

Nuclear Magnetic Resonance With No Magnets

Posted By [paulpreuss](#) On May 17, 2011 @ 12:32 pm In [Feature Stories](#) | [Comments Disabled](#)

Nuclear magnetic resonance (NMR), a scientific technique associated with outsized, very low-temperature, superconducting magnets, is one of the principal tools in the chemist's arsenal, used to study everything from alcohols to proteins to such frontiers as quantum computing. In hospitals the machinery of NMR's cousin, magnetic resonance imaging (MRI), is as loud as it is big, but nevertheless a mainstay of diagnosis for a wide range of medical conditions.

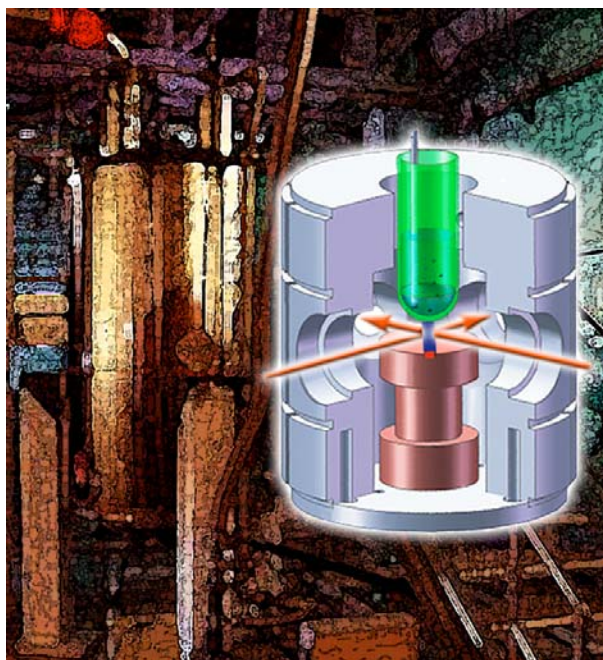
It sounds like magic, but now two groups of scientists at Berkeley Lab and UC Berkeley, one expert in chemistry and the other in atomic physics, long working together as a multidisciplinary team, have shown that chemical analysis with NMR is practical without using any magnets at all.

Dmitry Budker of Berkeley Lab's Nuclear Science Division, a professor of physics at UC Berkeley, is a protean experimenter who leads a group with interests ranging as far afield as tests of the fundamental theorems of quantum mechanics, biomagnetism in plants, and violations of basic symmetry relations in atomic nuclei. Alex Pines, of the Lab's Materials Sciences Division and UCB's Department of Chemistry, is a modern master of NMR and MRI. He guides the work of a talented, ever-changing cadre of postdocs and grad students known as the "Pinenuts" – not only in doing basic research in NMR but in increasing its practical applications. Together the groups have extended the reach of NMR by eliminating the use of magnetic fields at different stages of NMR measurements, and have finally done away with external magnetic fields entirely.

Spinning the information

NMR and MRI depend on the fact that many atomic nuclei possess spin (not classical rotation but a quantum number) and – like miniature planet Earths with north and south magnetic poles – have their own dipolar magnetic fields. In conventional NMR these nuclei are lined up by a strong external magnetic field, then knocked off axis by a burst of radio waves. The rate at which each kind of nucleus then "wobbles" (precesses) is unique and identifies the element; for example a hydrogen-1 nucleus, a lone proton, precesses four times faster than a carbon-13 nucleus having six protons and seven neutrons.

Being able to detect these signals depends first of all on being able to detect net spin; if the sample were to have as many spin-up nuclei as spin-down nuclei it would have zero polarization, and signals would cancel. But since the spin-up orientation requires slightly less energy, a population of atomic nuclei usually has a slight excess of spin ups, if only by a few score in a million.



