very regular fashion with long-range order. Interestingly, when the self-assembled molecular layer encountered defects in the underlying surface — such as step edges on the SiC crystal or carbon deposits at the interface between the SiC and the graphene layer — they would grow straight over the defects without interruption of their molecular packing. In fact, the PTCDA monolayer had fewer defects than the underlying graphene.

It is reasoned by Hersam and Wang that PTCDA's ability to pack in ordered arrays and its insensitivity to defects arises from the relative strengths of the molecule–surface and molecule–molecule interactions. PTCDA molecules bind fairly weakly to the underlying graphene through π–π interactions, but strongly to each other through hydrogen bonding and quadrupolar interactions. This fairly weak bonding of the molecular overlayer to the graphene substrate is shown by the lack of any registry between rows of carbon atoms of the graphene and the molecular rows of the PTCDA layer, and allows the robust molecular layer to traverse defects without disruption of its own packing structure.

In addition to the self-assembly work, the spectroscopic capabilities of the STM were used to characterize the electronic properties of the PTCDA layer and compare them with the bare graphene surface. The results revealed that the electronic properties of the PTCDA monolayer are distinct from those of the underlying graphene substrate, and seem to be largely unperturbed by the electronic properties of the epitaxial graphene. These observations support the idea that the PTCDA layer interacts weakly with the graphene surface and therefore maintains its own electronic properties.

Although graphene-based electronics are still a distant prospect, potential applications in the short term include conductive additives to plastics, battery parts and field emitters[7]. The demonstration that the same principles of molecular self-assembly — which are well understood on substrates such as graphite — can be transferred to graphene opens the possibility of using the existing bank of information about molecular assembly to functionalize graphene for a myriad of applications. Such well-ordered, stable and nearly defect-free molecular monolayers present many opportunities for exploring self-assembly chemistry on graphene, tailoring its chemical functionality, and templating the growth and deposition of other materials. In turn, these opportunities will offer potential routes towards realizing graphene-based molecular electronic and sensing devices. ❐

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NMR SPECTROSCOPY

Chemistry awakens a silent giant

Progress in NMR spectroscopy has been held back by sensitivity issues inherent to the way the measurements are taken. Now, two separate studies show how simple chemical processes can be used to unveil NMR's sensitive side

Lucio Frydman

Nuclear magnetic resonance (NMR) has a number of unique roles in science, such as characterizing molecular structures and contributing to the *in vivo* identification and localization of disease through magnetic resonance imaging (MRI). Further progress in the uses of NMR and MRI are hampered by sensitivity problems, and incremental 'bigger machine' approaches have reached a stage of diminishing returns. Writing in *Science*, Duckett and co-workers[1] and Warren and co-workers[2] deal with these sensitivity issues by relying on highly original propositions that result in NMR 'super-signals' that surpass those normally afforded by state-of-the-art spectrometers by factors of ~10^2–10^3. Uncharacteristically, these studies share a call for synthetic chemistry to come to the aid of NMR spectroscopy, rather than the other — and more common — way around.

The key to NMR/MRI is the alignment that nuclear spins from stable isotopes (^{1}H, ^{13}C, ^{19}F, ^{31}P) undergo, when samples are placed within the powerful magnetic fields in which these experiments take place. Once aligned, the spins can be excited away from equilibrium with a radiofrequency pulse, making them emit characteristic electromagnetic 'sounds' specific to either chemical locations (in NMR) or to spatial positions (in MRI). This nuclear symphony then affords accurate information about the structures of molecules and of objects, as well as unique information about their atomic-level dynamics.

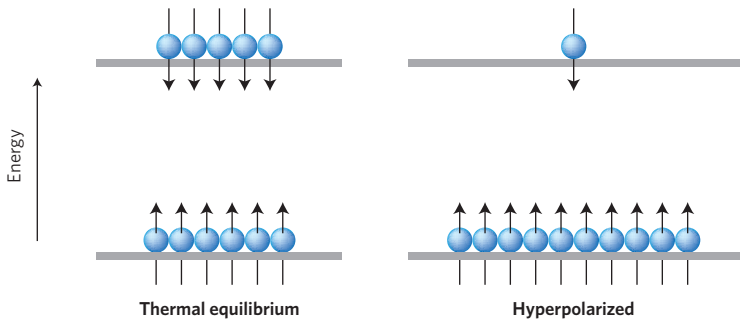

Figure 1 | Population differences between equilibrium and hyperpolarized states. Duckett and colleagues[1] and Warren *et al.*[2] propose new routes to defeat Boltzmann's frustratingly low degree of equilibrium spin alignment (left), through nuclear hyperpolarization methods capable of yielding correspondingly stronger NMR/MRI signals (right).

