

Expanding the Reach of Parahydrogen-Derived Hyperpolarization

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NMR is an insensitive technique due to poor alignment of the magnetic nuclei with the applied magnetic field. Equilibrium polarization is typically on the order of a few spins per million even in very strong magnets. PASADENA (parahydrogen and synthesis allow dramatically enhanced nuclear alignment)¹ is a method of generating nuclear spin hyperpolarization of order unity in seconds in fluids thus increasing the sensitivity of NMR many thousand fold. Recent developments have focused on hyperpolarization of sites with long T_1 by efficient conversion of the singlet state of the nascent proton pair to polarization of a heteronucleus not directly bound to protons by way of the scalar couplings among these three spins²⁻⁴. In principle, pulse sequences are now available to achieve unity hyperpolarization in such systems so long as the J couplings exceed T_2^{-1} . In practice, the limitations of this simple picture are still being explored for molecules of interest.

One practical issue is that, in order to achieve instrument simplicity and portability, a low field (1.8 mT) is used for the hydrogenation and spin order transfer. Desirable pulse lengths are comparable to several Larmor periods. One consequence is that the rotating frame approximation is inadequate to calculate the spin evolution. When linearly polarized pulses are used, choosing pulse lengths that are multiples of half the Larmor period mitigates some of the dependence of nutation angle on carrier phase. Still another issue peculiar to low field is that pulses at the Larmor frequency of one isotope cause appreciable nutation of other isotopes. We are able to moderate crosstalk between pulses aimed at different isotopes and further reduce dependence of the pulse on the carrier phase by shaped pulses. By implementing these ideas in the low-field tune-up procedure for PASADENA hyperpolarization of 1-¹³C-succinic acid-d₂, we have improved the C1 polarization to 28%, substantially higher than was achieved with earlier pulses using the same pulse spacings⁵. Sequences for both high and low pH have now been demonstrated, avoiding the region of intermediate carboxyl proton exchange⁴.

In many molecules of interest, other spins are present which call into question the efficacy of sequences designed with only three spins in mind. For example deuterons are introduced to increase the T_1 ⁴. Exact (lab frame) simulations with and without their inclusion indicate that, for typical proton-deuteron couplings, they are effectively decoupled by π pulses shaped to be selective for inversion of protons and the target nucleus. Another example is incorporation of fluorocarbon moieties, as has proven useful to achieve amphiphilic binding properties and labeling of lipids⁵. Effective decoupling of ¹H and ¹⁹F is also possible by using π pulses that are at least comparable in length to the period of the beat between the two Larmor frequencies. A tougher challenge is the case where protons other than those added as parahydrogen exist in the product molecule. These may be desirable for synthetic simplicity or so that they can be used for high-sensitivity detection after hyperpolarization transfer from the heteronucleus. At the low field of the current PASADENA apparatus, chemical shifts are negligible and cannot provide a basis for selective decoupling. One strategy that has been shown to mitigate the decrease in polarization due to the additional proton-proton J couplings is to numerically search for optimum pulse spacings starting from sequences that are designed for the three-spin case. We describe calculations and experimental examples of such strategies using ¹³C PASADENA.

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