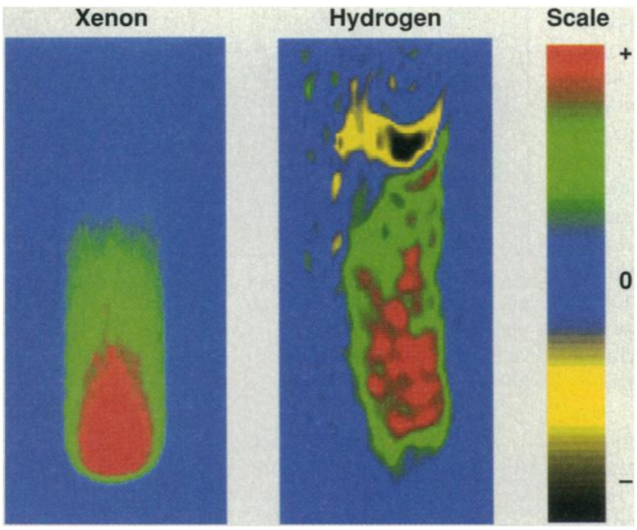
CHEMISTRY

"Amplifying" the Fine Details Of Molecular Structure Is a Gas

Proteins and other molecules are quiet—too quiet, say scientists straining to detect the signals that might reveal their structure. Certain atoms on molecules resonate at unique frequencies in a magnetic field, giving off signals that can indicate what these molecules are made of. But these signatures are inherently weak, even from the most abundant atoms, such as hydrogen. So researchers using this method, called nuclear magnetic resonance (NMR) spectroscopy, struggle to make out the fine details.

Now on page 1848 of this issue, a group of researchers from the University of California, Berkeley, Lawrence Berkeley National Laboratory, and Tel Aviv University in Israel report a way to get the atoms to sound off at a higher level. They can boost the resonance signals of hydrogen atoms at least twofold by using xenon gas as a "preamplifier." The xenon atoms are pretreated to give off a powerful magnetic signal, and they in turn raise the volume of the hydrogens when the two types of atoms come in contact. If the effect works with other atoms such as carbon-13—and the researchers say there's no reason why it shouldn't—NMR spectroscopists could bubble xenon gas into solutions spiked with proteins or other molecules and get a loud response.



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Higher sound. *(Left)* "Hyperpolarized" xenon gas gives off a high magnetic resonance signal in a solution containing hydrogen atoms; *(right)* 2 minutes later, that signal transfers to the hydrogens.

Scientists knew that xenon could give off a powerful NMR signal, but this is the first time they have transferred that power to another element. "It's a fantastic result," says G. Allan Johnson, a professor of radiology, physics, and biomedical engineering at Duke University Medical Center in Durham, North Carolina. "The applications in protein and molecular structure determination will be very high." The technique may also prove a boon to medical imaging, says Mitch Albert, an imaging expert at Brigham and Women's Hospital and Harvard Medical School in Boston. At present, magnetic resonance imaging (MRI) constructs images primarily from hydrogen signals. If a patient inhaled xenon, which is rapidly absorbed by the blood, it might increase the signal from less common atoms, revealing new information about tissues' chemical contents. Alternatively, if it boosts the hydrogen signal, it could increase the resolution of current MRI images.

Magnetic resonance takes place because certain types of atoms, or isotopes, have nuclei that act like tiny bar magnets, with two poles. When placed in an external magnetic field, these "nuclear magnets" attempt to align their axes with the magnetic field lines. They can't quite do it and instead wobble around those lines at a regular rate. The rate differs for each isotope: Hydrogen, for instance, rotates four times faster than carbon-13 does. And because these rates differ, each isotope emits an electromagnetic wave at a unique frequency when bombarded with a brief radio pulse.

Yet these signals are hard to detect. Although these nuclear magnets align roughly with the external field, their poles, known as up and down, often point in opposite directions like cars facing opposite ways on the same road. As a result, waves coming from these opposing nuclear magnets are out of phase: The peaks from one coincide with the troughs from the other, canceling each other out. What remains is a faint signal from the few excess up or down magnets, which can be as rare as one to 10 atoms out of every million. "It's only these excess spins in one orientation which contribute to the NMR signal," says Berkeley chemist Alex Pines, a coauthor on the current paper.

The Berkeley group, along with Tel Aviv chemist Gil Navon, wanted to exaggerate this magnetic imbalance to boost the signal. To tip the scales, they decided to use xenon gas. The magnetic orientation of xenon atoms, previous experiments had shown, could be imbalanced itself—a chain reaction starting with polarized light points the magnetic fields of most of the xenon atoms in the same direction. The common alignment of fields in this "hyperpolarized" xenon, the scientists thought, might tug other atoms, such as hydrogen, into alignment as well. To test that possibility, the researchers exposed a solution of benzene molecules—which are rich in hydrogen nuclei—to hyperpolarized xenon, either by allowing the gas to simply diffuse into the liquid or by bubbling it through.

To orient the hydrogens' magnetic axes, the xenon needed to overcome the magnetic influences of other atoms in the benzene molecules, which pull the hydrogens in various directions. And as the atoms in the xenon gas passed through the sample quickly, and were on average a long distance from each benzene molecule, they could give each hydrogen only a relatively weak tap in a particular spin direction. But because the gas was hyperpolarized, most of those taps pushed the same way. And they added up to a powerful effect, forcing a majority of the hydrogens to adopt the same orientation. When the group put the sample in an NMR apparatus, the result was an amplified signal.

The researchers expect that the xenon should be able to give an even stronger boost to the signal from proteins in solution. Xenon tends to be repelled by water, so in a water bath, Pines believes it should bind to water-free sites on proteins for a long period, giving it a greater chance to influence the orientation of neighboring magnetic fields in the molecule. The same effect might also might help researchers track proteins in the body with MRI, he says, as proteins are also bathed in a watery medium in the body.

If the technique does take to water as well as Pines hopes, that would be "quite exciting," says Alfred Redfield, an NMR spectroscopy expert at Brandeis University in Waltham, Massachusetts. But he notes that the technique faces several hurdles. First of all, the Berkeley group's technique is currently slow, requiring several minutes of exposure to the xenon gas for each NMR snapshot. Multiply that by the thousands of snapshots needed to compile enough information to determine the structure of a molecule, and it comes out to weeks of work, compared to the hours currently needed. Researchers must also show that the new signal enhancement effect works with atoms other than hydrogen.

Pines notes that efforts are already under way to overcome these obstacles. If they succeed, the achievement could resonate throughout chemistry and medical diagnostics.

–**Robert F. Service**