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Raman and CRDS isotopic resolution spectroscopy for biomedicine applications

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Abstract. SRS-sensor was developed for measuring absolute amount ratios of ¹³C/¹²C isotopes for medical application. Measuring absolute amount ratios of ${}^{13}C/{}^{12}C$ isotopes allows detection of Helicobacter pylori for medical diagnostics of human health. SRS method is used to measure the amount of carbon dioxide isotopes in exhaled air to detect Helicobacter pylori. This is used to determine influence of the bacterium on the occurrence of gastritis, gastric and duodenal ulcers. This paper includes methods and metrological characteristics for measuring isotopes ratios.

1. Introduction

Helicobacter pylori is a spiral-like gram-negative bacterium, one of the most frequent and persistent diseases in the world, such as gastric ulcer, lymphoma, stomach cancer, gastritis, and the World Health Organization has classified Helicobacter pylori as carcinogens in the first group [1].

Presence of Helicobacter pylori is not a disease of itself but is associated with several disorders of the upper gastrointestinal tract.

Several methods of detecting Helicobacter pylori exist.

The histological method has a sensitivity of 72-100 %, a specificity of 81-97 %. For carrying out such a method, qualified personnel and a morphological laboratory are required. The waiting time for results is a week, which is a significant drawback of this method.

The bacteriological method has 100 % specificity, but the sensitivity of this method requires a certain providing of a microbiological laboratory and qualified personnel.

Radionuclide methods for recording Helicobacter pylori based on urease activity. Urea labeled isotopes ¹³C, ¹⁴C is given to the patient. Urease Helicobacter pylori decomposes urea to carbon dioxide, while leaving the labeled carbon. Which diffuses into the blood, is exhaled via the lungs, and can be measured in the exhaled air.

¹⁴C is a radioactive isotope that has limitations in use and is strictly controlled, so it is less common than ¹³C isotope, which is not radioactive. When using urea ¹³C, samples are collected before and 30 minutes after ingestion. The ¹³C/¹²C ratio is measured in both samples. The result is expressed as the difference between the two measurements. Requirement in the initial value is due to the diet of

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patients with diuretic syndrome. For accuracy, the volume of urea taken ¹³C is 100ml. The amount of ¹³C of the isotope can be determined using a gas mass spectrometer, infrared or laser equipment. The sensitivity of this method is 99 %, specificity is 98 %.

IR-gas analyzers have high, but often insufficient selectivity.

Mass spectrometers have a high price and, due to the need for a vacuum, it is difficult to use outside the laboratory.

Measuring of $\delta^{13}C_{VPDB}$ allows exploring the actual issues of the modern world, such as global climate change, detection of falsification of food products, doping control, the determination of origin of explosives, drugs, petroleum products and natural gas, medical diagnostics of human health.

The application of CRDS for $\delta^{13}C_{VPDB}$ measurements gave an opportunity for making in situ, continuous $\delta^{13}C_{VPDB}$ observation in ambient conditions. Fundamentally, it can achieve accuracy similar to mass spectrometry [2].

This paper reviews a method for the analysis of human infection with Helicobacter pylori by measuring the ratios between ${}^{13}C/{}^{12}C$ isotopes in exhaled air. Existing methods of gas analysis do not always provide great speed or accuracy of analysis. Developed method can provide a high accuracy analysis of par with mass

2. SRS-sensor

The monostatic optical system with Cassegrain configuration was used for the experiment. The laser beam was moved into the region of atmosphere to be analyzed by a system of rotating mirrors. The probing was done at $\lambda = 261.7$ nm by utilizing solid state Nd:YLF laser with diode pumping and frequency conversion of the harmonics. The spectrometric channel is a double polychromator with dispersion addition and three detectors, for recording in nitrogen, methane, and hydrogen sulfide atmospheres. The polychromator is based of two concave holographic gratings. Verification of obtained data was done in Mendeleev Institute of Metrology. Verification was done by utilizing CRDS gas analyzer. Three samples of gases were prepared, on with isotopically pure ¹²CO₂, second one with ¹³CO₂ and the last one with a mixture of those gases. All samples were analyzed with CRDS gas analyzer, then with SRS-sensor. Obtained data was then compared.

3. CRDS calibration methods

During the experiment the accuracy of measurements of gas analyzer based on the principle of radiation damping spectroscopy in the resonator, which provide lower detection threshold and better speed than alternative methods.

CRDS-method allows to register a small absorption of radiation which passes through the sample. This makes it possible to measure the percentages of impurities at the level of ppb and ppt. It also became possible to measure the ratio of carbon isotopes ${}^{13}C/{}^{12}C$ in carbon dioxide on a par with isotope mass spectrometers.

When studying the absorption spectra of a substance with a small absorption coefficient in ordinary spectroscopy, it is necessary to increase the optical path length by placing the test substance in a multipath optical cell. Reflecting from its end mirrors, light repeatedly passes through it. In this case, we must take into account the loss of reflection of light from the mirrors. In the intracavity laser spectroscopy method, where the laser cavity plays the role of a multi-way cell, these losses are compensated by the amplification of light in its active medium. As a result, the sensitivity of the method increases sharply, which makes it possible to detect unprecedented low concentrations at levels of 104 atoms / cm^3 .

