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High-order multiple quantum excitation in ^{13}C nuclear magnetic resonance spectroscopy of organic solids

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Excitation and detection of high-order multiple quantum (MQ) coherences among ^{13}C nuclear spins in singly-^{13}C-labeled organic solids is demonstrated experimentally. MQ signals involving at least ten quanta of spin angular momentum are observed in nuclear magnetic resonance (NMR) measurements on polycrystalline *L*-methionine-*methyl*-^{13}C and *L*-alanine-*1*-^{13}C, using a time-reversible multiple pulse excitation sequence modified specifically for experiments on systems with weak homonuclear dipole–dipole couplings and strong inhomogeneous interactions such as anisotropic chemical shifts. The feasibility of high-order MQ excitation and detection in ^{13}C-labeled organic solids promises to expand significantly the range of applications of MQ NMR as a structural tool, to include such systems as ^{13}C-labeled synthetic polymers and biopolymers. © *1999 American Institute of Physics.* [S0021-9606(99)01906-6]

Over 15 years ago, Yen and Pines[1] demonstrated the possibility of exciting and detecting very high-order multiple quantum (MQ) coherences in strongly dipole-coupled, abundant nuclear spin-1/2 systems in solids, corresponding to nuclear magnetic resonance (NMR) transitions in which more than 30 nuclei simultaneously flip their spins.[2] A crucial element of this work was the use of radio-frequency (rf) pulse sequences designed to generate a time-reversible evolution of the coupled spin system and thereby minimize destructive interference among MQ coherences.[3] In subsequent years, MQ NMR was developed further as a tool for estimating the sizes of nuclear spin clusters in solids.[4–7] Applications in structural investigations of a wide variety of systems have been reported, including amorphous silicon hydride,[8,9] diamond films and powder,[10,11] doped synthetic polymers,[12–14] catalyst supports,[15] chromatographic materials,[16] and zeolites.[17] In addition, MQ NMR spectroscopy of solids has been the focus of several fundamental studies of the dynamics of many-spin systems.[18–23] The spin systems in these experimental demonstrations and applications were comprised of ^{1}H or ^{19}F nuclei, i.e., abundant nuclei with large magnetic moments. Homonuclear magnetic dipole–dipole couplings are the dominant nuclear spin interactions in such systems, resulting in *homogeneously broadened* line shapes. In this paper, we demonstrate the excitation and detection of high-order MQ coherences among ^{13}C nuclei in singly-^{13}C-labeled organic solids. High-order MQ NMR spectroscopy of ^{13}C nuclear spin systems has not been reported previously, although various techniques for and applications of double quantum[24–34] and triple quantum[35] excitation in solid state ^{13}C NMR have been described. The samples in our experiments differ qualitatively from samples in ^{1}H and ^{19}F MQ NMR experiments in that the nearest-neighbor internuclear distances are of order 4 Å and the magnetic moments are relatively small. The homonuclear dipole–dipole couplings in these ^{13}C systems are therefore weaker than in the ^{1}H and ^{19}F systems by a factor of 100 or more. The ^{13}C homonuclear couplings are also 30–100 times weaker than the heteronuclear ^{13}C–^{1}H couplings and 10–100 times weaker than the ^{13}C chemical shift anisotropies (CSA), resulting in *inhomogeneously broadened* line shapes. High-order ^{13}C MQ NMR may permit new approaches to structural studies of organic and biological solids, as discussed below.

The rf pulse sequence for ^{13}C MQ NMR experiments is shown in Fig. 1(a). It is a double-resonance sequence in which ^{13}C magnetization is first prepared by cross-polarization from ^{1}H nuclei and then stored along z by a $\pi/2$ pulse. Residual coherences dephase during a delay $\tau=4$ ms without ^{1}H decoupling. In the MQ preparation period, the multiple pulse MQ excitation sequence in Fig. 1(b), with an overall rf phase shift $\Delta\phi=\phi_k$, is applied for N_c cycles. In the MQ mixing period, the same multiple pulse sequence is applied with $\Delta\phi=\pi/2$ for N_c cycles. After a second τ delay, ^{13}C free-induction decay (FID) signals are excited with a final $\pi/2$ pulse and detected in the t_2 period. ^{13}C–^{1}H couplings are largely removed by strong irradiation of ^{1}H nuclei during the preparation, mixing, and detection periods. Two-dimensional (2D) data sets $S(\phi_k,t_2)$ are acquired[5] with phase shifts $\phi_k=(2\pi k/32)$, $k=0, 1, 2, ..., 31$.

