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Improved Proton Decoupling in NMR Spectroscopy of Crystalline Solids Using the SPINAL-64 Sequence

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Summary. The performance of three different spin decoupling schemes, CW, TPPM, and SPINAL-64 is compared, by recording proton decoupled ^{13}C NMR spectra of a crystalline glycine sample, with 20% isotopic labelling. At a magnetic field of $B_0 = 14.1$ T, the two phase modulated pulse schemes, TPPM and SPINAL-64, are shown to give decisively better results than CW decoupling, and the SPINAL-64 sequence is found to perform better than TPPM. It is suggested that in NMR of crystalline solids, SPINAL-64 offers a viable and competitive alternative to the well established TPPM decoupling technique, especially at higher magnetic fields.

Keywords. Glycine; NMR spectroscopy; Proton decoupling; Solid state; SPINAL-64.

Introduction

Spin decoupling is one of the most important techniques in Nuclear Magnetic Resonance (NMR) spectroscopy, because it allows the acquisition of highly resolved and simplified spectra. In NMR, spectra of rare spins such as ^{13}C are usually observed with simultaneous decoupling of the abundant spins, which are most often protons, ^{1}H. This is done to remove spin–spin interactions (*J* couplings in liquid-state, heteronuclear dipolar interactions in solid-state), which otherwise might have deleterious effects on the resolution of the ^{13}C spectra.

The most straightforward approach to decoupling is continuous-wave (CW) irradiation at the resonance frequency of the target nuclei. In liquid-state NMR, CW decoupling with a sufficiently strong radio frequency (RF) field can give satisfactory results. However, much better decoupling performances are obtained by purpose-designed pulse sequences such as MLEV-4 [1], WALTZ-16 [2] or PAR-75 [3], which are less sensitive to offsets of the decoupler frequency. This robustness with respect to the frequency offset is one major criterion to judge the performance

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of a decoupling technique, together with the desire to obtain good results for low RF power.

As opposed to liquid-state NMR, where decoupling aims to remove the relatively small scalar *J* couplings, the dominating effect in solid-state NMR is the dipolar interaction, which is generally comparable or even larger than the chemical shift range. For solids, much stronger RF fields are needed for CW decoupling, and the 'broad-band' pulse sequences devised for liquid-state NMR [1–3] are found mostly inefficient. In addition, the time dependence imposed on the proton resonance frequencies by the routinely used Magic Angle Spinning (MAS) technique [4] makes matters more complex. For rigid (crystalline) samples at modest MAS speeds and moderate magnetic fields, spin diffusion is still efficient enough for the proton lineshape to be largely unresolved. If the transmitter frequency is set to the middle of this broad ^{1}H line, CW usually gives better performance than other decoupling schemes. However, with the introduction of faster MAS speeds, and higher magnetic fields (and also for mobile samples), the proton lineshape starts to break up, rendering the spin diffusion process less efficient. This makes it essentially impossible to set the decoupler frequency precisely 'on resonance' [5], and decoupling performance tends to deteriorate.

The thus arising need for a decoupling technique more efficient than CW was addressed by the development of the Two Pulse Phase Modulated (TPPM) sequence [6]. This scheme relies on a windowless train of phase modulated pulses on the ^{1}H channel (see Fig. 1), and because of its significantly improved performance over CW decoupling, TPPM has found fairly widespread applications [7]. It has also been shown to be especially useful for triple-resonance experiments of the REDOR type [8], where the observed REDOR curves show an explicit dependence on the proton decoupler power [9], and converge to their 'true' shape only for high RF

