatives are vacuum electron devices, where an

accelerated electron beam is modulated by suitable slow wave structure or magnetic field. Slow wave devices exist in number of different forms -- backward wave oscillators (BWO's), orotrons, extended interaction oscillators and amplifiers (EIO and EIA's), etc. -- and operate in continuous wave or pulsed mode, with variable or fixed frequencies. Because of the presence of a slow wave structure, which has a size comparable to the microwave wavelength, the electron beam power density close to this structure is limited, and leads to maximum deliverable CW microwave powers in the 0.1-1 W range. Gyrotrons, which are fast wave devices, circumvent this problem by replacing the slow wave structure with a cavity immersed in a magnetic field. In this configuration CW output powers in the watt range are achieved in devices designed specifically for DNP at MIT¹⁸⁻²⁰, more recently at Fukui University^{21, 22}, and which are now available commercially²³. Gyrotrons are stable, spectrally pure, robust devices and can be operated continuously for weeks at a time which is essential for multidimensional NMR experiments. There are examples of the use of all of these sources -- diodes, slow wave devices, and gyrotrons -- in the papers in this issue²³⁻³¹.

Transmission of the microwaves to the sample in the probe with minimal loss, and monitoring the microwave power output is important experimentally. Fundamental mode waveguides have unacceptable insertion losses, and do not couple to a free-space propagation of a Gaussian beam, which is typically used for quasi-optical transmission outside of the probe. Corrugated overmoded or metallo-dielectric waveguides can be used inside the DNP probe for transmission^{32, 33}. These differ from classical fundamental waveguides in that the losses in such systems are <1-2 dB. Detection of the EPR signal requires quasioptical duplexing devices to prohibit the strong excitation power from reaching the microwave detector. Again different designs of such microwave transmission and detection systems are described in this issue in detail.

Figure 1 schematically illustrates some typical spectrometer configurations for DNP/NMR experiments at high magnetic fields. The upper two instruments are configured to polarize liquid samples, whereas the DNP polarization step in the lower two is performed in the solid, often frozen state. Several applications of **HF-liquid DNP** with *in-situ* microwave excitation at the NMR detection field are reported in this issue with very promising enhancements at high magnetic fields (up to 10 T)^{31, 34-37}. Theoretical and experimental investigations of the success of the electron-nuclear polarization transfer will be important to understand the underlying physical principles of these results. Similarly, this understanding is also important to choose the optimum polarizing field for the **Shuttle DNP** apparatus²⁵. In this type of spectrometer the liquid sample is rapidly moved from the low field, where the



polarization is performed, to a high field region for NMR detection. A new two-center magnets for such a DNP system is described in this issue²⁶. High field **MAS DNP** was developed at MIT^{19, 38-41} and enhancements of up to ~300 have been observed with biradical polarizing agents⁴². In most experiments the enhanced ¹H polarization is transferred to ¹³C with cross polarization and used for 1D- and 2D MAS NMR applications in proteins^{19, 40, 43, 44}. A much misunderstood part of this process is the fact that ¹H spin-diffusion distributes this polarization uniformly throughout the sample, even if it is heterogeneous, such as is the case with a membrane protein in a bilayer or a protein in an amyloid fibril. This

issue, and resolution in low temperature MAS experiments is addressed by Barnes, et al.³⁰.

Recently a commercial **MAS DNP** spectrometer became available that is described in this issue²³. In addition, in this volume direct transfers to low- γ nuclei (^2H , ^{13}C , etc) are discussed and the enhancements, field profiles, and preferred polarizing agents are shown to be system dependent^{45, 46}. In the **Dissolution DNP** experiment the sample is polarized in the solid state at very low temperatures (typically 1-4 K) at magnetic fields of 3-7 T. The polarization step is followed by rapid dissolution with a suitable solvent, and is finally transferred to either a high resolution NMR spectrometer or a MR imager^{26, 47}. Very high enhancements (relative to room temperature) for ^{13}C can be retained within the dissolution and transfer process, and arise from a product of DNP enhancement (~ 250) and Boltzmann polarization (~ 250). In this issue several new approaches and improvements to the experiment are introduced. Applications of this method range from MRI imaging of metabolites to studies of chemical reaction mechanisms⁴⁷⁻⁵⁰.

