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Advances in Magnetic Resonance: From Stem Cells to Catalytic Surfaces

In assembling this *JACS* Select issue, I was once again struck by the startling diversity of roles that magnetic resonance methods play in modern chemistry. Indeed, looking back, we can see how nuclear magnetic resonance—as well as electron paramagnetic resonance and magnetic resonance imaging—has grown since its introduction in the 1940s, hand in hand with the explosion in molecular and materials sciences. Today experimental NMR continues to reflect new developments in chemistry, and it confirms its central position as the chemical analysis technique *par excellence*. In almost all areas of modern chemistry, NMR is present in an essential role. (I like to think that NMR is to chemistry like sugar is to baking: it's hard to do without it, it's almost always better with it, and some would argue that the more of it you use, the better the result!) This omnipresence is due to a number of factors that mean that NMR spectroscopy can grow and adapt as new challenges appear. Spectral resolution and sensitivity have always been the key limiting factors for application of NMR, but both are improving continuously. This improvement is the result of a textbook combination of, on the one hand, technological advances in superconducting magnets (with the 1 GHz barrier being broken in 2010[1]), in probes, and in sample handling and control systems, and, on the other hand, the introduction of creative new NMR experiments using multi-pulse and multi-dimensional methods, which together mean that today there are as many NMR experiments as there are NMR spectroscopists or problems to which magnetic resonance could be applied. Above all, the diversity of applications of frontier methods in magnetic resonance simply reflects the incredible vivacity of modern chemistry, as it always has.

JACS has always been the premier forum for the best NMR spectroscopy in the chemical sciences. Selecting the articles to highlight in this issue was tough, with many more papers on the short list than could be included. I have tried to select articles so as to focus on some of the currently most active areas, and on the most transformative recent developments, and in such a way that the ensemble is intended to inspire as wide a community as possible.

As mentioned above, low sensitivity has always been the Achilles' heel of NMR, preventing its application to some of today's most challenging characterization problems in chemistry. One of the most revolutionary steps forward of the past few years has been the introduction of strategies that allow highly polarized NMR samples to be generated by dynamic nuclear polarization (DNP), either for solutions or for solid-state NMR. DNP provides a sensitivity gain of more than 2 orders of magnitude, which translates to acceleration in acquisition times by a factor of over 10 000. This is obviously a game changer, and as DNP instrumentation becomes available more widely, it is rapidly opening up completely new application areas for NMR that would have been unthinkable only a few years ago. Recent advances in magnetic resonance allow the study of more and more complex molecular or materials problems, with a clear shift toward the study of systems *in situ* and toward real-time spectroscopy. Spectacular examples are appearing in the studies of human metabolism, the surface chemistry of catalysis or materials for energy, and the biological function of large assemblies. It is no coincidence that these are some of the most dynamics areas of chemistry today.

Sensitivity Enhanced by Dynamic Nuclear Polarization. DNP is rapidly enabling structural studies in systems as diverse as membrane proteins and materials surfaces. Even though commercial DNP systems for magic-angle-spinning (MAS) solid-state NMR only became available about 3 years ago, we are already seeing tremendously exciting results from this technology. For example, the ability to carry out structural studies of membrane-integrated receptor proteins without the necessity for purification would be attractive, but is severely sensitivity limited. **Linden** et al.[2] use DNP to obtain well-resolved spectra for the study of neurotoxin II bound to acetylcholine receptors in native membranes. Another key area of application of NMR today is in determining the structures of the insoluble deposits that appear in many neurodegenerative diseases. **Bayro** et al.[3] use DNP to increase the number of observable contacts and determine the intermolecular structure of amyloid fibrils. They study fibrils of the 86-residue SH3 domain of PI3 kinase, and their experiments establish a parallel, in-register alignment of the proteins in the amyloid fibrils.

Magic-angle-spinning DNP NMR in combination with cross-polarization methods can also be used to selectively enhance the signals from the surfaces of materials. **Lelli** et al.[4] show how this could be done to achieve fast characterization of functionalized hybrid silica materials, by DNP silicon-29 surface-enhanced NMR spectroscopy. They are able to determine differences in surface bonding patterns that depend on the synthetic approach in a matter of minutes.