The multiple pulse MQ excitation sequence in Fig. 1(b), with cycle time τ_c, is derived from sequences developed earlier.[1–3] Ideally, this sequence coherently averages the homonuclear dipole–dipole coupling Hamiltonian $H_d=\Sigma_{i>j}d_{ij}(I_{zi}I_{zj}-\frac{1}{3}\mathbf{I}_i\cdot\mathbf{I}_j)$, where $\mathbf{I}_i$ is the angular momentum operator for spin i and d_{ij} is the coupling constant, to an effective coupling $H_{\rm eff}(\Delta\phi)=e^{2i\Delta\phi}\Sigma_{i>j}d_{ij}/3\,(I_{yi}I_{yj}-I_{xi}I_{xj})$. $H_{\rm eff}$ is two-quantum selective,[3] so that time reversal (i.e., $H_{\rm eff}\rightarrow -H_{\rm eff}$) is accomplished by the $\pi/2$ phase

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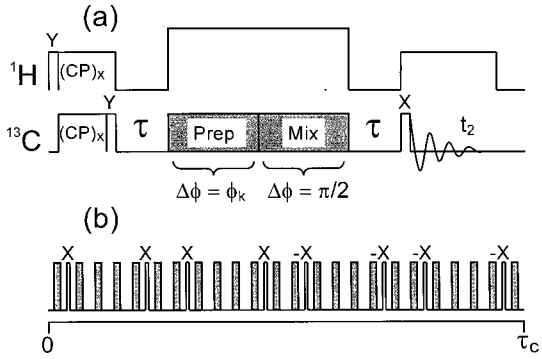

FIG. 1. Pulse sequence for ^{13}C MQ NMR spectroscopy. (a) Overall sequence, showing the creation of ^{13}C magnetization by cross-polarization (CP), dephasing periods τ, MQ preparation and mixing periods, and signal detection period t_2. (b) Multiple pulse cycle used in preparation and mixing periods, with overall phase shifts $\Delta\phi$. The cycle consists of eight $\pi/2$ pulses, with the indicated phases, centered about times $\tau_c/24$, $5\tau_c/24$, $7\tau_c/24$, $11\tau_c/24$, $13\tau_c/24$, $17\tau_c/24$, $19\tau_c/24$, and $23\tau_c/24$. Twenty-four π pulses (shaded rectangles), inserted to average out anisotropic chemical shifts on a time scale of $\tau_c/24$, are centered about times $(2m+1)\tau_c/48$, $m=0,1,2,...,23$. The π pulses phases follow the pattern $X,-X,-X,X$, repeated six times.

shift of the mixing period. In singly-^{13}C-labeled samples, the CSA interaction $H_{\mathrm{CSA}}=\Sigma_i \nu_i I_{zi}$ generally exceeds the homonuclear couplings. Because $[H_{\mathrm{CSA}},H_d]\neq 0$ in the laboratory frame or in the interaction representation of the rf pulse sequence, H_{CSA} interferes with coherent averaging of H_d either by truncating H_d or by producing large CSA/dipole–dipole cross-terms in H_{eff}. To overcome this problem, 24 ^{13}C π pulse are inserted into each cycle to average out chemical shifts on the time scale of $\tau_{\mathrm{echo}}=\tau_c/24$. τ_c is then chosen so that $\|H_d\|\tau_c<1$ and $\|H_{\mathrm{CSA}}\|\tau_{\mathrm{echo}}<1$. Experimental attempts to excite MQ coherences using the multiple pulse sequence in Fig. 1(b), but with no π pulses, were unsuccessful.

