Multiplet Asymmetry and Multi-Spin Order in Liquid-State NMR Spectra of Hyperpolarized Compounds

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Introduction: NMR spectroscopy with DNP hyperpolarized metabolites has become well established in biomedical NMR, since the pioneering studies of Golman and coworkers (*1, 2*). These investigators have typically used compounds with selective enrichment of a single target spin ½ nucleus *e.g.* [^{13}C] urea or [1-^{13}C] pyruvate, but have also observed hyperpolarization of other, secondary, nuclei, at natural abundance, whose spectra may then also be recorded, albeit at lower SNR. If the primary and secondary nuclei are scalar coupled, multiplet asymmetry is observed, from which the polarization of the primary nucleus may then be estimated *in situ*. In the case of a heteronuclear AX system, such as the ^{15}N doublet of [^{13}C] urea, the asymmetry is due purely to hyperpolarization, and the measurement is straighforward. For a homouclear two-spin system, with appreciable AB character, such as doubly labelled [1, 2 -$^{13}C_2$] pyruvate, the two doublets are asymmetric even without hyperpolarization, whose estimation then requires a more sophisticated analysis. In this abstract we present theoretical calculations aimed at facilitating this, and also point out that the multiplet asymmetry from hyperpolarization is due to the creation of multi-spin order (*3*).

Methodology: Calculations were done using standard density matrix methods (*4*) augmented by operator expansions (*3, 5*). Chemical shift difference (δ) and scalar couping (J) parameters were kindly provided by Dr. Albert Chen, from measurements at 14.1 tesla. The temperature for a desired degree of polarization was determined from the equation $P_{\pm} = ½(1 \pm \tanh(\omega_0 / 2kT)$ for the Boltzmann populations a spin ½ system, and then applied to the equilibrium density matrix $\rho = \exp(-H / kT)$ where H is the spin Hamiltonian excluding J coupling, which does not in fact contribute to the level populations. Free induction decays were calculated by evolving the density matrix in time with the full Hamiltonian followed by application of artificial 3 Hz line broadening.

Results and Discussion: The polarized equilibrium density matrix of doubly labelled [1, 2 -$^{13}C_2$] pyruvate is expressible as a sum of the identity plus 3 spin operator terms: the magnetizations I_{z1} and I_{z2}, plus the two-spin order term $I_{z1}I_{z2}$. Figure 1 shows the simulated room temperature spectrum of doubly labelled pyruvate at 3.0 tesla; the appearance of the spectrum is independent of pulse tip angle. The higher intensity of the inner doublet members results purely from the partial AB character of the spin Hamiltonian. Figure 2 gives the spectrum at 15% polarization and for a pulse tip of 5 degrees. Note the marked asymmetry, corresponding to an increased intensity of the upfield member of each doublet. This increase is due entirely to the two-spin order term of the density matrix; and its appearance is strongly dependent upon tip --being most apparent at small angles, and disappearing completely at 90 degrees, due the complete conversion of two spin order into double and zero quantum coherences, which are invisible in a conventional pulse and acquire experiment. Similar variations in spectral character with tip angle have been noted in NMR studies, at sub-kelvin temperatures (*6*). Although polarization cannot be directly read from the intensities, a nomogram serving this purpose is easily constructed from the type of calculation shown. The fact that the upfield component of each doublet enhances may be seen intuitively from an energy level diagram, which shows that these components both originate from the lowest energy spin state, $|\alpha\alpha\rangle$. Figure 3 gives an expanded scale view of singly labelled [1-^{13}C] pyruvate, showing the doublet splitting due the natural abundance of ^{13}C at C-2; the nutation is also 5 degrees. The intensities lowfield C-2 doublet match those of doubly enriched pyruvate, suggesting a measurement *in situ* available in studies with singly labelled pyruvate.

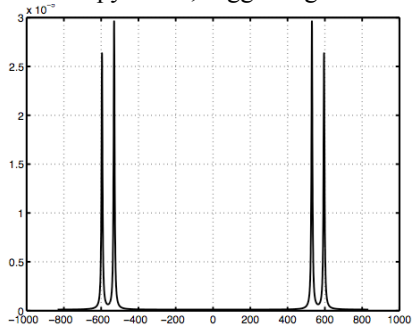

Figure 1

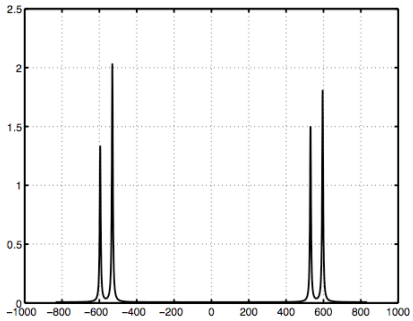

Figure 2

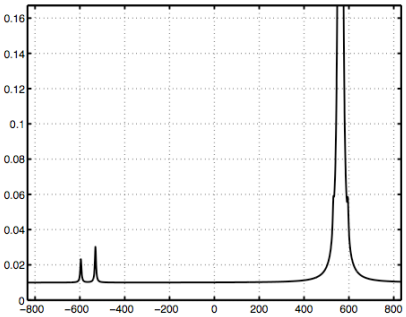

Figure 3

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