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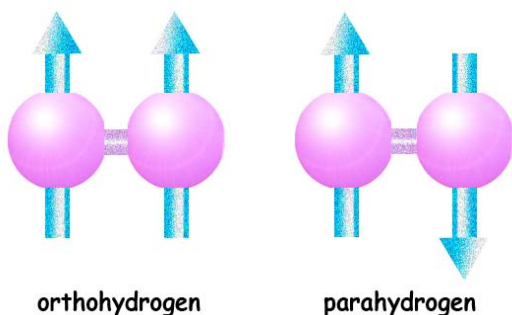
Spectroscopy with conventional nuclear magnetic resonance (NMR) requires large, expensive, superconducting magnets cooled by liquid helium, like the one in the background. The Pines and Budker groups have demonstrated NMR spectroscopy with a device only a few centimeters high, using no magnets at all (foreground). A chemical sample in the test tube (green) is polarized by introducing hydrogen gas in the parahydrogen form. The sample's NMR is measured with an optical-atomic magnetometer, at center; laser beams crossing at right angles pump and probe the atoms in the microfabricated vapor cell. (Click on image for best resolution.)

“Conventional wisdom holds that trying to do NMR in weak or zero magnetic fields is a bad idea,” says Budker, “because the polarization is tiny, and the ability to detect signals is proportional to the strength of the applied field.”

The lines in a typical NMR spectrum reveal more than just different elements. Electrons near precessing nuclei alter their precession frequencies and cause a “chemical shift” — moving the signal or splitting it into separate lines in the NMR spectrum. This is the principal goal of conventional NMR, because chemical shifts point to particular chemical species; for example, even when two hydrocarbons contain the same number of hydrogen, carbon, or other atoms, their signatures differ markedly according to how the atoms are arranged. But without a strong magnetic field, chemical shifts are insignificant.

“Low- or zero-field NMR starts with three strikes against it: small polarization, low detection efficiency, and no chemical-shift signature,” Budker says.

“So why do it?” asks Micah Ledbetter of Budker’s group. It’s a rhetorical question. “The main thing is getting rid of the big, expensive magnets needed for conventional NMR. If you can do that, you can make NMR portable and reduce the costs, including the operating costs. The hope is to be able to do chemical analyses in the field – underwater, down drill holes, up in balloons – and maybe even medical diagnoses, far from well-equipped medical centers.”



[2]

Hydrogen molecules consist of two hydrogen atoms that share their electrons in a covalent bond. In an orthohydrogen molecule, both nuclei are spin up. In parahydrogen, one is spin up and the other spin down. The orthohydrogen molecule as a whole has spin one, but the parahydrogen molecule has spin zero.

“As it happens,” Budker says, “there are already methods for overcoming small polarization and low detection efficiency, the first two objections to low- or zero-field NMR. By bringing these separate methods together, we can tackle the third objection – no chemical shift – as well. Zero-field NMR may not be such a bad idea after all.”

Net spin orientation can be increased in various ways, collectively known as hyperpolarization. One way to hyperpolarize a sample of hydrogen gas is to change the proportions of parahydrogen and orthohydrogen in it. Like most gases, at normal temperature and pressure each hydrogen molecule consists of two atoms bound together. If the spins of the proton nuclei point in the same direction, it’s orthohydrogen. If the spins point in opposite directions, it’s parahydrogen.

By the mathematics of quantum mechanics, adding up the spin states of the two protons and two electrons in a hydrogen molecule equals three ways for orthohydrogen to reach spin one; parahydrogen can only be spin zero, however. Thus orthohydrogen

molecules normally account for three-quarters of hydrogen gas and parahydrogen only one-quarter.

Parahydrogen can be enhanced to 50 percent or even 100 percent using very low temperatures, although the right catalyst must be added or the conversion could take days if not weeks. Then, by chemically reacting spin-zero parahydrogen molecules with an initial chemical, net polarization of the product of the hydrogenation may end up highly polarized. This hyperpolarization can be extended not only to the parts of the molecule directly reacting with the hydrogen, but even to the far corners of large molecules. The Pinenuts, who devised many of the techniques, are masters of parahydrogen production and its hyperpolarization chemistry.