Using DNP to enhance the polarization of solutions is also gaining popularity. The objective is often to be able to follow the fate of a polarized metabolite after its injection into an *in vivo* subject, and here the lifetime of the polarization is often a limiting factor. **Tayler** et al.[5] show how they could achieve direct DNP enhancement of nuclear singlet order. This is important since the singlet states have much longer lifetimes than ordinary polarization, allowing the fate of the molecule to be observed further into the metabolic cycle.

Magnetic Resonance Imaging of Metabolism. This leads us naturally to another area where magnetic resonance is developing rapidly today, with many highly creative new ideas: that of magnetic resonance imaging of metabolic processes. The range of processes that can be imaged with MRI is expanding rapidly, and is no longer by any means limited to anatomical details, but is now applied to target various metabolic processes. This is a particularly vigorous area of chemistry, and the following are but three recent illustrations.

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Reactive oxygen species such as hydrogen peroxide cause oxidative stress that is associated with a wide range of diseases, and the ability to detect and image them *in vivo* is obviously of great interest. A prime example of how DNP can be used to detect such species *in vivo* is given by **Lippert** et al.,[6] who develop a reaction-based approach for the detection of hydrogen peroxide using hyperpolarized ^{13}C MRI and the H_2O_2-mediated oxidation of α-ketoacids to carboxylic acids.

Also, using MRI methods, **Kim** et al.[7] develop mesoporous silica-coated hollow manganese oxide nanoparticles as contrast agents to track adipose-derived mesenchyrnal stem cells. The new particles were used to monitor cell transplants over 14 days. In another example, **Ratnakar** et al.[8] develop europium-(III) DOTA-tetraamide complexes as redox-active MRI sensors. To achieve noninvasive mapping of redox potential around the body, they exploit reduction by β-NADH of the complex, which produces a clear NMR signature.

***In Situ* Biological NMR: Crowded Solutions, In-Cell NMR.** There is also much interest in current structural biology in reproducing the effects of the crowded in-cell environment on the structure and dynamics of proteins. NMR is well placed to do this, as it either can be applied to solutions mimicking the crowded environment or, increasingly, can be used to measure signals from inside cells themselves.

In two landmark contributions, **Heddi** and **Phan**[9] determine the structure of human telomeric DNA in a crowded solution, finding that the strucutre is significantly modified by water depletion, and **Miklos** et al.[10] show how protein crowding tunes protein stability. For the latter study the theory predicted that crowding should stabilize proteins; however, the authors find that protein crowders can in fact be mildly destabilizing.

Widening the range of systems that can be studied, **Zandomeneghi** et al.[11] describe the maturation processes in living *Salmonella enterica* serovar Typhimurium, a prevalent cause of human gastroenteritis. They follow the composition of the O-antigen on the outer bacterial membrane with high-resolution MAS NMR spectroscopy.

To increase the reliability of in-cell NMR studies, **Waudby** et al.[12] show how NMR measurements of the diffusion behavior of proteins within bacterial cells can provide a rapid and nondestructive probe of localization, notably in order to define whether observed signals are from intracellular species rather than from components of the extracellular medium.

Structure and Dynamics of Proteins by NMR and EPR. Determining the structure and dynamics of proteins has been a primary driving force for high-field NMR for the past 20 years. This is still very much true today, with the quest for structures from more and more challenging and complex systems. Solid-state NMR in particular has been experiencing tremendous development over the past few years, and is finally coming of age. As examples of this, at the frontier of what multi-dimensional NMR can do currently, **Das** et al.[13] report the structure determination of a membrane protein in proteoliposomes. By merging elements of oriented sample and MAS solid-state NMR, they are able to measure a series of restraints that allow the determination of the structure of the 60-residue integral membrane core of the mercury transporter MerF. In another very topical study using MAS solid-state NMR, **Hu** et al.[14] determine the mechanism of transmembrane proton conduction in the acid-activated proton channel formed by the influenza M2 protein, which is important for the life cycle of the virus. Again using solid-state NMR, **Parthasarathy** et al.[15] examine atomic-level details of Cu^{2+} binding to amyloid fibrils by detecting paramagnetic signal quenching in 1D and 2D high-resolution carbon-13 solid-state NMR for full-length 40-residue Aβ(1−40). Cu^{2+} binding in amyloid fibrils is thought to be important, as elevated Cu ion concentration is observed in Alzheimer's plaques, triggering the production of neurotoxic reactive oxygen species.