Experiments were carried out at a ^{13}C carrier frequency of 100.8 MHz (9.39 T field), using a Varian/Chemagnetics Infinity-400 spectrometer and a Varian/Chemagnetics NMR probe fitted with a horizontal, 4 mm diam, 10-turn solenoidal sample coil. ^{13}C rf field strengths ($\gamma B_1/2\pi$) were 50 kHz. ^{1}H decoupling field strengths were 125 kHz during the MQ preparation and mixing periods and 50 kHz during t_2. Spectral artifacts were minimized by phase-cycling the first ^{1}H pulse (spin-temperature alternation) and the last ^{13}C pulse (CYCLOPS). Effects of spectrometer instabilities were minimized by block averaging of 2D data sets. The phases of the π and $\pi/2$ pulses in Fig. 1(b) were selected empirically to maximize signals in the MQ NMR spectra after testing several alternatives. *L*-methionine-*methyl*-^{13}C (Sigma), unlabeled *L*-methionine, and *L*-alanine-*1*-^{13}C (Cambridge Isotopes, labeled at carboxyl carbon) were recrystallized from aqueous solution and ground to fine powders for MQ NMR measurements. $(CH_3)_2C(OH)SO_3Na$ (bisulfite adduct of acetone, or BSA) powder, in which doubly-methyl-labeled molecules are diluted to 5% in unlabeled molecules, was prepared as previously described.[26]

Figure 2 shows ^{13}C NMR spectra $F(\phi_k,\omega_2)$ of *L*-methionine-*methyl*-^{13}C, *L*-alanine-*1*-^{13}C, and 5%-$^{13}C_2$-BSA, obtained by complex Fourier transformation of $S(\phi_k,t_2)$ with respect to t_2, i.e., $F(\phi_k,\omega_2)=\int_0^\infty dt_2 e^{-i\omega_2 t_2}S(\phi_k,t_2)$. Differences in the linewidths (0.85 kHz for *L*-methionine-*methyl*-^{13}C; 12.1 kHz for *L*-alanine-*1*-^{13}C; 3.2 kHz for 5%-$^{13}C_2$-BSA) reflect differences in the CSA magnitudes. For all three samples, the signals are strongly modulated as a function of ϕ_k, with maxima at $k=0$ and $k=16$. For 5%-$^{13}C_2$-BSA, the modulation appears to be of the form $\cos 2\phi_k$, both when $N_c\tau_c=4.8$ ms and when $N_c\tau_c=14.4$ ms. For *L*-methionine-*methyl*-^{13}C and *L*-alanine-