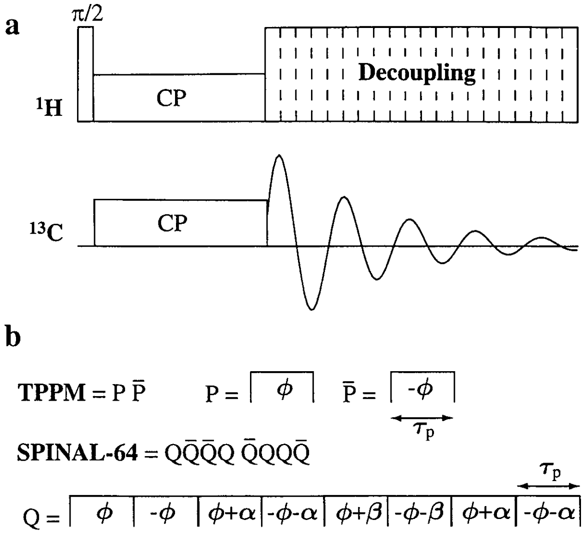

Fig. 1. Schematic representation of (a) the pulse sequence of the cross-polarization (CP) experiment, and (b) the TPPM and SPINAL-64 decoupling schemes, both using windowless pulse sequences with phase modulation on the ^{1}H channel. The phase angle ϕ, the pulse duration τ_p, and the phase increments α and β can be optimized for best performance

power. Since triple-resonance probes usually allow only for fairly limited RF field strengths, the implementation of decoupling schemes performing well at low RF power can improve REDOR results considerably [9, 10].

Following the success of TPPM, other decoupling schemes for solid-state NMR have been suggested [11–14]. The SPINAL-64 sequence [12] uses super-cycles of a basic phase modulated sequence (see Fig. 1). Although SPINAL-64 was shown to be a considerable improvement over TPPM in liquid crystalline systems, and to be somewhat better than TPPM and CW in at least one crystalline solid (*L*-tyrosine hydrochloride) [12], there is not much evidence of its use in the literature. Recently, however, the application of the SPINAL-64 sequence for proton decoupling of ^{13}C spectra of a fluorinated liquid crystal and a fluorinated alkane in an urea inclusion compounds has been reported [15]. In this study, SPINAL-64 gave better resolution than both CW and TPPM, the observed improvement was partly attributed to the high mobility of the decoupled species.

In this work, we demonstrate superior decoupling performance of the SPINAL-64 sequence at high magnetic field ($B_0 = 14.1$ T), for a crystalline sample of isotopically labelled glycine. In comparing the ^{13}C spectral linewidth obtained with CW, TPPM and SPINAL-64 decoupling, it is shown that SPINAL-64 produces the best line narrowing, and maintains good performance even at lower RF power levels. These results emphasize that the SPINAL-64 sequence can be successfully employed not only in systems with a relatively high mobility [12, 15], but also in rigid, crystalline samples.

Results and Discussion

The performance of the different decoupling schemes was tested on ^{13}C spectra of a glycine sample, which contained 20% of molecules isotopically labelled at both the α-carbon and the amino nitrogen, $^{15}NH_3^+{-}^{13}CH_2{-}COO^-$. The ^{13}C spectra of both labelled and unlabelled glycine are shown in Fig. 2a and 2b. For both samples, it can be seen that the α-carbon peak is conspicuously broader than the carbonyl resonance. For the unlabelled sample, a splitting of the α-carbon peak could be observed, which is most likely caused by the interaction of the ^{13}C spin with the neighbouring ^{14}N nucleus, which has spin $I = 1$ and a relatively large quadrupolar moment. This interaction cannot be the reason for the peak broadening seen in the 20% doubly labelled sample, because here practically all observed ^{13}C nuclei are bonded to ^{15}N nuclei with spin $I = 1/2$. For the labelled glycine, the carbonyl resonance broadens as well, although not to the extent that is seen for the α-carbon peak. One possible explanation of this effect is the presence of more than one crystalline modification in the sample. Three polymorphic forms are known to exist for crystalline glycine [16], and their slightly differing chemical shifts (amplified at the high magnetic field) could lead to inhomogeneous line broadening. However, for the purpose of this article, we will only focus on the effect of different decoupling methods on the ^{13}C spectrum of this sample, and not address the origin of the line broadening further.