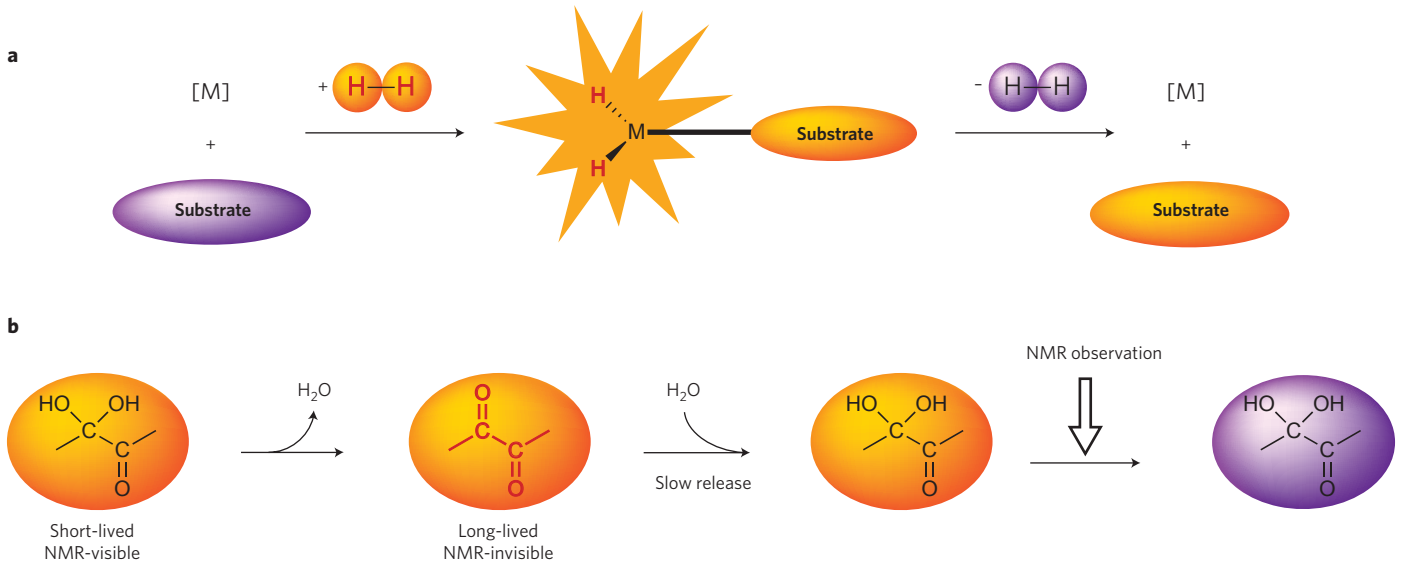

Figure 2 | Chemistry comes to the aid of NMR — and *vice versa*. Highly aligned singlet spin states (red) are exploited **a**, by Duckett *et al.* to hyperpolarize a substrate of interest (figure used with permission from ref. 1; © 2009 AAAS); and **b**, by Warren *et al.* to increase the lifetimes during which nuclear hyperpolarization is stored. Unpolarized states are depicted in purple, and hyperpolarized in gold. Spin alignment in **a** is transferred through the formation of a transient organometallic complex, which passes the spin order of *p*-H_2 onto the targeted substrate, and thereby significantly enhances its NMR signal. Hyperpolarization in **b** is first generated in a magnetically active substrate like diacetyl monohydrate — for instance by dynamic nuclear polarization[5]; this is then locked into a magnetically silent, symmetric form by dehydration (diacetyl, red), and slowly used up by an NMR measurement that then becomes compatible with the timescales required for *in vivo* molecular imaging.