The recommended by the World Meteorological Organization expanded uncertainty of $\delta^{13}C_{VPDB}$ measurements in atmospheric air is 0,1 ‰. To ensure such quality of measurements it is necessary to determine the factors that affect measurements of $\delta^{13}C_{VPDB}$ and develop a method for making corrections.

There are several methods for decreasing the expanded uncertainty of $\delta^{13}C_{VPDB}$ measurements by CRDS: proper calibration, averaging time, correction for concentration dependence, and gas matrix effects.

Two different methods of calibration exist. Method used in conducted experiments is described by [3] and requires two or more CRM's with different molar fractions of ${}^{12}CO_2$ and ${}^{13}CO_2$. If two CRM's are used the calibration equations are

$$x_{at}^{12} = \frac{x_{2t}^{12} - x_{1t}^{12}}{x_{2m}^{12} - x_{1m}^{12}} (x_{am}^{12} - x_{1m}^{12}) + x_{1t}^{12}$$
$$x_{at}^{13} = \frac{x_{2t}^{13} - x_{1m}^{13}}{x_{2m}^{13} - x_{1m}^{13}} (x_{am}^{13} - x_{1m}^{13}) + x_{1t}^{13}$$

where

 x_{am} – measured ¹²CO₂ or ¹³CO₂ mole fraction value in analyzed material; x_{1m} – measured ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2m} –measured ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº2; x_{1t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM Nº1; x_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM N¹ · v_{2t} – reference ¹²CO₂ or ¹³CO₂ mole fraction value in CRM N¹ · v_{2t} – reference ¹²CO₂ · v_{2t} – reference ¹³CO₂

The $\delta^{13}C_{VPDB}$ in analyzed material is calculated by formula

$$\delta^{13}C_{VPDB} = \left(\frac{x_{at}^{13} / x_{at}^{12}}{0,011237} - 1\right) \cdot 1000$$

This method of calibration was chosen because it leads to lesser expanded uncertainty of $\delta^{13}C_{VPDB}$ measurements.

Also influence of gas matrix composition and averaging time were studied.

The absorption line broadening and narrowing of ${}^{12}CO_2$, and ${}^{13}CO_2$ molecules can lead to growth of expanded uncertainty of $\delta {}^{13}C_{VPDB}$. There are different causes of the absorption line broadening and narrowing such as random thermal motion and collisions. Different gas matrix compositions produce different absorption line broadening and narrowing which means different gas matrix compositions differ $\delta {}^{13}C_{VPDB}$ measurements [4].

Using this method of calibration, calculations and measurements with nitrogen and argon were performed (Table 1).

Table 1. The experimental gas matrix offset factors and a prediction based on calculated Lorenz profile heights.

	$\delta^{13}C_{VPDB(nitrogen)}$ - $\delta^{13}C_{VPDB(air)}$	$\delta^{13}C_{VPDB(argon)}$ - $\delta^{13}C_{VPDB(air)}$
Result of calculation	8,4	-40,1
Result of measurement	5,3	-42,6

4. Results

During the experiment with Raman sensor the spectra of analyzed gases were obtained. It was found that for ¹²CO₂ Raman shift is 1388 cm⁻¹, for ¹³CO₂ – 1370 cm⁻¹. Stokes shifts for these isotopes lay close to each other (Figure 1). Thus, we can conclude that this method provides spectral selection at the level of $\lambda/\Delta\lambda >> 1000$. We were able to reach this level of spectral selectivity by utilizing high resolution polychromators and high sensitive photomultipliers. Experiments were conducted in UV range of spectra which provides more accurate results, but conducting analysis is IR range is better as Stokes shifts are not as close to each other as in UV range. Ratios of ¹³C/¹²C were measured using CRDS analyzer PICARRO G2131-I [5].

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Figure 1. Raman shifts of CO₂ isotopes.

5. Conclusion

CO₂ isotopes have Stokes shifts located close to each other. The sensitivity of the Raman method is inversely proportional to the fourth power of the scattering wavelength, based on the difference in the Stokes shifts of the isotopes ¹²CO₂ and ¹³CO₂, equal to ($\Delta v = 2 \text{ cm}^{-1}$), which in the wavelength range of less than 2.0 µm (v>5000 cm⁻¹) The method allows spectral selection at a level v/ $\Delta v = \lambda/\Delta \lambda >> 1000$. The method provides spectral resolution, noise immunity and sufficient selectivity for gas analysis. Using the methods of SCR and CARS, it is possible to resolve isotopic shifts of the indicator substances of the simulator in the ultraviolet and infrared ranges at levels not less than 5 cm⁻¹, which allows to judge the isotopic composition of methane and determine the source of methane generation from the ¹³C/¹²C concentration ratio. The CRDS method makes it possible to measure impurities at the ppb and ppt levels and the ¹³C/¹²C ratio in carbon dioxide at a level with mass spectrometers. CRDS was a method of verification of data.

Acknowledgements

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