State-of-the-art solution-state biomolecular NMR studies are providing more and more detailed pictures of protein dynamics. This is important since, for example, long-range correlated motions are candidate mechanisms for information transfer across protein structures, enabling signal transduction. **Fenwick** et al.[16] identify weak, long-range correlated motions on the surface of ubiquitin, in areas that link molecular recognition sites.

NMR is also playing a key role in understanding the atomic-level features of intrinsically disordered proteins. The conformational plasticity of such proteins allows them to access functional modes not achievable by folded proteins, but also places their molecular characterization beyond the reach of classical structural biology. In pioneering work, **Ozenne** et al.[17] show how to map the complete potential energy landscape of intrinsically disordered proteins at amino acid resolution using a combination of chemical shifts and residual dipolar couplings.

EPR is now being applied to sophisticated mechanistic questions related to protein function. Several examples have appeared in *JACS* recently, illustrated here by a study by **Wang** et al.,[18] who use EPR and ^{2}H, ^{17}O, and ^{57}Fe isotopic labeling to characterize and assign two key reaction intermediates in IspH catalysis, thereby solving the debate over the mechanism of action of this [4Fe-4S] protein in the methylerythritol phosphate isoprenoid biosynthesis pathway (an important anti-infective drug target).

NMR Crystallography and the Structure of Materials. As materials chemistry develops in all directions today, so does solid-state NMR characterization. In favorable cases, complete 3D structures of powdered solids can be determined, driving the fast-maturing field of NMR crystallography. Even when this is not the case, solid-state NMR is rapidly becoming the method of choice for solving structural questions in many materials. Very often these studies depend on a combination of density functional theory computation of chemical shifts with high-resolution solid-state NMR and X-ray diffraction. For example, in this way **Mafra** et al.[19] determine the packing interactions in hydrated and anhydrous forms of the antibiotic ciprofloxacin. In a similar vein, but on a larger scale, **Lai** et al.[20] use chemical shifts to determine the nature of the indoline quinonoid intermediate in tryptophan synthase under conditions of active catalysis.

In other applications of solid-state NMR to materials, **Neyshtadt** et al.[21] use NMR and other techniques to show how the chemical compositions and structures of organic−inorganic interfaces in mesostructurally ordered conjugated polymer−titania nanocomposites have a predominant influence on their photovoltaic properties. They determine the compositions, structures, and distributions of inorganic and organic species within the materials over multiple length scales. This enables the design, synthesis, and control of the photovoltaic properties of hybrid functional materials. In more landmark work, **Tsao** et al.[22] attempt for the first time to shed light on donor−acceptor interactions between neighboring polymer chains with the help of solid-state NMR. The work allows the authors to establish a design paradigm for cyclopentadithiophene−benzothiadiazole donor−

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acceptor copolymers for field-effect transistors with ultrahigh mobilities. Finally, **Key** et al.[23] use NMR to study the changes in short-range order that occur during the initial charge and discharge cycles in silicon electrodes for lithium ion batteries in order to shed new light on the delithiation mechanisms.

In conclusion, I hope this JACS Select leaves the reader with a feeling for how magnetic resonance is developing today. I am looking forward to see where magnetic resonance, and chemistry, will take us in the future, and I hope that some of these horizons are perceptible in the papers coming out in *JACS* today.