Despite the increasing strengths (and costs) of contemporary NMR/MRI magnets, the amount of spin alignment that these machines can provide remains woefully small. This reflects the weakness of magnetic resonance interactions, which under conventional conditions are orders-of-magnitude smaller than room-temperature energies. As a result, the difference between the lower- and higher-energy populations targeted by NMR spectroscopy is very small (Fig.1, left): at room-temperature equilibrium, only about one out of every 10^5 targeted spins will change its orientation on being inserted in the NMR/MRI magnet and thereby contribute to the observable signal. This is in stark contrast to what happens in optical spectroscopy, where usually every one of the targeted molecules is situated in a low-energy state, and can thus contribute to the observed electromagnetic absorption. A main effort in present-day NMR research focuses on developing methods that will mimic this latter state of affairs, yielding 'hyperpolarized' states where a majority of nuclear spins are aligned with one another (Fig. 1, right). Both Duckett and Warren build on this particularly exciting possibility, and exploit the dramatic sensitivity enhancements that metastable hyperpolarized states can yield in high-resolution liquid-state NMR spectroscopy — with ensuing potential applications to *in vivo* NMR imaging. To do so they rely on different and somewhat complementary aspects of so-called spin singlets, best exemplified by a state of the hydrogen molecule known as *para*-hydrogen (*p*-H_2).

Although frequently overlooked, hydrogen molecules come in two isomers: *ortho* and *para* forms. This isomerism is defined by the relative spin alignment of the two protons that make up a hydrogen molecule: nuclear moments are parallel to one another in *o*-H_2 and antiparallel in *p*-H_2. At ambient temperature, molecular hydrogen is a mixture of the two forms; but by cryogenic cooling it is possible to shift this equilibrium towards the energetically favoured *p*-H_2. The anti-alignment of the nuclear spins in the *para* isomer implies that although its overall bulk polarization will be zero, these molecules contain a very high degree of microscopic-level order — in the sense that the orientation of one of the protons will fully dictate the spin state of its bonded partner. Quantum-mechanically, the opposed — but otherwise indistinguishable — nuclear spins of *p*-H_2 have zero overall magnetic moment and form a singlet state, which can neither emit nor interact with the electromagnetic radiation involved in NMR experiments. It was shown years ago, however, that if such an anti-aligned state is subjected to a chemical reaction that abruptly breaks its symmetry and induces a chemical distinction between the two hydrogens[3,4], an unusual, highly polarized pair of proton spins results. An example of such a state is provided by the addition of *p*-H_2 to a C_a=C_b double bond; a reaction that under suitable conditions can boost the NMR signal arising from the added hydrogen pair by factors of 10^3–10^4. Although these sensitivity gains are outstanding, in general they will affect only a subset of the protons in the molecule, and require the design of a suitable olefinic substrate for their implementation.

Now, Duckett *et al.* have developed an original way to exploit *p*-H_2 as a source of NMR hyperpolarization but bypass the need for an irreversible, substrate-altering chemical reaction[1]. Instead, they demonstrate that binding together *p*-H_2 with a substrate in a transient organometallic complex, is enough to break the symmetry of the hydrogen molecule and induce a net transfer of polarization from the highly ordered *p*-H_2 'reservoir', to the disordered, unpolarized analyte of interest (Fig. 2a). Using such transient complexation, the authors extend the generality of the original *p*-H_2 signal-enhancement approach to molecules other than olefins, as illustrated for a variety of heterocyclic compounds with NMR spectroscopy signals that include not only proton→proton transfers, but also the hyperpolarization of other important NMR targets such as ^{13}C, ^{19}F and ^{15}N.

Besides its potential as an analytical tool, much of the excitement sparked by research into hyperpolarization has been driven by the promise these techniques show with regard to *in vivo* imaging and diagnosis[5]. Such applications demand that NMR hyperpolarizations survive for several minutes; a timespan that will often exceed the lifetimes of these metastable spin arrangements. This is the challenge addressed by Warren and co-workers[2], who propose new ways to extend the hyperpolarization lifetimes, and enable them to survive the long transit delays involved when attempting to use these super-signals in a clinical setting.