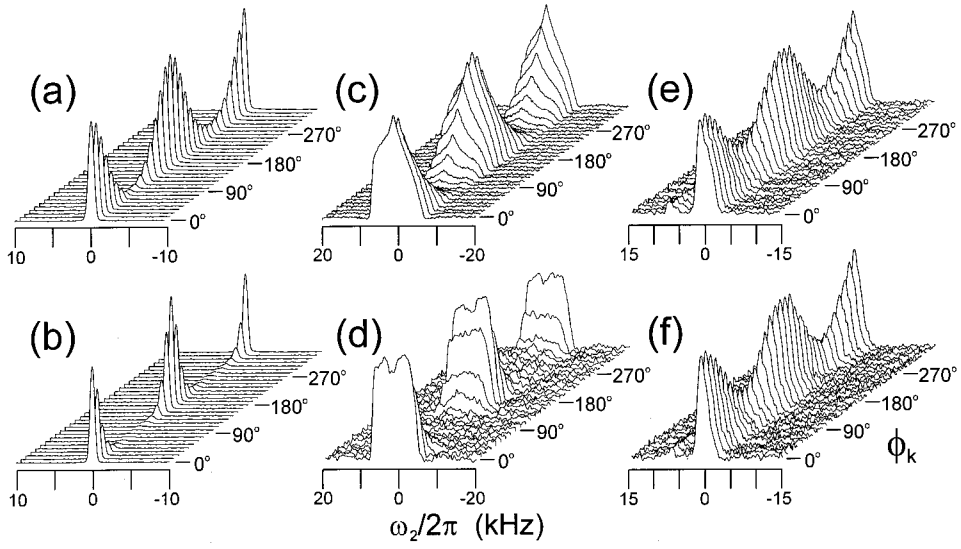

FIG. 2. Modulation of ^{13}C NMR signals as a function of the phase of the MQ preparation period ϕ_k, after complex Fourier transformation with respect to t_2. Results are shown for 50 mg powder samples of *L*-methionine-*methyl*-^{13}C (a,b), *L*-alanine-*1*-^{13}C (c,d), and 5%-$^{13}C_2$-BSA (e,f). MQ preparation and mixing times $N_c\tau_c$ are 4.8 ms (a,c,e) and 14.4 ms (b,d,f). τ_c is 4.8 ms (a,b,e,f) or 2.4 ms (c,d). The number of signal-averaging scans per ϕ_k value is 8, 32, 32, 288, 320, and 640 (a–f, respectively). Frequency scale is relative to the carrier frequency of 100.8 MHz.

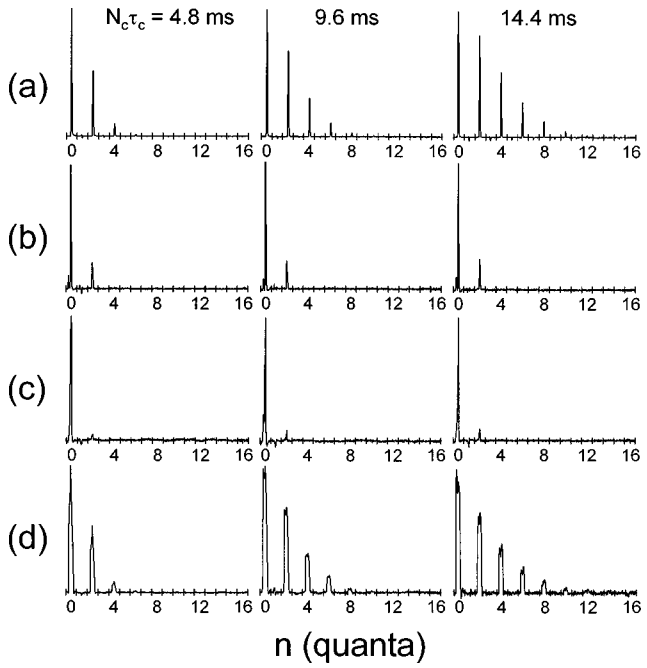

FIG. 3. ^{13}C MQ excitation spectra, obtained by Fourier cosine transformation of data such as in Fig. 2 with respect to ϕ_k. Results are shown for *L*-methionine-*methyl*-^{13}C (a), 5%-$^{13}C_2$-BSA (b), unlabeled *L*-methionine (c), and *L*-alanine-*1*-^{13}C (d). MQ preparation and mixing times $N_c\tau_c$ are 4.8 ms, 9.6 ms, and 14.4 ms in the first, second, and third columns. τ_c is 4.8 ms (a,b,c) or 2.4 ms (d). Each trace represents 17 *n*-quantum excitation spectra ($0 \leqslant n \leqslant 16$), plotted side-by-side and delineated by vertical tick marks. The range of $\omega_2/2\pi$ in each spectrum is ± 5 kHz (a), ± 15 kHz (b,d), or ± 10 kHz (c).

1-^{13}C, the form of the modulation is not as simple and depends on the value of $N_c\tau_c$.