“With a high proportion of parahydrogen you get a terrific degree of polarization,” says Ledbetter. “The catch is, it’s spin zero. It doesn’t have a magnetic moment, so it doesn’t give you a signal! But all is not lost....”

And now for the magic

In low magnetic fields, increasing detection efficiency requires a very different approach, using detectors called magnetometers. In early low-field experiments, magnetometers called SQUID were used (superconducting quantum interference devices). Although exquisitely sensitive, SQUID, like

the big magnets used in high-field NMR, must be cryogenically cooled to low temperatures.

Optical-atomic magnetometers are based on a different principle – one that, curiously, is something like NMR in reverse, except that optical-atomic magnetometers measure whole atoms, not just nuclei. Here, an external magnetic field is measured by measuring the spin of the atoms inside the magnetometer's own vapor cell, typically a thin gas of an alkali metal such as potassium or rubidium. Their spin is influenced by polarizing the atoms with laser light; if there's even a weak external field, they begin to precess. A second laser beam probes how much they're precessing and thus just how strong the external field is.

Budker's group has brought optical-atomic magnetometry to a high pitch by such techniques as extending the "relaxation time," the time before the polarized vapor loses its polarization. In previous collaborations, the Pines and Budker groups have used magnetometers with NMR and MRI to image the flow of water using only the Earth's magnetic field or no field at all, to detect hyperpolarized xenon gas (but without analyzing chemical states), and in other applications. The next frontier is chemical analysis.

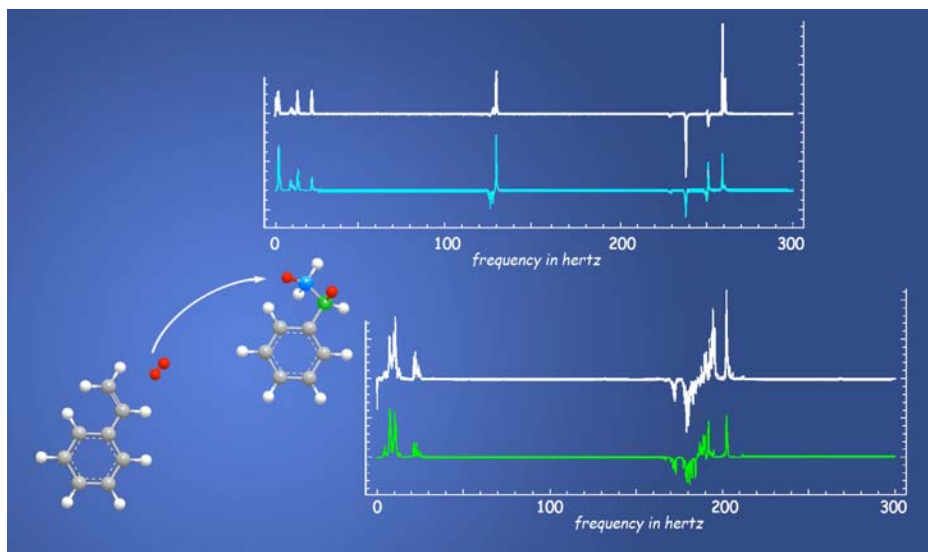
"No matter how sensitive your detector or how polarized your samples, you can't detect chemical shifts in a zero field," Budker says. "But there has always been another signal in NMR that can be used for chemical analysis – it's just that it is usually so weak compared to chemical shifts, it has been the poor relative in the NMR family. It's called J-coupling."

Discovered in 1950 by the NMR pioneer Erwin Hahn and his graduate student, Donald Maxwell, J-coupling provides an interaction pathway between two protons (or other nuclei with spin), which is mediated by their associated electrons. The signature frequencies of these interactions, appearing in the NMR spectrum, can be used to determine the angle between chemical bonds and distances between the nuclei.

"You can even tell how many bonds separate the two spins," Ledbetter says. "J-coupling reveals all that information."

The resulting signals are highly specific and indicate just what chemical species is being observed. Moreover, as Hahn saw right away, while the signal can be modified by external magnetic fields, it does not vanish in their absence.