An essential ingredient of every DNP experiment is a polarizing agent, and for the first 50 years of DNP these consisted of readily available monomeric paramagnetic centers such as a metal, or organic radicals like BDPA or TEMPO. More recently, several new polarizing agents have been introduced that are more efficient in that they are effective at lower concentrations and produce larger enhancements⁵¹⁻⁵⁴. Four articles describing these new agents – narrow line trityl radicals, biradicals and spin labeled polymers that separate at higher temperatures and therefore preserve resolution – are described in this issue.⁵⁵⁻⁵⁸

Finally, there are two other important and exciting topics discussed in contributions to this volume. Namely, the possibility of solid state imaging using the enhanced sensitivity of DNP²⁷ which may lead to considerable increases in the resolution of images cells and other biological systems. In addition, theoretical methods for optimizing time domain DNP experiments are considered by Pomplum and Glaser⁵⁹, an area that has thus far received little attention.

All of these approaches are potentially applicable to a wide range of NMR experiments important in biology, chemistry, physics and medicine, and their successful development will have an enormous impact on the field. Accordingly, a number of academic and industrial research groups have recently initiated research efforts to overcome the current limitations of the techniques. Technical advances in the area of high-frequency microwave sources and components and of the various DNP spectrometers will be of vital importance for the further development of the DNP method, especially to bring the technique into use at the highest

magnetic fields available for NMR ($< 20\text{T}$). In addition, the implementation of time domain experiments should open many new areas of application, just as it did for high resolution solid state and solution NMR. Other areas such as the optimization of polarizing agents, the development of new types of polarization transfer methods, and the design of new experiments focusing on selectivity, contrast and additional structural restraints are research areas ripe for investigation. Thus, collaborative efforts among researchers from chemistry, physics, biology and the engineering disciplines will be required to optimize DNP for applications in high-field NMR and MRI. We foresee a very bright and expansive future for this field, well into the 21st century.

Literature

- 1 A. W. Overhauser, *Phys. Rev.*, 1953, 92 411-415.
- 2 T. R. Carver and C. P. Slichter, *Physical Review*, 1953, 92 212-213.
- 3 T. R. Carver and C. P. Slichter, *Phys. Rev.*, 1956, 102 975-980.
- 4 K. H. Hausser and D. Stehlik, *Advances in Magnetic Resonance*, 1968, 3 79.
- 5 C. D. Jefferies, *Physical Review*, 1957, 106 164-165.
- 6 A. Abragam and W. G. Proctor, *Comptes Rendus Hebdomadaires des Seances de L'Academia des Sciemces*, 1958, 246 2253-2256.
- 7 C. D. Jefferies, *Physical Review*, 1960, 117 1056-1069.
- 8 A. V. Kessenikh and A. A. Manenkov, *Soviet Physics- Solid State*, 1963, 5 835-837.
- 9 C. F. Hwang and D. A. Hill, *Phys. Rev. Letters*, 1967, 19 1011-1013.
- 10 C. F. Hwang and D. A. Hill, *Phys. Rev. Letters*, 1967, 18 110-112.
- 11 D. S. Wollan, *Phys. Rev. B*, 1976, 13 3671-3685.
- 12 M. Goldman, *Spin Temperature and Nuclear Magnetic Resonance in Solids*, Oxford University Press, London, 1970.
- 13 R. A. Wind, M. J. Duijvestijn, C. Vanderlugt, A. Manenschijn and J. Vriend, *Progress in Nuclear Magnetic Resonance Spectroscopy*, 1985, 17 33-67.
- 14 L. R. Becerra, G. J. Gerfen, R. J. Temkin, D. J. Singel and R. G. Griffin, *Phys Rev Lett*, 1993, 71 3561-3564.
- 15 G. J. Gerfen, L. R. Becerra, D. A. Hall, R. G. Griffin, R. J. Temkin and D. J. Singel, *J Chem Phys*, 1995, 102 9494-9497.
- 16 J. H. Ardenkjaer-Larsen, B. Fridlund, A. Gram, G. Hansson, L. Hansson, M. H. Lerche, R. Servin, M. Thaning and K. Golman, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, 100 10158-10163.
- 17 T. F. Prisner and W. Koeckenberger, *Applied Magnetic Resonance*, 2008, 34.
- 18 L. R. Becerra, G. J. Gerfen, B. F. Bellew, J. A. Bryant, D. A. Hall, S. J. Inati, R. T. Weber, S. Un, T. F. Prisner, A. E. McDermott, K. W. Fishbein, K. E. Kreisler, R. J. Temkin, D. J. Singel and R. G. Griffin, *Journal of Magnetic Resonance Series A*, 1995, 117 28-40.
- 19 V. S. Bajaj, C. T. Farrar, M. K. Hornstein, I. Mastovsky, J. Viereg, J. Bryant, B. Elena, K. E. Kreisler, R. J. Temkin and R. G. Griffin, *J. Mag. Res.*, 2003, 160 85-90.
- 20 V. S. Bajaj, M. K. Hornstein, K. E. Kreisler, J. R. Sirigiri, P. P. Woskov, M. L. Mak-Jurkauskas, J. Herzfeld, R. J. Temkin and R. G. Griffin, *J Magn Reson*, 2007, 189 251-279.
- 21 T. Idehara, I. Ogawa, S. Mitsudo, M. Pereyaslavets, N. Nishida and K. Yoshida, *IEEE Trans. Plasma Sci.*, 1999, 27 340-354.

