

Method for continuous measurement of nuclear para state enrichment in hydrogen gas with applications to hyperpolarized heteronuclear contrast agents

V. Vahdat¹, S. Kadlec¹, S. Rajaei¹, J. Yu¹, K. Emami¹, J. MacDuffie Woodburn¹, M. Ishii², F. Hammond¹, R. R. Rizi¹

¹Department of Radiology, University of Pennsylvania, Philadelphia, PA, United States, ²Johns Hopkins University, Baltimore, MD, United States

Introduction: MR imaging and spectroscopy require spin order in the species to be studied. This order is most commonly imposed by the application of a magnetic field, but it may also arise from spin-polarized photons (e.g. hyperpolarized gas imaging) or from rotational symmetry considerations in hydrogen. As the H₂ dimer approaches the moderately low temperature of tens of Kelvin in the presence of a paramagnetic relaxation site, the proton nuclei spontaneously order into the nuclear singlet state preferentially over the three triplet states. While this order cannot itself be imaged, it can be transferred to polarization of protons or heteronuclei through hydrogenation of a double bond [1]. The resulting images of hyperpolarized ¹³C and other heteronuclei show great promise for angiography, quantitative perfusion measurements and molecular imaging applications [2].

In our laboratory, we create parahydrogen using a continuous-flow apparatus shown in Figure 1. In order to quantify the fraction of H₂ in the para state during operation and to verify the quality of the reactant before use, we have developed a testing apparatus based on a measurement of the speed of sound in the gas. The speed of sound differs slightly in the two forms of hydrogen because of its dependence on the heat capacity which is in turn altered by the parahydrogen's restriction to exist in only the even-numbered rotational states ([2] contains a quantitative discussion of this effect, and a calculated ratio of para- to normal-H₂ speeds of sound is shown in Figure 2). At 20°C, where this experiment is performed, the speeds of sound differ by 0.81%.

Method: A drawing of our apparatus appears in Figure 1. It consists of two identical spherical resonant cavities of 2" diameter, machined from a single block of aluminum and temperature-controlled to approximately 20°C. The choice of a spherical cavity maximizes the separation between resonant modes. Each cavity is driven by a bare bimorph piezo element and a second element, positioned at 90° may be used to detect the resonating gas. One cavity is filled with the flowing parahydrogen and the other with ordinary H₂, regulated to be at the same pressure. Note that the speed of sound depends very weakly on pressure and any value between 0.1 and 3 bars can be used while introducing negligible variation. Comparison of the two cavities is advantageous because it cancels out pressure and temperature effects to a very high degree. The resonant frequency difference is measured, either by sweeping each cavity independently across its resonance, or by maintaining each cavity at resonance with a feedback circuit and digitally subtracting the counted frequencies.

Results and Discussion: Figure 3 shows a sample frequency difference between normal and parahydrogen created using our apparatus. The parahydrogen was stored in an aluminum cylinder with internal volume 300 cc and it was refreshed periodically in an effort to measure the decay of the para state in the storage cylinder. At the beginning of the experiment, both cavities were filled with ordinary hydrogen to verify that the frequencies were identical. After the

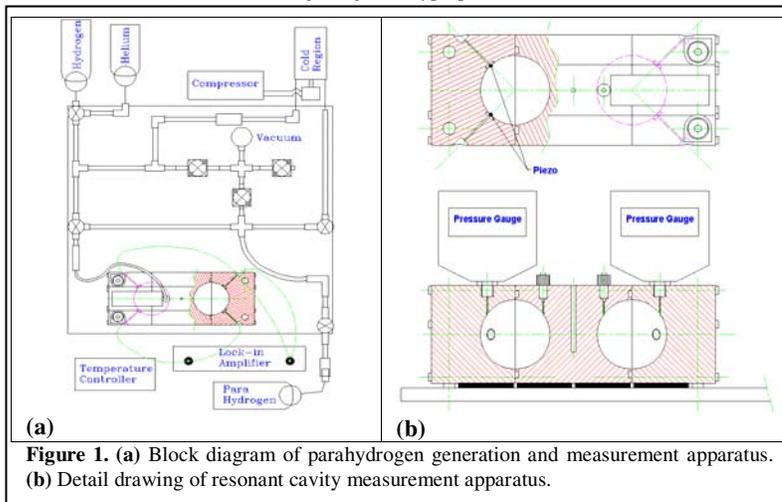


Figure 1. (a) Block diagram of parahydrogen generation and measurement apparatus. (b) Detail drawing of resonant cavity measurement apparatus.