Figure 3 shows data for *L*-methionine-*methyl*-^{13}C, 5%-$^{13}C_2$-BSA, unlabeled *L*-methionine, and *L*-alanine-*1*-^{13}C after Fourier cosine transformation with respect to ϕ_k, i.e., $G(n,\omega_2)=\Sigma_{k=0}^{31}\cos(n\phi_k)\mathrm{Re}\{F(\phi_k,\omega_2)\}$ with $n=0$, 1, ..., 16. The MQ order is represented by *n*. Each trace in Fig. 3 is a concatenation of all 17 slices of $G(n,\omega_2)$ with fixed *n*. We refer to each slice as an *n-quantum excitation spectrum*, rather than simply an *n*-quantum spectrum, because it represents the probability amplitude for excitation (at the end of the preparation period) and detection (after the mixing period) of *n*-quantum coherence as a function of the single-quantum NMR frequency ω_2. The *n-quantum frequency spectra* could be measured by introducing an incremented evolution period t_1 between the preparation and mixing periods in Fig. 1(a).[1,2] Spectral intensity appears primarily in even-order excitation spectra in Fig. 3, as expected for a two-quantum selective H_{eff} and an initial condition of longitudinal ^{13}C spin polarization.[1–7] For *L*-methionine-*methyl*-^{13}C [Fig. 3(a)] and *L*-alanine-*1*-^{13}C [Fig. 3(d)], the intensity spreads to higher MQ orders with increasing $N_c\tau_c$. At $N_c\tau_c=14.4$ ms, significant intensity is observed in *n*-quantum excitation spectra with $n \leqslant 10$, indicating that a coherent superposition of spin states involving a correlation of spin angular momenta of at least 10 different nuclei has been excited and detected. The nearest-neighbor distances among ^{13}C labels are 3.77 Å in *L*-methionine-*methyl*-^{13}C (Ref. 36) and 4.16 Å in *L*-alanine-*1*-^{13}C.[37] Spin angular momentum correlations therefore must exist over volumes of approximately 100 Å^3. For 5%-$^{13}C_2$-BSA, which serves as an experimental control, no spectral intensity is observed in MQ orders above two. Because this sample consists of dilute two-spin systems, excitation of higher MQ coherences is not expected. In unlabeled *L*-methionine, spectral intensity in MQ orders above two is also not observed. The small peak in the two-quantum excitation spectrum arises from couplings among natural abundance ^{13}C nuclei.

The signal intensity $S(\phi,0)$ for any crystallite in the sample can be expressed as

$$S(\phi,0)=\mathrm{Tr}\{I_zU_MR_z(\phi)U_PR_z(-\phi)\rho(0)R_z(\phi)U_P^{-1} \times R_z(-\phi)U_M^{-1}\}, \tag{1}$$

where I_z is the operator for the *z*-component of total ^{13}C spin angular momentum, U_M and U_P are the evolution operators for the mixing and preparation periods, $R_z(\phi)$ is the operator for a rotation about *z* by ϕ, and $\rho(0)$ is the initial spin density operator. Taking $\rho(0)=I_z$, using the expressions $U_PI_zU_P^{-1}=\Sigma_{q,n}a_{q,n}A_{q,n}$ and $U_M^{-1}I_zU_M=\Sigma_{q,n}b_{q,n}A_{q,n}$, where $\{A_{qn}\}$ are operators for *n*-quantum coherences that satisfy $\mathrm{Tr}\{A_{q,n}^{\dagger}A_{q',n'}\}=\delta_{n,n'}\delta_{q,q'}$, $A_{q,n}^{\dagger}=A_{q,-n}$, and $R_z(\phi)A_{q,n}\times R_z(-\phi)=e^{-in\phi}A_{q,n}$, and using the relations $a_{q,n}^*=a_{q,-n}$ and $b_{q,n}^*=b_{q,-n}$ (because $U_PI_zU_P^{-1}$ and $U_MI_zU_M^{-1}$ are Hermitean), Eq. (1) becomes

$$S(\phi,0)=\sum_{q,n}e^{-in\phi}a_{q,n}b_{q,n}^* \tag{2a}$$

$$=\sum_{q,n}\cos n\phi\,\mathrm{Re}\{a_{q,n}b_{q,n}^*\}+\sin n\phi\,\mathrm{Im}\{a_{q,n}b_{q,n}^*\}. \tag{2b}$$

