Improved throughput of hyperpolarized substrates by 1H → 13C cross-polarization DNP

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Target audience: Scientists interested in hyperpolarization in general, and eager to learn about new possibilities for ^{13}C *in-vitro* and *in-vivo* metabolic imaging.

Purpose: ^{13}C hyperpolarization offers new avenues for in-vivo metabolic imaging as it can provide sensitivity enhancements by factors exceeding four orders of magnitude. Recently the group of S. Nelson *et al.* has demonstrated the usefulness of the method for detecting human tumors and monitoring drug response.[1] A major drawback of ^{13}C hyperpolarization stems from the intolerably long preparation times for achieving decent polarization levels $P(^{13}C)>20\%$, which usually takes an hour or more. Sophisticated systems have been designed for parallel hyperpolarization of up to 6 samples per day.[2] However, routine preclinical or clinical implementation of ^{13}C hyperpolarization would require a much higher sample throughout, say about 24 samples per day with $P(^{13}C)>20\%$ at intervals of, say, 30 minutes

Methods: We show herein an efficient route for rapidly generating ^{13}C hyperpolarization on molecules such as pyruvate at polarization levels exceeding $P(^{13}C)>40\%$ in less than 30 minutes. The method begins by the rapid and efficient hyperpolarization of ^{1}H spins ($P(^{1}H)>80\%$ in less than 5 minutes) at low temperature and high field (T = 1.2 K and B_0 = 6.7 T) using the inexpensive polarizing agent TEMPOL, in combination with rapid $^{1}H\rightarrow{}^{13}C$ polarization transfer by cross-polarization (CP) at low temperature in typically less than 2 ms. If there are no ^{1}H spins in the (deuterated) molecule of interest, it is sufficient to add some H_2O to the frozen glassy solution.[3-5]

Results: Figure 1a shows the ^{13}C polarization build-up in [1-^{13}C]pyruvate T = 1.2 K and B_0 = 6.7 T with 50 mM TEMPOL as polarizing agent. The ^{13}C polarization builds up by applying CP every four minutes while the proton DNP is sustained by microwave irradiation. A polarization level $P(^{13}C)>30\%$ is attained in 16 minutes and $P(^{13}C)>45\%$ in 30 minutes. After dissolution and transfer to the liquid state, a significant part of the polarization is preserved, with $P(^{13}C)>40\%$. Figure 2b shows the relaxation of [1,2-^{13}C]acetate in solution hyperpolarized by CP-DNP.

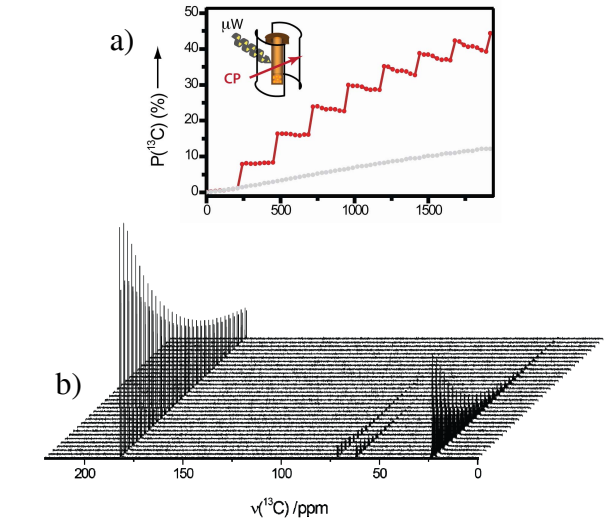

Figure 1. (a) ^{13}C polarization build-up without (light grey) and with (dark red) cross-polarization. (b) Decay of hyperpolarized [1,2-^{13}C]acetate signals measured every 5 seconds.

Discussion and Conclusion: Dissolution CP-DNP enables high throughput of highly polarized solutions and is fully compatible with *in-vivo* metabolic imaging studies. CP-DNP is best carried out with inexpensive nitroxide radicals such as TEMPOL and is also readily applicable to other low-γ nuclei such as lithium-6 or nitrogen-15.

References: [1] Nelson, S. *et al.* Sci Transl Med 2013, **5**, 198ra108 [2] Ardenkjaer-Larsen, J. H. *et al.* NMR Biomed. 2011, **24**, 927. [3] Jannin, S. *et al.* Chem. Phys. Lett. 2011, **517**, 234. [4] Jannin, S. *et al.* Chem. Phys. Lett. 2012, **549**, 99. [5] Bornet, A. *et al.* J. Phys. Chem. Lett. 2013, **4**, 111-114