- 22 T. Idehara, T. Saito, I. Ogawa, S. Mitsudo, Y. Tatematsu, L. Agusu, H. Mori and S. Kobayashi, *Applied Magnetic Resonance* 2008, 34 265.
- 23 M. Rosay, L. Tometich, S. Pawsey, R. Bader, R. Schauwecker, M. Blank, P. M. Borchard, S. R. Cauffman, K. L. Felch, R. T. Weber, R. J. Temkin, R. G. Griffin and W. E. Maas, *Phys. Chem. Chem. Phys.*, 2010 10.1039/c003685b.
- 24 B. D. Armstrong, D. T. Edwards, R. J. Wylde, S. A. Walker and S. Han, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c002290j.
- 25 A. Krahn, P. Lottmann, T. Marquardsen, A. Tavernier, M.-T. Türke, M. Reese, A. Leonov, M. Bennati, P. Hofer, F. Engelke and C. Griesinger, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c003381b.
- 26 J. Leggett, R. Hunter, J. Granwehr, R. Panek, A. J. Perez-Linde, A. J. Horsewill, J. McMaster, G. Smith and W. Köckenberger, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c002566f.
- 27 K. R. Thurber and R. Tycko, *Phys. Chem. Chem. Phys.*, 2010 10.1039/c0cp00157k.
- 28 Y. Matsuki, H. Takahashi, K. Ueda, T. Idehara, I. Ogawa, M. Toda, H. Akutsu and T. Fujiwara, *Phys. Chem. Chem. Phys.*, 2010 10.1039/c002268c.
- 29 R. I. Hunter, P. A. S. Cruickshank, D. R. Bolton, P. C. Riedi and G. M. Smith, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c002251a.
- 30 A. B. Barnes, B. Corzilius, M. L. Mak-Jurkauskas, L. B. Andreas, V. S. Bajaj, Y. Matsuki, M. L. Belenky, J. Lugtenburg, J. R. Sirigiri, R. J. Temkin, J. Herzfeld and R. G. Griffin, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c003763j.
- 31 V. Denysenkov, M. J. Prandolini, M. Gafurov, D. Sezer, B. Endeward and T. F. Prisner, *Phys. Chem. Chem. Phys.*, 2010, 2010 10.1039/c003697h.
- 32 P. W. Woskov, V. S. Bajaj, M. K. Hornstein, R. J. Temkin and R. G. Griffin, *IEEE Transactions on Microwave Theory and Techniques*, 2005, 53 1863-1869.
- 33 V. P. Denysenkov, M. J. Prandolini, A. Krahn, M. Gafurov, B. Endeward and P. T.F., *Appl. Magn. Reson.* , 2008, 34 289.
- 34 E. V. Kryukov, M. E. Newton, K. J. Pike, D. R. Bolton, R. M. Kowalczyk, A. P. Howes, M. E. Smith and R. Dupree, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c003189e.
- 35 M.-T. Türke, I. Tkach, M. Reese, P. Höfer and M. Bennati, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c002814m.
- 36 M. Bennati, C. Luchinat, G. Parigi and M.-T. Türke, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c002304n.
- 37 J. A. Villanueva-Garibay, G. Annino, P. J. M. v. Bentum and A. P. M. Kentgens, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c002554m.
- 38 D. A. Hall, D. C. Maus, G. J. Gerfen, S. J. Inati, L. R. Becerra, F. W. Dahlquist and R. G. Griffin, *Science*, 1997, 276 930-932.
- 39 M. Rosay, V. Weis, K. E. Kreischer, R. J. Temkin and R. G. Griffin, *J Am Chem Soc*, 2002, 124 3214-3215.