The index *q* reflects the fact that there are many different *n*-quantum operators in a many-spin system. In the limit of perfect time reversal (i.e., $U_M=U_P^{-1}$), $b_{q,n}=a_{q,n}$ and $S(\phi,0)=\Sigma_{q,n}|a_{q,n}|^2\cos n\phi$. Then $S(0,0)=\mathrm{Tr}\{I_z^2\}$, so that the full signal would be obtained for any value of $N_c\tau_c$. $S(\phi,\omega_2)$ would also be symmetric with respect to the substitution $\phi\rightarrow 2\pi-\phi$. In practice, because pulse imperfections and higher-order correction terms cause H_{eff} to differ from its ideal form, time reversal is imperfect in real experiments. Some asymmetries in $S(\phi,\omega_2)$ with respect to $\phi\rightarrow 2\pi-\phi$ are apparent, particularly in Fig. 2(d). As an indication of experimental signal losses with increasing $N_c\tau_c$, total signals per scan for $\phi=0$ in Figs. 2(b) and 2(d) are 46% and 9% of the corresponding signals in Figs. 2(a) and 2(c). Pulse imperfections and correction terms also lead to the small odd-order signals in Fig. 3. True spin relaxation processes, due to stochastic fluctuations in the nuclear spin interactions, make an undetermined contribution to the signal losses.

The experiments described above have been carried out on static solids. It may also prove possible to perform similar ^{13}C MQ NMR measurements under magic-angle spinning (MAS), using appropriate homonuclear dipolar recoupling pulse sequences,[23–35,38–42] as has been demonstrated previously for ^{1}H MQ NMR.[23,43–45] Line-narrowing brought about by MAS may improve the sensitivity and resolution of

these measurements. On the other hand, potential gains in sensitivity are mitigated by the lower filling factors (especially for small samples), the tilt of the sample coil, and the comparative difficulties of achieving high decoupling fields and low temperatures in MAS NMR probes. Better spectral resolution may also not be essential in MQ spin-counting experiments when only one or two chemically distinct carbon sites are labeled. Natural abundance ^{13}C background signals do not contribute significantly to the high-order MQ spectra, as shown by Fig. 3(c). MAS is therefore not a prerequisite for many applications of ^{13}C MQ NMR.

We expect the feasibility of high-order MQ excitation and detection in singly-^{13}C-labeled organic solids to expand significantly the utility of MQ NMR as a structural tool. For example, ^{13}C MQ NMR measurements on synthetic polymers with singly-^{13}C-labeled monomer units may permit new investigations of miscibility, phase separation, and intermolecular interactions in polymer blends. We are particularly interested in applications to biopolymers. For example, measurements of ^{13}C MQ excitation spectra of singly-^{13}C-labeled amyloidogenic peptides may permit a determination of the sizes and geometries of structurally ordered domains in amyloid deposits. Analyses of ^{13}C MQ frequency spectra of peptides and proteins that are labeled at the carbonyl (or other) sites of several sequential amino acid residues may permit determinations of local secondary structure and secondary structure distributions. Measurements of ^{13}C MQ excitation spectra of proteins with labels at nonsequential residues that are involved in secondary or tertiary interactions may be useful for structural characterization of partially-folded states of proteins. These measurements may be carried out on insoluble aggregates, noncrystalline solids, frozen solutions, and membrane-associated forms of biopolymers. Similar ^{15}N MQ NMR measurements may be feasible, although the weaker dipole–dipole couplings in ^{15}N-labeled systems will necessitate much longer excitation periods.

While analogous structural studies of biopolymers using ^{1}H MQ NMR might be possible if samples could be prepared with ^{1}H at a small number of specific hydrogen positions and full deuteration of other positions, the experimental difficulty of preparing such selectively protonated samples makes this approach impractical. ^{19}F MQ NMR measurements on biopolymers, using double-resonance techniques identical to those described above for ^{13}C MQ NMR, may be useful but require the introduction of non-natural fluorinated analogs of the relevant monomers.

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