The efficiency of the phase modulated decoupling sequences was optimized by iteratively testing arrays of the variable parameters, *i.e.* the phase angle ϕ, the pulse duration τ_p, and the additional phase increments α and β for SPINAL-64 (*cf.* Fig. 1). The original publications [6, 12] suggest $\tau_p \approx (11/12)\pi$, and the use of a small

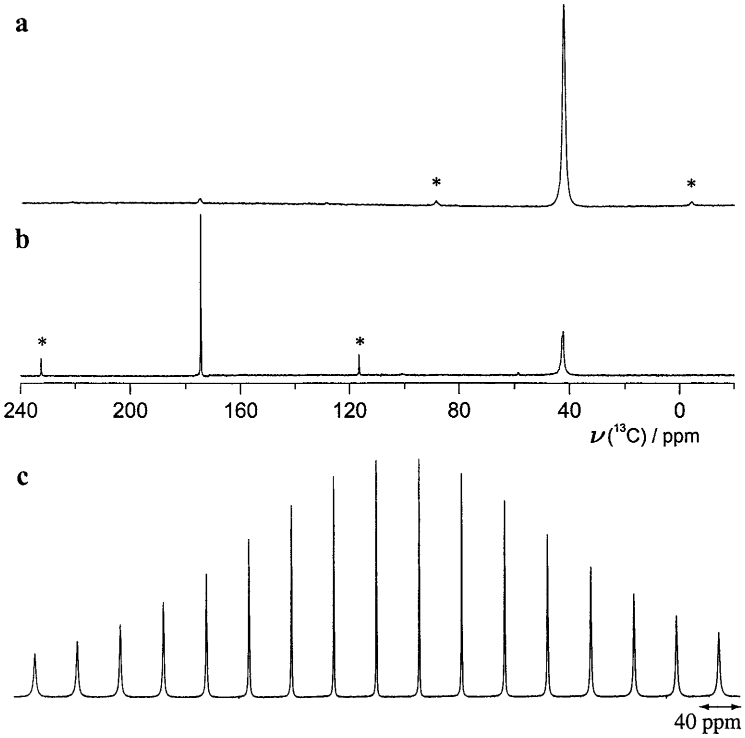

Fig. 2. (a) ^{13}C CP spectra with CW decoupling of (a) 20% doubly labelled glycine, at $\nu_0(^{13}C) = 150.9\,MHz$, $\nu_r = 7.0\,kHz$, and (b) unlabelled glycine, at $\nu_0(^{13}C) = 75.43\,MHz$, $\nu_r = 4.4\,kHz$. Asterisks indicate spinning side bands. (c) The dependence of the ^{13}C line shape (α-carbon peak at 42 ppm) in 20% labelled glycine on the decoupler offset (1 kHz stepwidth, 77 kHz RF power) for the SPINAL-64 sequence

angle for the phase modulation. For a decoupler strength of 77 kHz, we found the optimal values for τ_p to be $(11/12)\pi$ for SPINAL-64, and $(10/12)\pi$ for TPPM. Both sequences performed best with the originally reported phase values $\phi = 10°$ [6], and $\alpha = 5°$, $\beta = 10°$ [12].

The thus optimized sequences were first tested for their tolerance against the offset of the decoupler frequency. As an example, the line shapes obtained with SPINAL-64 are shown in Fig. 2c. The offset test was run for all three decoupling methods under consideration, and the full width at half maximum (FWHM) of the α-carbon peak determined as a measure of decoupling performance. The results are plotted in Fig. 3b. Clearly, both the phase modulated sequences outperform simple CW decoupling. It can also be seen that for frequency offsets up to $\pm 5\,kHz$, SPINAL-64 delivers the best line narrowing. Although TPPM produces less efficient decoupling in the $\pm 5\,kHz$ offset range, its performance is slightly more robust than that of SPINAL-64 for very large frequency offsets.

In addition, we tested the tolerance of the different decoupling techniques with respect to the RF field strength applied to the ^1H channel. This was done deliberately without re-optimizing the pulse duration τ_p for the phase modulated sequences. Thus, with decreasing RF power, τ_p will increasingly deviate from the optimal value of $\approx (11/12)\pi$. As can be seen from Fig. 3a, SPINAL-64 shows

