Chemical & Engineering News
Serving the chemical, life sciences and laboratory worlds

Science & Technology

November 22, 2010
Volume 88, Number 47
p. 36

Ultrasensitive Detection

Three groups use absorption to detect single molecules at room temperature

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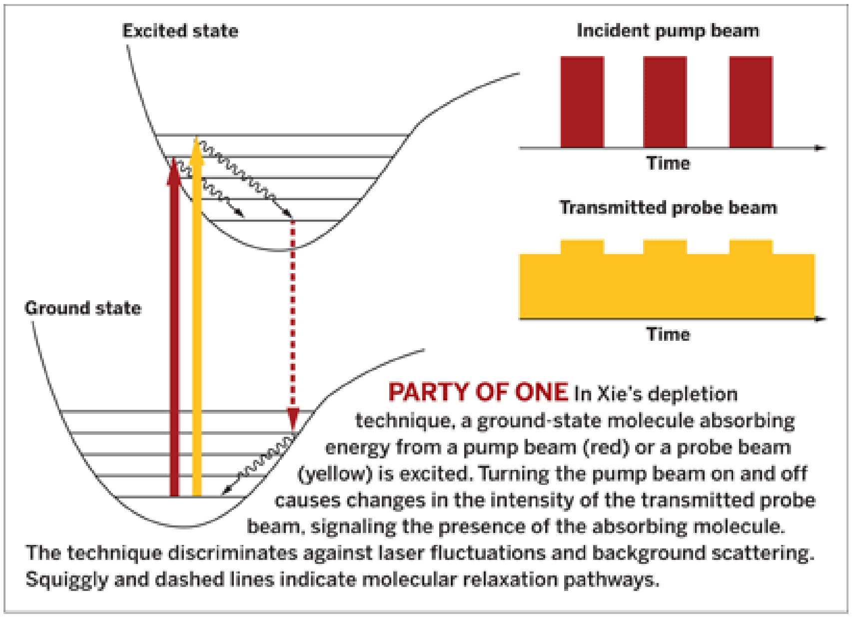

Adapted from *J. Phys. Chem. Lett.*

For the first time, scientists have detected single molecules at room temperature by their tendency to absorb light. Because the amount of light one molecule absorbs is so small, its detection requires very high sensitivity.

Single-molecule spectroscopy has up to now focused primarily on fluorescence emission, which is a lot easier to detect but is limited to molecules containing fluorophores. Detecting single-molecule absorption "is a major scientific advance since it will allow detection of weakly or nonfluorescent molecules and allow new types of measurements," says Gregory V. Hartland, a nanomaterials spectroscopist at the University of Notre Dame.

Optical detection of single molecules goes back to 1976, when Tomas B. Hirschfeld of Block Engineering, in Cambridge, Mass., used an optical microscope to image, at room temperature, individual protein molecules labeled with multiple fluorophores. In 1989, spectroscopist W. E. Moerner of Stanford University and a coworker detected single organic molecules by absorption at cryogenic temperatures. In 1990, techniques were developed to detect single-molecule fluorophores, first at cryogenic temperatures and then at room temperature. Since then, single-molecule fluorescence has been widely used.

Detecting single-molecule absorption at room temperature is much more challenging than detecting room-temperature single-molecule fluorescence and had never been achieved. Now, three groups have succeeded.

"It's very exciting to see absorption of single molecules at room temperature" a little more than 20 years after it was first done at low temperatures, Moerner says. "I expect that people will think of lots of ways to use this."

To detect single molecules at room temperature, single-molecule optics specialist Michel Orrit and coworkers at Leiden University, in the Netherlands, use a technique called photothermal microscopy (*Science*, DOI: 10.1126/science.1195475). They excite a molecule with a modulated heating laser; the excitation warms up nearby glycerol solvent molecules and causes a change in the solvent's index of refraction that the researchers detect with a probe laser.

At Harvard University, spectroscopist and microscopist X. Sunney Xie and coworkers use ground-state depletion microscopy (*J. Phys. Chem. Lett.*, DOI: 10.1021/jz1014289). In this technique, modulation of a pump laser tuned to a molecule's absorption band causes small changes in the intensity of a transmitted probe beam of slightly different wavelength. The method discriminates against variations in laser-beam intensities and background interference, making single-molecule sensitivity possible.

Nano-optics researcher Vahid Sandoghdar of the Swiss Federal Institute of Technology, Zurich, and coworkers directly measure the light transmitted through a single molecule (*J. Phys. Chem. Lett.*, DOI: 10.1021/jz101426x). This simple approach is similar to that used in freshman chemistry lab spectrophotometry experiments. To achieve single-molecule sensitivity, the researchers minimize sample inhomogeneities to reduce scattering and normalize the probe beam to a reference beam to account for laser fluctuations.

"Orrit's paper uses a significantly more novel approach than the others, which are essentially just approaches that use conventional apparatus and pay careful attention to noise sources," says Warren S. Warren, a biomedical imaging expert at Duke University. "But the general message of all three papers—that even though the signatures are weak, they are detectable—is an interesting one to convey."

With three methods for single-molecule absorption at room temperature now in hand, researchers are already looking toward overcoming other barriers. For example, they hope to figure out how to use absorption to determine the identity of single molecules, instead of just detecting single molecules whose identities are already known.

To identify single molecules, scientists would need to combine single-molecule absorption detection with spectroscopy so that "the absorption spectrum of a species serves as its characteristic signature," Sandoghdar says. "I am very optimistic that this will come soon."

Chemical & Engineering News
ISSN 0009-2347