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J-Coupling Nuclear Magnetic Resonance Spectroscopy of Liquids in nT Fields

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Nuclear magnetic resonance (NMR) has become indispensable for physics, chemistry, biology, and medicine. High magnetic fields of up to 20 T flux density impose serious technical demands on field homogeneity necessary to resolve line widths of a few hertz. At ultralow magnetic fields around 1 μT, line widths of 1 Hz and less are easily achieved.[1,2] The corresponding low Larmor frequencies prohibit the use of narrow-band radio frequency circuits, but amplitude and precession of the nuclear magnetic moments can be detected with a SQUID (Superconducting Quantum Interference Device).[3] SQUIDs are very sensitive magnetic sensors measuring the precession of a nuclear paramagnetic moment in a broad band receiving mode, enabling the novel simultaneous detection of the precession of different nuclei, such as ^{1}H and ^{31}P. At low fields, chemical shifts in liquids are negligible, and the spectra reflect predominantly the electron-mediated scalar interaction.[4] To demonstrate the potential and limits of heteronuclear *J*-coupling spectroscopy, we present spectra of 2,2,2-trifluoroethanol and trimethyl phosphate. Following recent pioneering works,[1,5] the detection fields were further decreased, and the instrumental spectral resolution was improved to 50 mHz at 100 Hz Larmor frequency.[2] This enabled a detailed numerical analysis of *J*-coupling-dominated spectra in the nT range.

The liquid sample was kept at room temperature and polarized for 2 s by a magnetic field of 250 μT. After switching off the polarizing field, the sample was left in a 2 orders of magnitude weaker detection field, which was oriented perpendicular to the polarization field. The precession of the sample's nuclear magnetic moment about this field was detected by a low T_c SQUID gradiometer.[6] The signal was Fourier transformed to obtain the spectra. The whole setup was operated in a magnetically shielded room of less than 10 nT residual field.[7] To adapt the well-known numerical analysis of high-field spectra,[8] the presented ultralow field experiment is analyzed in greater detail; the polarization field, pointing in the *x*-direction, was perpendicular to the detection field, pointing in the *z*-direction.[2] After switching off the polarizing field, the magnetization relaxes toward the *z*-axis due to the detection field. The SQUID measures the *x*-component as an oscillating signal. This is equivalent to the usual high field case, where the initial polarization directed along *z* is rotated into the *x*−*y*-plane, for example, by a 90° pulse. However, all relevant operators are in the laboratory frame and not in the rotating frame. The relevant parts of the Hamiltonian for *k* nuclei are therefore given by

$$\hat{H}_x = \sum_k \omega_k^{(p)}\, \hat{S}_{kx} + \sum_{k<j} J_{kj}\, \hat{S}_k \hat{S}_j \tag{1}$$

where J_{kj} are the strengths of the mutual spin−spin couplings, and $\omega_k^{(p)}$ are the individual Larmor frequencies of the spins according to the polarizing field. Assuming a sufficiently long polarizing time, the system will reach thermal equilibrium in the polarizing field of 250 μT. Applying the high temperature approximation and considering that in the applied polarization field the spin interactions are much smaller than the Larmor frequencies $\omega_k^{(p)}$, the initial density matrix ρ_0 is given by

$$\rho_0 = \sum_k \omega_k^{(p)}\, \hat{S}_{kx} \tag{2}$$

where constant terms have been neglected. After turning off the polarization field at $t = t_0$, the spins evolve in the much weaker detection field directed along *z*. The Larmor frequencies $\omega_k^{(d)}$ of the different nuclei are very close (similar to strongly coupled homonuclear systems in high-field NMR), and their separation is of the same order as the *J*-coupling energies. The Hamiltonian for $t \geq t_0$ includes therefore (a) the full scalar coupling, and (b) the Zeeman interaction of the different nuclei in the detection field with the frequencies $\omega_k^{(d)}$

$$\hat{H}_z = \sum_k \omega_k^{(d)}\, \hat{S}_{kz} + \sum_{k<j} J_{kj} \hat{S}_k \hat{S}_j \tag{3}$$

The signal $I(t)$ is given by the expectation value of the transversal component of the magnetization of the different nuclei:[4]

$$I(t) = \mathrm{trace}(\rho(t) \sum_k \gamma_k \hat{S}_{kx}),\ \rho(t) = \exp(-i\hat{H}_z t)\rho_0 \exp(i\hat{H}_z t) \tag{4}$$

The Larmor frequencies of ^{1}H at different detection fields were determined by measuring distilled water prior to the experiments.