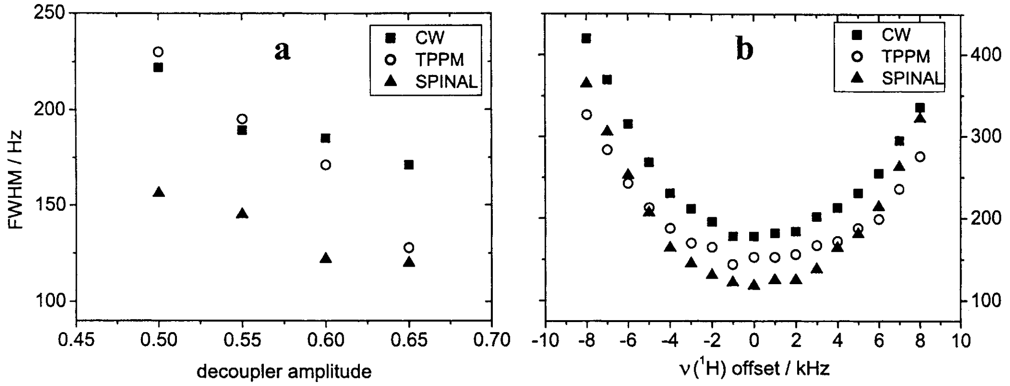

Fig. 3. Full Width at Half Maximum (FWHM) of the α-carbon peak of 20% doubly labelled glycine observed for CW, TPPM and SPINAL-64 decoupling. (a) Dependence on the decoupler amplitude, where 0.45 corresponds to an RF field strength of ≈ 54 kHz, and 0.65 to ≈ 77 kHz. (b) Dependence on the decoupler offset from the ideal value, $\nu(^1\mathrm{H}) = 0$, acquired with a decoupler RF strength of ≈ 77 kHz

a remarkable tolerance to the decline in RF power, and is still performing well at low power levels. In contrast, TPPM displays a marked drop in decoupling efficiency, which can be restored again by using the τ_p values appropriate for the respective power settings.

Interestingly, we could not reproduce the same performance pattern when testing the decoupling sequences at the lower magnetic field ($B_0 = 7.05$ T). Here, all three decoupling methods gave similar results. Apparently, at this magnetic field and rotor spinning speed, proton spin diffusion is still efficient enough for simple CW decoupling to work well.

The reasons for the good performance of the SPINAL-64 sequence described here are not quite clear, as the physics of spin decoupling in solids is still only poorly understood. In general, decoupling of dipolar interactions has to cope with both dipolar and offset effects. SPINAL-64 was developed and optimized for liquid crystal systems, where molecular motion reduces the effective strength of the dipolar interactions. Since higher magnetic fields also tip the balance away from dipolar couplings towards chemical shift offsets, it is perhaps unsurprising that SPINAL-64 becomes more effective under these conditions.

In conclusion, both TPPM and SPINAL-64 offer decoupling performance superior to traditional CW irradiation, whenever experimental conditions (high B_0 and/or ν_r) lead to the breaking up of the broad ^{1}H lineshape and interfere with the proton spin diffusion process. The TPPM and SPINAL-64 sequences deliver quite robust decoupling when using the specified standard parameters, and require only minimal adjustments for optimal performance. In certain cases, SPINAL-64 may give the most efficient decoupling, as has been shown for highly mobile systems before [12, 15], and for relatively rigid crystalline samples in Ref. [12] and in this work. More experimental data and theoretical analysis on the application of this sequence are needed, but it seems that especially at high magnetic fields, SPINAL-64 can be considered a viable and competitive alternative to the well-established TPPM decoupling scheme.

Experimental

The doubly spin-labelled glycine, $^{15}NH_3^+{-}^{13}CH_2{-}COO^-$, was co-crystallized with the unlabelled compound to create a $\approx 20\%$ labelled sample. ^{13}C NMR spectra were acquired using cross-polarization (CP) with a contact time of 1 ms. All decoupler test spectra were run on a Chemagnetics Infinity spectrometer operating at $\nu_0(^{13}C) = 150.9$ MHz, and $\nu_0(^1H) = 600.11$ MHz, using a 4 mm Chemagnetics T3 probe, with a rotor spinning speed of $\nu_r = 7$ kHz. The spectrum of unlabelled glycine was acquired on a Varian INOVA spectrometer, operating at $\nu_0(^{13}C) = 75.43$ MHz, and $\nu_0(^1H) = 299.95$ MHz, using a Doty Scientific 7 mm probe, with a spinning speed of $\nu_r = 4.4$ kHz. The SPINAL-64 decoupling was conveniently programmed by a suitable modification of the Chemagnetics TPPM pulse program.

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