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Inside Creative Minds

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The Clinical Spectrum

Medical diagnoses sometimes depend on the ability to trace or detect minute amounts of biological species. Now researchers at the General Motors Research Laboratories have developed a method of spectrometry using a tunable diode laser that could lead to simpler, less costly, non-invasive diagnostic techniques.

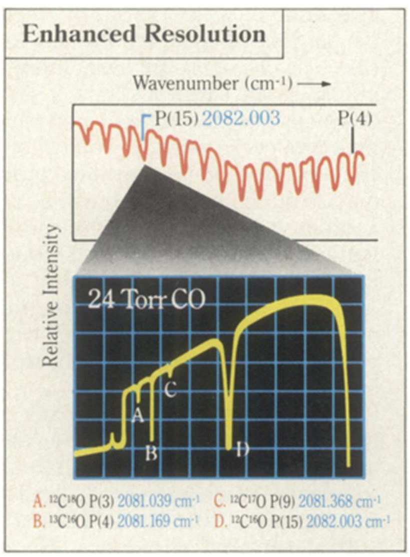


Figure 1: (Top) The absorption spectrum of CO obtained with a conventional spectrometer showing the P series rotation-vibration transitions separated by about 4 cm^{-1}. (Bottom) The diode laser spectrum centered at $^{12}C^{16}O$ P(15) region showing the complete resolution of $^{12}C^{17}O$ P(9), $^{12}C^{18}O$ P(3) and $^{13}C^{16}O$ P(4) transitions.

Figure 2: The second harmonic detection of the $^{13}C^{16}O$ and $^{12}C^{16}O$ as naturally present in exhaled human breath.

In the process of living and growing, the body routinely takes in chemicals in the air we breathe and the food we eat, uses them, and converts them into other chemicals. These chemical activities, therefore, are often very good indicators of the health of the body or of its individual systems. The detection and measurement of particular chemical species is also of value in environmental, scientific and engineering studies.

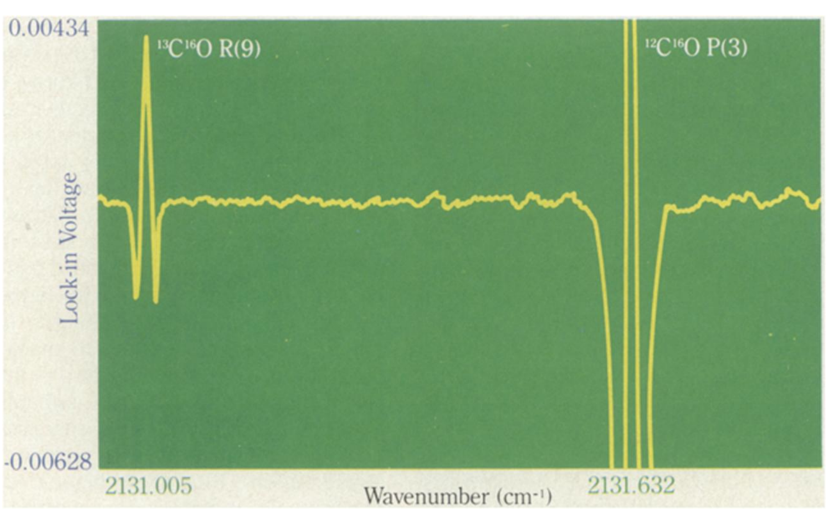
Radioactive isotopes of elements in these chemicals have been extensively used as tracers. Many investigations, however, preclude their use either because no suitable radioisotope is available, or because radiation exposure raises health or environmental concerns.

The use of stable, non-radioactive isotopes for detection and tracing predates that of radioisotopes. But routine application of stable isotopes has been hindered by the lack of a detection method as versatile and simple as the scintillation counting used for radioisotopes. Mass spectrometry is the traditional method of detection of stable isotopes, but it requires extensive sample preparation, expensive equipment, and a highly trained operator to distinguish and measure chemically different molecules of the same nominal mass—nitrogen gas $^{14}N^{14}N$ and carbon monoxide $^{12}C^{16}O$, for example.

