PASADENA and the Hyperpolarization Renaissance

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The prospects for magnetic resonance imaging of metabolic events on the time scale of seconds relies on sensitivity improvements that are only possible by increasing the nuclear spin polarization from the several parts per million, characteristic of spin equilibrium under MRI conditions, to order unity. This goal is attainable by an increasing list of methods all of which must be implemented *ex vivo*. For *in vivo* purposes, this largely limits their use to sites in molecules with liquid-state T_1 values of tens of seconds, in order to allow time for injection into and transport within the organism. Among the hyperpolarization methods able to meet this challenge for small molecules of biomedical interest, PASADENA (parahydrogen and synthesis allow dramatically enhanced nuclear alignment) is unique both in taking place in the liquid aqueous environment and in requiring only several seconds. The spin order originates in the long-lived singlet relationship of the two protons of dihydrogen, previously equilibrated at low temperature, and is convertible to observable spin magnetization after catalytic molecular addition to an unsaturated bond. The proton sites in the product need to be magnetically inequivalent and have a resolvable spin-spin coupling.

Clearly, these conditions restrict PASADENA to a subset of those species of potential interest as hyperpolarized contrast agents. Much of our recent effort has focused on expanding the domain of applicability. In addition to a suitable precursor, a suitable network of scalar couplings is needed in the product in order to transfer the spin order to polarization on the target site, typically ^{13}C or ^{15}N. For the case of the two nascent protons (other sites deuterated) and one such target spin, we have developed design strategies which together efficiently cover the range of couplings present in diverse metabolites. Similar spin gymnastics, but run in reverse, points the way to efficient preparation of long-lived proton singlet states, an intriguing alternative way to store spin order during metabolism, including order which originates from other hyperpolarization methods. Transfer of the hyperpolarization of a heteronucleus to protons for detection is another strategy now demonstrated with PASADENA, but of general relevance.

Carboxylic acids form a large class of metabolites with1-^{13}C succinate as a prototypical case. The dephasing of 1-^{13}C coherence due to chemical exchange between ionization states was avoided by working at pH 3, where only the doubly protonated acid form is present. This low pH proved suitable for the measurement of the J couplings, for the PASADENA chemistry and for the spin order transfer. After neutralization to pH 7, the T_1 is 27 s in H_2O and 56 s in D_2O. These times are encouraging for the prospect of following uptake and metabolism, both in the normal metabolism of certain tissues (e.g. kidney) and in brain tumor, where transport of succinate and/or its metabolites serves as a biomarker for a compromised blood-brain barrier.

An appealing aspect of PASADENA relative to other hyperpolarization methods is its easy portability. Parahydrogen in the gas phase at 30 atm equilibrates with a time constant in excess of a week at ambient temperature with no applied field. The catalyst can be stored indefinitely either dry or frozen in solution. The experimental work on spin order transfer to ^{13}C has been done primarily at 1.8 mT, readily supplied by a lightweight electromagnet. The heteronuclear pulse sequences needed for this purpose were initially designed with the usual multiply-rotating frame approximation. We find that this is not adequate for a quantitative description. The Larmor frequencies are low enough that isotope selectivity of pulses is imperfect. Furthermore, at these low frequencies, the action of a pulse as a rotation in spin space depends not only on its phase in the rotating frame, but additionally on the phase of the carrier wave at the beginning of the pulse. Pulse envelope functions have been developed to mitigate both of these effects. Exact calculation in the laboratory frame allows for optimization and comparison with the ideal behavior.