Lyndon Emsley, Associate Editor

AUTHOR INFORMATION

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

REFERENCES

(1) Bhattacharya, A. *Nature* **2010**, *463*, 605.
(2) Linden, A. H.; Lange, S.; Franks, W. T.; Akbey, U.; Specker, E.; van Rossum, B.-J.; Oschkinat, H. *J. Am. Chem. Soc.* **2011**, *133*, 19266.
(3) Bayro, M. J.; Debelouchina, G. T.; Eddy, M. T.; Birkett, N. R.; MacPhee, C. E.; Rosay, M.; Maas, W. E.; Dobson, C. M.; Griffin, R. G. *J. Am. Chem. Soc.* **2011**, *133*, 13967.
(4) Lelli, M.; Gajan, D.; Lesage, A.; Caporini, M. A.; Vitzthum, V.; Miéville, P.; Héroguel, F.; Rascón, F.; Roussey, A.; Thieuleux, C.; Boualleg, M.; Veyre, L.; Bodenhausen, G.; Coperet, C.; Emsley, L. *J. Am. Chem. Soc.* **2011**, *133*, 2104.
(5) Tayler, M. C. D.; Marco-Rius, I.; Kettunen, M. I.; Brindle, K. M.; Levitt, M. H.; Pileio, G. *J. Am. Chem. Soc.* **2012**, *134*, 7668.
(6) Lippert, A. R.; Keshari, K. R.; Kurhanewicz, J.; Chang, C. J. *J. Am. Chem. Soc.* **2011**, *133*, 3776.
(7) Kim, T.; Momin, E.; Choi, J.; Yuan, K.; Zaidi, H.; Kim, J.; Park, M.; Lee, N.; McMahon, M. T.; Quinones-Hinojosa, A.; Bulte, J. W. M.; Hyeon, T.; Gilad, A. A. *J. Am. Chem. Soc.* **2011**, *133*, 2955.
(8) Ratnakar, S. J.; Viswanathan, S.; Kovacs, Z.; Jindal, A. K.; Green, K. N.; Sherry, A. D. *J. Am. Chem. Soc.* **2012**, *134*, 5798.
(9) Heddi, B.; Phan, A. T.. *J. Am. Chem. Soc.* **2011**, *133*, 9824.
(10) Miklos, A. C.; Sarkar, M.; Wang, Y.; Pielak, G. J. *J. Am. Chem. Soc.* **2011**, *133*, 7116.
(11) Zandomeneghi, G.; Ilg, K.; Aebi, M.; Meier, B. H. *J. Am. Chem. Soc.* **2012**, *134*, 17513.
(12) Waudby, C. A.; Mantle, M. D.; Cabrita, L. D.; Gladden, L. F.; Dobson, C. M.; Christodoulou, J. *J. Am. Chem. Soc.* **2012**, *134*, 11312.
(13) Das, B. B.; Nothnagel, H. J.; Lu, G. J.; Son, W. S.; Tian, Y.; Marassi, F. M.; Opella, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 2047.
(14) Hu, F.; Schmidt-Rohr, K.; Hong, M. *J. Am. Chem. Soc.* **2012**, *134*, 3703.
(15) Parthasarathy, S.; Long, F.; Miller, Y.; Xiao, Y.; McElheny, D.; Thurber, K.; Ma, B.; Nussinov, R.; Ishii, Y. *J. Am. Chem. Soc.* **2011**, *133*, 3390.
(16) Fenwick, R. B.; Esteban-Martín, S.; Richter, B.; Lee, D.; Walter, K. F. A.; Milovanovic, D.; Becker, S.; Lakomek, N. A.; Griesinger, C.; Salvatella, X. *J. Am. Chem. Soc.* **2011**, *133*, 10336.
(17) Ozenne, V.; Schneider, R.; Yao, M.; Huang, J.-r.; Salmon, L.; Zweckstetter, M.; Jensen, M. R.; Blackledge, M. *J. Am. Chem. Soc.* **2012**, *134*, 15138.
(18) Wang, W.; Wang, K.; Span, I.; Jauch, J.; Bacher, A.; Groll, M.; Oldfield, E. *J. Am. Chem. Soc.* **2012**, *134*, 11225.
(19) Mafra, L.; Santos, S. M.; Siegel, R.; Alves, I.; Almeida Paz, F. A.; Dudenko, D.; Spiess, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 71.
(20) Lai, J.; Niks, D.; Wang, Y.; Domratcheva, T.; Barends, T. R. M.; Schwarz, F.; Olsen, R. A.; Elliott, D. W.; Fatmi, M. Q.; Chang, C.-e. A.; Schlichting, I.; Dunn, M. F.; Mueller, L. J. *J. Am. Chem. Soc.* **2011**, *133*, 4.
(21) Neyshtadt, S.; Jahnke, J. P.; Messinger, R. J.; Rawal, A.; Segal Peretz, T.; Huppert, D.; Chmelka, B. F.; Frey, G. L. *J. Am. Chem. Soc.* **2011**, *133*, 10119.
(22) Tsao, H. N.; Cho, D. M.; Park, I.; Hansen, M. R.; Mavrinskiy, A.; Yoon, D. Y.; Graf, R.; Pisula, W.; Spiess, H. W.; Müllen, K. *J. Am. Chem. Soc.* **2011**, *133*, 2605.
(23) Key, B.; Morcrette, M.; Tarascon, J.-M.; Grey, C. P. *J. Am. Chem. Soc.* **2011**, *133*, 503.