- 40 M. Rosay, J. C. Lansing, K. C. Haddad, W. W. Bachovchin, J. Herzfeld, R. J. Temkin and R. G. Griffin, *J. Am. Chem. Soc.*, 2003, 125 13626-13627.
- 41 P. C. A. van der Wel, K. N. Hu, J. Lewandowski and R. G. Griffin, *J Am Chem Soc*, 2006, 128 10840-10846.
- 42 C. Song, K.-N. Hu, C.-G. Joo, T. M. Swager and R. G. Griffin, *J. Am Chem. Soc*, 2006, 128 11385-11390.
- 43 K. N. Hu, H. H. Yu, T. M. Swager and R. G. Griffin, *J Am Chem Soc*, 2004, 126 10844-10845.
- 44 V. S. Bajaj, M. L. Mak-Jurkauskas, M. Belenky, J. Herzfeld and R. G. Griffin, *Proc. Nat'l. Acad. Sci.*, 2009, 106 9244-9249.
- 45 T. Maly, L. B. Andreas, A. A. Smith and R. G. Griffin, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c003705b.
- 46 T. Maly, A.-F. Miller and R. G. Griffin, *Chemphyschem*, 2010, 11 999-1001.
- 47 S. Bowen and C. Hilty, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c002316g.
- 48 C. Ludwig, I. Marin-Montesinos, M. G. Saunders, A.-H. Emwas, Z. Pikramenou, S. P. Hammond and U. L. Günther, *Phys. Chem. Chem. Phys.*, 2010 10.1039/c002700f.
- 49 R. Panek, J. Granwehr, J. Leggett and W. Köckenberger, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c002710n.
- 50 C. Cudalbu, A. Comment, F. Kurdzesau, R. B. v. Heeswijk, K. Uffmann, S. Jannin, V. Denisov, D. Kirik and R. Gruetter, 2010, 12 10.1039/c002309b.
- 51 K.-N. Hu, C. Song, H.-h. Yu, T. M. Swager and R. G. Griffin, *J. Chem. Phys.*, 2008, 128 052321.
- 52 K.-N. Hu, V. S. Bajaj, M. M. Rosay and R. G. Griffin, *J. Chem. Phys.*, 2007, 126 044512.
- 53 K. N. Hu, Ph.D., MIT, 2008.
- 54 Y. Matsuki, T. Maly, O. Ouari, S. Lyubenova, J. Herzfeld, T. Prisner and P. T. R. G. Griffin, *Angewandte Chemie*, 2009, 000 0000.
- 55 J. C. Paniagua, V. Mugnaini, C. Gabellieri, M. Feliz, N. Roques, J. Veciana and M. Pons, *Phys. Chem. Chem. Phys.*, 2010 10.1039/c003291n.
- 56 B. C. Dollmann, M. J. N. Junk, M. Drechsler, H. W. Spiess, D. Hinderberger and K. Münnemann, *Phys. Chem. Chem. Phys.*, 2010 10.1039/c003349a.
- 57 C. Ysacco, E. Rizzato, M.-A. Virolleaud, H. Karoui, A. Rockenbauer, F. L. Moigne, D. Siri, O. Ouari, R. G. Griffin and P. Tordo, *Phys. Chem. Chem. Phys.*, 2010 10.1039/c002591g.
- 58 S. Macholl, H. Jóhannesson and J. H. Ardenkjaer-Larsen, *Phys. Chem. Chem. Phys.*, 2010 10.1039/c002699a.
- 59 N. Pomplun and S. J. Glaser, *Phys. Chem. Chem. Phys.*, 2010, 12 10.1039/c003751f.