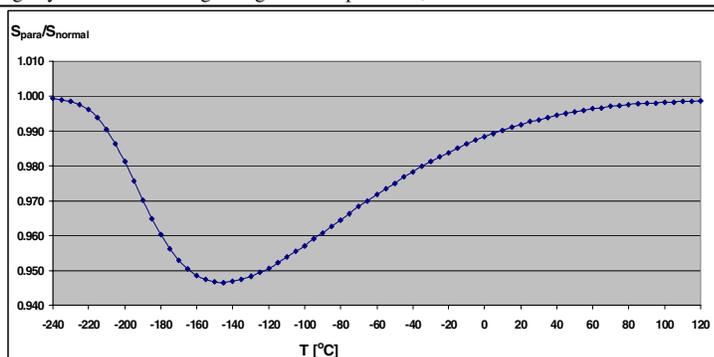


Figure 2. Calculated ratio of speeds of sound in pure parahydrogen to 'normal' (unenriched) hydrogen. Note that the maximum difference of >5% occurs at -150 C, but the difference of nearly 1% at room temperature is sufficient for accurate measurement of the difference.

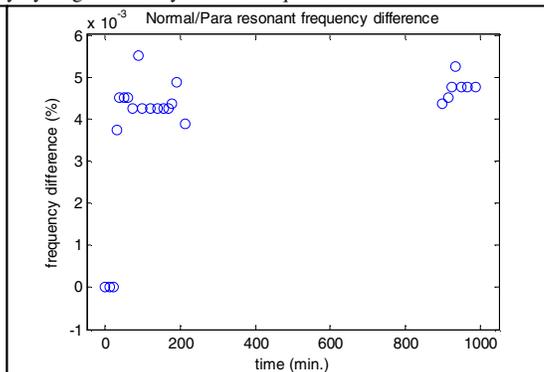


Figure 3. Measured difference in the speed of sound between normal and parahydrogen as a function of time. The first three measurements are done with normal hydrogen only for comparison.

experiment, a small, high-pressure sample tube was filled with first normal hydrogen and then the parahydrogen sample, both at 10 bars. Averaged NMR spectra at 4.7T showed that the normal sample signal was larger by a factor of approximately 3.6, corresponding to a para fraction of 79% +/- 6% in the para sample. The average measured frequency difference in our apparatus during the measurement was 0.485%, consistent with a para fraction of 70%. We note that the resonant frequency of each cavity is extremely stable, fluctuating by less than 0.02% during a measurement, but that the frequency occasionally shifts when the gas is evacuated and replaced. This may be due to introduction of an impurity and is currently under investigation. No decay in the para fraction was measured over two days of storage, indicating a lower bound on storage time in our cylinders of approximately one month.

Conclusion: Using the speed of sound difference in parahydrogen and ordinary hydrogen is an accurate way to detect parahydrogen and to calculate its fraction. This method becomes more valuable when there is no NMR spectrometer available and there is a need to measure parahydrogen fraction continuously while generating.

References:

- [1] Natterer et al. *Parahydrogen induced polarization*, Prog Nucl Mag Res 1997; 31: 293-315
- [2] Golman et al. *Parahydrogen-induced polarization in imaging: Subsecond C-13 angiography*, Mag. Res. Med. 2001; 46: 1-5
- [3] An excellent theoretical discussion appears at <http://scienceworld.wolfram.com/physics/Ortho-ParaHydrogen.html>