With Ledbetter in the lead, the Budker/Pines collaboration built a magnetometer specifically designed to detect J-coupling at zero magnetic field. Thomas Theis, a graduate student in the Pines group, supplied the parahydrogen and the chemical expertise to take advantage of parahydrogen-induced polarization. Beginning with styrene, a simple hydrocarbon, they measured J-coupling on a series of hydrocarbon derivatives including hexane and hexene, phenylpropene, and dimethyl maleate, important constituents of plastics, petroleum products, even perfumes.



[3]

A molecule of parahydrogen hydrogenates a styrene molecule to form ethylbenzene. J-coupling reveals the position and orientation of the hydrogen atoms and the carbon-13 atoms to which they bond. The upper panel shows a simulated spectrum, in blue, of coupling between a hydrogen and a carbon in the methyl position. The actual experimental data are in white. The lower panel shows simulation of coupling in the methylene position, in green, with actual data in white. Simulation and

"The first step is to introduce the parahydrogen," Budker says. "The top of the set-up is a test tube containing the sample solution, with a tube down to the bottom through which the parahydrogen is bubbled." In the case of styrene, the parahydrogen was taken up to produce ethylbenzene, a specific arrangement of eight carbon atoms and 10 hydrogen atoms.

Immediately below the test tube sits the magnetometer's alkali vapor cell, a device smaller than a fingernail, microfabricated by Svenja Knappe and John Kitching of the National Institute of Standards and Technology. The vapor cell, which sits on top of a heater, contains rubidium and nitrogen gas through which pump and probe laser beams cross at right angles. The mechanism is surrounded by cylinders of "mu metal," a nickel-iron alloy that acts as a shield against external magnetic fields, including Earth's.

Ledbetter's measurements produced signatures in the spectra which unmistakably identified chemical species and exactly where the polarized protons had been taken up. When styrene was hydrogenated to form ethylbenzene, for example, two atoms from a parahydrogen molecule bound to different atoms of carbon-13 (a scarce but naturally occurring isotope whose nucleus has spin, unlike more abundant carbon-12).

J-coupling signatures are completely different for otherwise identical molecules in which carbon-13 atoms reside in different locations. All of this is seen directly in the results. Says Budker, "When Micah goes into the laboratory, J-coupling is king."

Of the present football-sized magnetometer and its lasers, Ledbetter says, "We're already working on a much smaller version of the magnetometer that will be easy to carry into the field."

Although experiments to date have been performed on molecules that are easily hydrogenated, hyperpolarization with parahydrogen can also be extended to other kinds of molecules. Budker says, "We're just beginning to develop zero-field NMR, and it's still too early to say how well we're going to be able to compete with high-field NMR. But we've already shown that we can get clear, highly specific spectra, with a device that has ready potential for doing low-cost, portable chemical analysis."

More information

"Parahydrogen-enhanced zero-field nuclear magnetic resonance," by Thomas Theis, Paul Ganssle, Gwendal Kervern, Svenja Knappe, John Kitching, Micah Ledbetter, Dmitry Budker, and Alexander Pines, appears in *Nature Physics* and is available online at <http://www.nature.com/nphys/journal/vaop/ncurrent/abs/nphys1986.html> [4]. Theis, Ganssle, and Pines are with Berkeley Lab's Materials Sciences Division and the UC Berkeley Department of Chemistry, as was Kervern, now at the University of Lyon. Knappe and Kitching are with the National Institute of Standards and Technology. Ledbetter is with UC Berkeley's Department of Physics, as is Budker, who is also a member of Berkeley Lab's Nuclear Science Division. This work was supported by the National Science Foundation and DOE's Office of Science.

More about Alex Pines, the "Pinenuts," and parahydrogen is at <http://newscenter.lbl.gov/feature-stories/2007/08/06/pines-talking/> [5].

More about the work of Dmitry Budker and his group on optical-atomic magnetometers is at <http://newscenter.lbl.gov/feature-stories/2010/09/14/putting-a-spin-on-light-and-atoms/> [6].

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