It was this need for high resolution and greater versatility that prompted Dr. Peter S. Lee and Richard F. Majkowski to develop a system for stable isotopic tracer analysis based on the molecular absorption of infrared light. A tunable, single-mode diode laser, developed originally by the Physics Department of the General Motors Research Laboratories to measure automobile exhaust gases, was used as the IR emitting source in what has proved to be a remarkably sensitive spectrometer.

The infrared absorption spectrum of molecules normally consists of transitions between series of vibration-rotation energy levels. When an atom in a molecule is replaced by an isotope of the same element, there is a shift in the energy levels due to a change in mass. The resulting frequency shift in the transitions forms the basis of the laser spectroscopic analysis system.

In the case of carbon monoxide, for example, there are six possible forms of the molecule involving stable isotopes: $^{12}C^{16}O$, $^{12}C^{17}O$, $^{12}C^{18}O$, $^{13}C^{16}O$, $^{13}C^{17}O$, and $^{13}C^{18}O$. Consequently, there would be six sets of overlapping spectral lines. Within a region of 1 cm^{-1}, there can be lines from several isotopic molecules, with as little as 0.1 cm^{-1} or



Carbon monoxide in exhaled human breath.
The scale has been expanded to show the excellent signal-to-noise ratio for $^{13}C^{16}O$.
Other than removal of water vapor, no specific sample preparation or separation was needed.

less between adjacent lines.

This adjacency presents no problem for a diode laser system. The spectral resolution (the laser linewidth) is typically better than 10^{-4} cm^{-1}, which is orders of magnitude less than the isotopic line spacings. Since the diode laser is tunable, it can be centered in a region where the absorption lines of several isotopic molecules can be scanned within a single longitudinal laser mode (Figure 1).

In the initial experimental system, the source of the monochromatic IR radiation was a diode laser, made out of a single crystal containing layers of doped lead telluride and a lead-europium-selenium-telluride alloy. The IR light was collimated through a cell containing the sample to be studied and then focused onto an IR detector.

The cell was designed to have two optical path lengths that can be varied so that isotopic molecules with vastly different abundances can be determined from the measurement of the incident and transmitted laser intensities. U.S. Patent 4,684,805 covers this spectroscopic detection system.

The laser system can be made extremely sensitive using wavelength modulation and harmonic detection. Figure 2 shows the detection of $^{13}C^{16}O$ in exhaled human breath, where $^{13}C^{16}O$ is naturally present at a typical level of 1 to 10 parts per 100 million.

The present system can be used to measure stable oxygen isotopes in biological and organic samples that can be converted into CO. However, the method is applicable to any sample that can be converted into a gas with a suitable IR absorption spectrum.

"The use of radioisotopes as tracers is already well established," says Dr. Lee. "The potential is just as great for stable isotopes if more versatile analytical methods are made readily accessible.

"Packaged as a simpler, relatively inexpensive instrument, a tunable laser IR system could be adapted to many clinical tests—for fat malabsorption, ileal dysfunction, small-intestine bacterial overgrowth, alcoholic cirrhosis and liver function, lung function, nutritional assessment, and diabetes, to name a few.

"Diabetes could be diagnosed from the lung exhalate of a subject who had been fed a stable isotopically tagged sugar sample. No taking blood, no long waits, no radiation health and safety concerns.

"Simpler isotopic tracer measurements could broaden the scope of tracer methodologies, could supplement some of the radioisotope studies now common, and could have significant economic implications."

General Motors

GM MARK OF EXCELLENCE

THE MEN BEHIND THE WORK

Dr. Peter S. Lee (right) is a Senior Staff Research Scientist in the Biomedical Science Department at the General Motors Research Laboratories. He received his undergraduate degree in Chemistry from the National Taiwan University. Dr. Lee also holds a Ph.D. in Physical Chemistry from the University of Illinois at Urbana-Champaign. His current research interests at GMRL include the study of biosensors and laser spectroscopy along with his work in stable isotopes. Dr. Lee came to GM in 1977 from the University of Illinois Medical Center in Chicago.

Richard F. Majkowski was, at the time of the work described here, a Staff Research Scientist in the GMRL Physics Department. Both his B.S. and M.S. degrees are from the University of Detroit in Physics and Mathematics. His research interests have included emission spectroscopy, coherent optics, holography and laser spectroscopy. Dick joined General Motors Research Laboratories in 1955 and retired in September, 1987, to become a Professor of Physics at Lawrence Institute of Technology.