J-coupling constants were determined by high-field measurements at 500 MHz to ^3J(H,F) = 8.8 ± 0.3 Hz and ^4J(H,F) < 0.1 Hz in trifluoroethanol, and to ^3J(H,P) = 11.0 ± 0.5 Hz in trimethyl phosphate. Larmor frequencies were referenced to 1 μT with 42.57 Hz for ^{1}H, 40.05 Hz for ^{19}F, and 17.23 Hz for ^{31}P. The stick spectra were calculated using eq 4. Stick spectra were convolved using T_2 values between 0.5 and 1.2 s until the best visual fit to the experimental data was given.

Spectra of 2,2,2-trifluoroethanol acquired at detection fields between 444 nT and 3.34 μT are shown in Figure 1. The spectra were simulated as an (A_3B_2B') system. B′ refers to the uncoupled OH group. Note that the spectrum at 993 nT was displayed already in,[2] where the vertical axis erroneously was scaled an order of magnitude too high.

Spectra of trimethyl phosphate exhibit two major groups of proton signals (Figures 2 and 3a). The spectra were simulated as an (AB_9) system. Although the transition frequencies were too close to be separated, the frequency window allowed the differentiation of two additional groups of transitions (Figure 2, arrows). To analyze the dependence of the spectral separation Δ of the two main peaks from the detection field, the trimethyl phosphate spectra were simulated in steps of 10 Hz and broadened with a T_2 of 0.3 s (Figure 3b).

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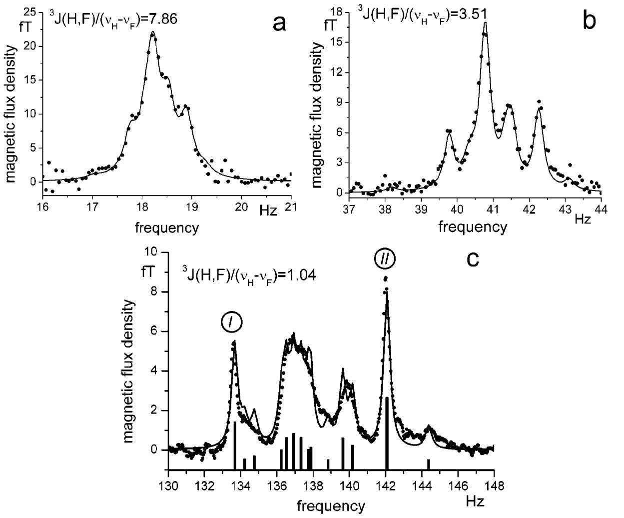

Figure 1. 2,2,2-Trifluoroethanol at (a) 444 nT, (b) 993 nT, and (c) 3.34 μT. The solid line was calculated by convolving the stick spectra with a T_2 of 1 s (a, b) and 0.78 s (c). The Larmor frequencies of uncoupled ^{19}F (*I*) and ^{1}H (*II*) nuclei were determined by a simulation with ^3J(H,F) = 0 Hz.

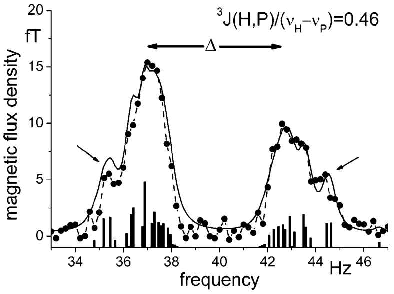

Figure 2. Trimethyl phosphate at 937 nT. The solid line was calculated by convolving the stick spectra with a T_2 of 0.55 s.