Like the Duckett study, Warren and colleagues also rely on singlet states and on their chemistry-driven dissociation — this time not to create nuclear spin order, but rather to preserve it. Indeed, owing to their lack of overall magnetic moment and ensuing absence of magnetic interactions, antiparallel singlet arrangements can be extremely long-lived. The proposed scheme exploits this by targeting a molecule that can be taken in and out of the highly symmetric structures associated with singlet states, by a simple, reversible chemical reaction — for instance via the gain or loss of a water of hydration (Fig. 2b). It is thus shown using diacetyl as a test case, that a magnetically active asymmetric hydrate can be hyperpolarized, dehydrated into a symmetric chemical structure that 'locks-in' the hyperpolarization, and then slowly shifted from these long-lived singlets back into magnetically active forms for observation over a timescale of minutes. This shifting of the chemical equilibrium is driven in the study by Warren *et al.* by the addition of acetone, but more biologically compatible systems involving temperature jumps and/or the action of native enzymes, could also be conceived.

Both of the methods described here deliver the kind of NMR sensitivities that would arise if measurements were carried out using magnets that are orders of magnitude stronger than today's conventional fields, or using conventional NMR magnets but after months of signal averaging. The excitement that such developments bring about is thus easy to understand. Still, issues remain to be solved regarding the generality underlying these NMR experiments. In particular, Warren and co-workers deal with a relatively confined chemical system amenable to full quantum-mechanical analysis, whereas the spin physics underlying the research of Duckett and co-workers is more difficult to define. Conversely, although a straightforward complexation reaction endows Duckett's system with immediate analytical applications, it is not entirely evident which chemical process would enable an optimal *in vivo* exploitation of the concepts demonstrated by Warren and co-workers. Yet in any case it is already clear that, in both instances, fascinating new fields of research straddling the roads of NMR spectroscopy and of chemistry have been opened. ❐

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MACROMOLECULAR CHEMISTRY

Polymers kept in the loop

Cyclic molecules have fascinated chemists for many years and researchers have now made nanoscale macromolecular 'doughnuts' that are large enough to be imaged with an atomic force microscope — providing direct visual proof of their cyclic topologies.

Scott M. Grayson

The fact that chemists can make a wide range of complex molecules with tailored connectivity and stereochemistry is testament to the impressive control they wield over ångström-scale molecular structure. But the ability to synthesize, functionalize and assemble nanometre-scale components in an analogous fashion has only been explored relatively recently, and the field of nanoscience remains in its adolescence.

The seeds for what has proved to be a large-scale exploration of nanoscale materials were sown in 1985, with the discovery of C_{60} and related fullerenes, followed in later years by other carbon-based nanomaterials such as nanotubes and graphene. Refinements in the preparation of inorganic nanomaterials such as metal nanoparticles, nanocrystals and quantum dots have provided an additional set of building blocks with a range of electronic, photonic and materials properties. In addition, modifications of biologically self-assembled components — such as the tobacco mosaic virus — offer a third route to well-defined nanosized objects. The relatively rigid structures and well-defined shapes of these materials make each of them ideal components for the assembly of nanostructures.

Although methods of preparing highly anisotropic nanostructures have been investigated, most of the readily available nanomaterials have a spherical or cylindrical morphology. Constructing nanoscale components with more complex architectures remains a challenge for the synthetic community. Now, a paper in *Journal of the American Chemical Society*, the result of a collaboration between the groups of Robert H. Grubbs at Caltech and Jean M. J. Fréchet at the University of California, Berkeley, describes the synthesis[1] of a particularly complex nanoscale morphology — macromolecular 'doughnuts'.

By preparing high-molecular-mass cyclic polymers with dendritic side-chains, the authors have synthesized doughnut-shaped macromolecules that can be visualized using atomic force microscopy (Fig. 1). These covalently assembled macromolecules have been prepared with molecular mass as high as 5,300,000 daltons, and atomic force microscopy confirms the overall macromolecular width of 35 to 40 nm with 'doughnut holes' between 5 and 7 nm in diameter. This elegant preparation of a rare nanoscale topology has built on a number of recent advances in synthetic control over polymer architecture.