

Time evolution of [1,2-¹³C]Pyruvate doublet asymmetry in hyperpolarized ¹³C MRS

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Background: In-vivo hyperpolarized ¹³C Magnetic Resonance Spectroscopy (MRS) allows the interrogation of multiple key metabolic pathways, with applications in studying cancer metabolism, cardiovascular pathologies and other metabolic disorders. Absolute quantitation is desirable for fully interpreting in-vivo imaging data, and a necessary parameter is the liquid-state polarization of the injected substrate. Asymmetry of the C₂ doublet, arising from 1% naturally abundant [1,2-¹³C]Pyr in any hyperpolarized [1-¹³C]Pyr sample, has been suggested as a direct measure of the instantaneous C₁ polarization¹. The unexpected finding was that the time evolution of the asymmetry parameter seemed to evolve independently of the eventual thermal equilibrium value given by the residual J_{CC} strong coupling effects. Last year we proposed an ad-hoc model for the asymmetry by assuming that the peaks of the doublet had independent apparent T₁ relaxation times². Here we present a more complete theory in which the combination of dipolar coupling of carbon and adjacent protons, dipolar coupling between carbon nuclei and chemical shift anisotropy (CSA) interactions fully account for the observed time evolution of asymmetry.

Theory: The full spin density operator for an I-S spin system at equilibrium is given by $\hat{\sigma}(t) = \frac{1}{4} \hat{E} + \langle I_z \rangle(t) \hat{I}_z + \langle S_z \rangle(t) \hat{S}_z + \langle 2I_z S_z \rangle(t) 2\hat{I}_z \hat{S}_z$. While the 2I_zS_z term is negligible at normal thermal equilibrium, it can be significant in the hyperpolarized case and is the dominant source of asymmetry of the doublet peaks. The asymmetry parameter for the C₂ doublet, $a_{c2} = (\text{inner peak} - \text{outer peak}) / (\text{inner peak} + \text{outer peak})$, after a non-selective RF pulse of flip angle β is:

$$a_{c2}(t) \approx \left(\frac{\langle I_z \rangle(t) + \langle S_z \rangle(t)}{2\langle I_z \rangle(t)} \right) \sin \theta + \left(\frac{\langle 2I_z S_z \rangle(t)}{\langle I_z \rangle(t)} \right) \cos \beta, \text{ with } \sin \theta = J/\Delta\Omega = 0.056 \text{ for } [1,2\text{-}^{13}\text{C}]\text{Pyr at } 3\text{T. In the case of spins with similar longitudinal relaxation}$$

rates, the first term approximates to a constant, and the I_z and 2I_zS_z terms dominate. From the Solomon equations, the time evolution of I_z, S_z, and 2I_zS_z are related by a matrix, R, containing the relaxation and cross-relaxation rates (Fig. 1a,b). We used Wangness-Bloch-Redfield (WBR) relaxation theory³ to find analytic solutions to the elements of R by including three sources of relaxation in the Hamiltonian, 1) C_{1,2}-H dipolar coupling, 2) C₁-C₂ dipolar coupling, and 3) CSA of the C_{1,2} nuclei. Fig 1c gives these expressions in terms of the corresponding T₁ decay times.

Simulations and Experimental Results:

Simulations and experimental data (80 mM [1-¹³C]Pyr hyperpolarized to ~25% using an Oxford Instruments HyperSense system) acquired with a 32μs hard RF pulse, 5.6° flip angle on both C₁ and C₂ resonances with TR=3s are shown in Figure 2. For simulations, we used [1,2-¹³C]Pyr parameter values estimated from the literature^{4,5} of τ_c=3ps, r=1.1Å, T_{1DDCH1,2}=80/70s, T_{1DDCC}=260s and T_{1CSAC}=200s.

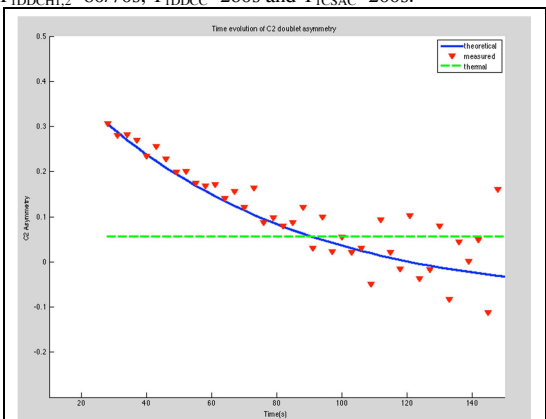
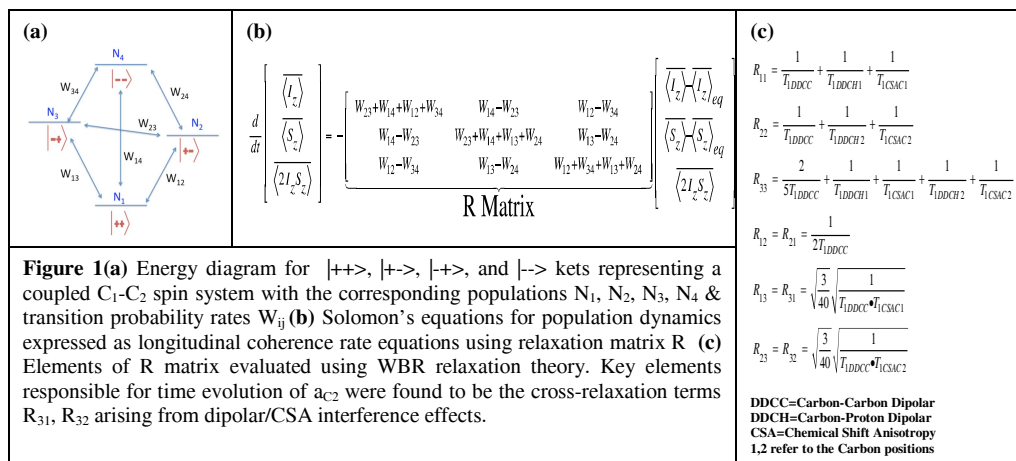


Figure 2. Time evolution of a_{c2} for a hyperpolarized pyruvate experiment: Theoretical (blue line) and measured (red triangles). Initially governed by the C₂-H dipolar interactions, the dipolar/CSA interference effect dominates later evolution to drive the asymmetry beyond the thermal equilibrium value (green dotted line).



Conclusions: The theoretical model and experimental data fit well, and a key feature, not previously appreciated, is the cross-relaxation between longitudinal coherences occurring due to dipolar/CSA interference effects⁶. For hyperpolarized [1,2-¹³C]Pyr, the time evolution of C₁, C₂ doublet asymmetry is characterized by three effects: (1) initial rapid relaxation at twice the rate of T_{1C1} (or T_{1C2}) from the decay of 2I_zS_z term due to H-C dipolar relaxation (could also include paramagnetic effects), (2) evolution past the thermal equilibrium value as a result of C-C dipolar/CSA cross-relaxation effects, and (3) decay to the thermal equilibrium value given by the residual strong coupling characteristics of the C-C J coupling. During the ~2 min time course of a typical in vivo hyperpolarized ¹³C experiment, factors (1) and (2) dominated the measured asymmetry values.

For use with absolute quantitation, the field dependence of the CSA T₁ relaxation implies that the C₂ doublet asymmetry at any time point can be used to estimate the instantaneous C₁ polarization only if the complete time history of the sample as it exits the polarizer (magnetic field vs time) is known.

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