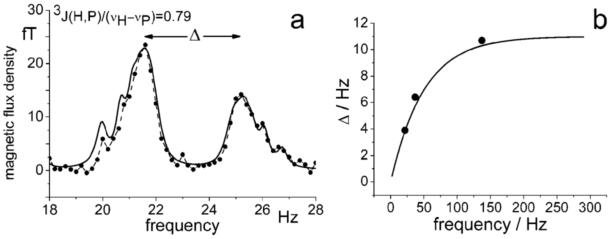

Figure 3. (a) Trimethyl phosphate and numerical simulation at 549 nT. (b) Solid line: heuristical fit to the numerical simulation of the spectral separation △ of the main peaks as a function of the ^{1}H Larmor frequency. Dots: experimental results.

Trifluoroethanol has the same primary molecular structure as ethanol, except that the methyl protons are exchanged by fluorine. Ethanol exhibits only a single line at low fields because without a chemical shift all ^{1}H are magnetically equivalent and the multiplets disappear. In trifluoroethanol, fluorine and hydrogen have different Larmor frequencies and make up an A_3B_2 system with an additional singlet of the OH proton.

In ultralow detection fields, *J*-coupling is of the same order of magnitude as the Larmor frequency difference $\delta\nu$ ($=\nu_H - \nu_F$). Variation of the detection field strength yields spectra reflecting the transition from $J/\delta\nu = 7.86$ over $J/\delta\nu = 3.51$ to $J/\delta\nu = 1.04$ (Figure 1). Our instrumental resolution allowed a separation of four main peaks even at $J/\delta\nu = 3.51$.[5] Increasing $J/\delta\nu$ further led to merged lines due to their natural lifetime broadening $1/(\pi T_2)$. These physical rather than technical constraints limit the resolution of pure *J*-spectroscopy.

A different situation is met in trimethyl phosphate, an AB_9 system of nine equivalent protons and one phosphorus nucleus. Simulating the AB_9 system reproduces the main features of the spectra (Figure 2). The corresponding stick spectra make clear that a large number of lines causes broadening into two asymmetric peaks where most of the substructure remains hidden: however, in the intermediate detection field at $J/\delta\nu = 0.46$, two shoulders in the outer wings of either doublet peak indicate some substructure (Figure 2) which coincides with the simulated spectrum. Above 150 Hz, the peak separation Δ approaches the value of the coupling constant ^3J(H,P) (Figure 3b).[5]

The ^{31}P multiplet was below noise level as the expected intensity of the ^{31}P signal is about $(N_P\gamma_P^2)/(N_H\gamma_H^2) = 1/60$ less than the ^{1}H intensity, where N_P and N_H are the number of ^{31}P and ^{1}H nuclei in the molecule. The detection of the ^{31}P multiplet would therefore require an increase of the SNR by several orders of magnitude.

The presented technique allows one to vary the magnetic field of the low-field NMR spectrometer over several octaves. The set of spectra recorded in this way enables a broad variation of $J/\delta\nu$, providing specific information on the coupled spin system. Homogeneous line broadening may blur details of the spectra, but spectral simulations help to disentangle the resonance lines and to identify the detection windows where the spectral resolution reveals the maximum information. This may allow new measurement techniques to analyze SQUID-based broad band *J*-coupling-dominated spectroscopy at ultralow fields.

The instrumental resolution of our setup scales with the Larmor frequency. At the low fields of our study, it ranges from around 10 to 75 mHz,[2] and it is beyond the physical limit which is given by the natural homogeneous line width of the investigated model systems ($\sim$300 mHz). The instrumental and natural linewidths will become equal to 15 μT.

The signal-to-noise level of our setup could be further amended by 1−2 orders of magnitude by (i) increasing the polarization field to a few mT, and (ii) by increasing the filling factor using a pick-up coil, which is wound around the sample. Low-field NMR could open up a whole new set of new applications, ranging from simultaneously monitoring NMR/EPR reactions,[8a] low-field imaging[8b] to simultaneous NMR/MEG measurements[8c] or even to NMR quantum computing, where different isotopes could be used simultaneously as qubits.[8d]

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