High–resolution $^1$H NMR in the solid state using symmetry based pulse sequences

P.K.Madhu$^{a,b}$, Xin Zhao$^a$, and Malcolm H.Levitt$^{a,b,*}$

$^a$Division of Physical Chemistry, Arrhenius Laboratory, Stockholm University, S–10691, Stockholm, Sweden

$^b$Department of Chemistry, University of Southampton, Southampton SO17 1BJ, United Kingdom

Abstract  We demonstrate new rotor synchronised pulse sequences for obtaining high–resolution $^1$H NMR spectra in the presence of fast magic angle spinning. The new sequences exploit selection rules generated by appropriate synchronisation of the radio–frequency field modulations and the sample rotation. We show preliminary results demonstrating the feasibility of high–resolution proton NMR spectroscopy in the presence of fast magic angle spinning, and also demonstrate the resolution of $^1$H–$^{13}$C $J$–couplings in the solid state.

1. Introduction

The solid state NMR of abundant protons is relatively difficult. The large homonuclear dipole–dipole couplings broaden the peaks and obscure the chemical shift interactions [1].

*To whom correspondence should be addressed at mhl@physc.su.se
There have been two main approaches towards obtaining high–resolution proton spectra in the solid state. The first approach exploits rapid mechanical rotation of the sample about an axis that subtends $\tan^{-1}\sqrt{2}$ (the magic angle, 54.7°) with respect to the main magnetic field (magic angle spinning, MAS). In the second approach, resonant radio–frequency fields (rf) are applied to the sample in order to rotate the spin polarisations so as to average out the spin parts of the dipolar interactions [4–11].

When used in isolation, both of these methods have disadvantages. Pure MAS does not generally achieve very high resolution, even when spinning frequencies as high as 50 kHz are employed [12]. This is because the homonuclear dipole–dipole couplings are usually also tens of kHz. Spin–space averaging by rf fields is capable of higher absolute resolution, but does not average out chemical shift anisotropies (CSA). As a result, $^1$H peaks in static powder spectra are still relatively broad.

An obvious remedy is to apply both strategies at the same time. This is the aim of the so–called CRAMPS (Combined Rotation And Multiple Pulse Sequence) method [13–16]. An accurate theory of CRAMPS is not straightforward, since the sample often rotates on the same time scale as the rf pulse sequence. As a result early applications of CRAMPS used a quasi–static approximation, in which low spinning frequencies ensure an approximately static sample on the time scale of the rf pulse sequence [16]. This approach led to the application of averaging methods such as WHH4 [5], MREV8 [6,8], BR24 [10], BLEW12 [11], MSHOT3 [17], FSLG [4,7,18–20], PMLG [21,22] and DUMBO [23,?]. In general these methods fail at high magic angle rotation frequencies, due to so–called “interference effects” between the sample spinning and the resonant rf field [9].

A more subtle approach was employed by Hafner and Spiess, who used symmetry
arguments to avoid undesirable interference between the sample rotation and the rf cycles. Good resolution of $^1$H spectra was demonstrated at MAS frequencies up to 15 kHz [24,25].

The problem of synchronising the MAS sample rotation and applied rf fields has also been approached in a more general way. In particular, two general sets of rotor–synchronised pulse sequence symmetries, denoted $CN_n^\nu$ and $RN_n^\nu$, have been developed, which give rise to simple selection rules for the average Hamiltonian terms [26–29]. The symmetry numbers $N, n$ and $\nu$ are selected according to the desired and undesired spin interactions for a particular task. These symmetry–based sequences have been used in a wide range of decoupling and recoupling experiments [26–29].

One of the strengths of the symmetry–based approach, apart from its generality, is the existence of simple rules for predicting the number of symmetry–allowed higher order average Hamiltonian terms [27–29]. In many cases, the higher order terms have a decisive effect on the practical performance of a pulse sequence. For example, the Hafner and Spiess synchronisation schemes [24,25] have $CN_1^0$ symmetries, with $N \geq 3$, using the notation of Refs.[27–29]. These symmetries generate appropriate first–order selection rules for high–resolution $^1$H NMR in the solid state. However, $CN_1^0$ symmetries lead to a large number of symmetry–allowed higher order average Hamiltonian terms. For example, the symmetry $C3_1^0$ allows 80 second–order average Hamiltonian terms involving the commutator of homonuclear dipole–dipole interactions evaluated at two different time points. The symmetry $C4_1^0$ allows 60 terms of this kind. Similarly, the symmetry $C3_1^0$ allows 104 cross terms between the homonuclear dipole–dipole couplings (DD) and the $^1$H chemical shift anisotropy (CSA). The symmetry $C4_1^0$ allows 78 cross terms of this type.

In this letter, we present preliminary results for pulse schemes conforming to the sym-
metry $R18^8_2$, in the notation of Ref.[29]. As discussed below, this symmetry also has appropriate first–order selection rules for high–resolution $^1H$ NMR in solids, but allows only a relatively small number of higher order terms. $R18^8_5$ symmetry permits only 8 DD×DD second–order terms, and 24 DD×CSA cross terms. The reduced number of symmetry–allowed second–order terms is expected to lead to improved $^1H$ resolution.

A commonly used test of homonuclear decoupling performance is to acquire the $^{13}C$ signals of adamantane at the same time as applying a modulated rf field to the $^1H$ spins. We show good resolution of the adamantane $^{13}C$–$^1H$ $J$–couplings by using $R18^8_2$ irradiation of the protons. We also demonstrate preliminary results showing high resolution $^1H$ spectroscopy of a rigid organic compound at a MAS frequency of 20 kHz.

2. Theory

The general strategy for constructing pulse sequences of the type $RN^\nu_n$ is as follows [29]:

- Select a pulse sequence element $R$, that rotates resonant spins by $\pi$ around the $x$–axis. This element may be a single $\pi$ pulse, a composite $\pi$ pulse, or a smoothly modulated rf pulse.

- Derive the pulse sequence element $R'$ by changing the sign of all rf phases in the element $R$.

- Choose the rf field amplitude such that the duration of $R$ and $R'$, denoted by $\tau_R$, is equal to $\tau_R = n\tau_r/N$, where $\tau_r = (2\pi/\omega_r)$ is the rotor period, $N$ is an even integer, and $n$ is any integer. Here $\omega_r$ is the angular spinning frequency (in rad s$^{-1}$).
Form the sequence $RN_n^\nu$ by concatenating $N/2$ phase shifted $\{R, R'\}$ pairs as follows:

$$RN_n^\nu = (R)_\phi (R')_{-\phi} (R)_\phi (R')_{-\phi} \cdots (R')_{-\phi} \equiv \{R_\phi R'_{-\phi}\}^{N/2}$$

(1)

where the extra phase shifts are specified by $\phi = \pi \nu/N$, and $\nu$ is an integer.

The entire sequence $RN_n^\nu$ consists of $\frac{N}{2}$ contiguous $RR'$ pairs spanning $n$ rotational periods.

The spin interaction terms are conveniently indexed $\{l, m, \lambda, \mu\}$, where $(l, m)$ indicates the symmetry of the Hamiltonian terms with respect to rotation of the sample, and $(\lambda, \mu)$ indicate the symmetry with respect to rotations of the spins by resonant rf fields. The space quantum number $m$ takes values $-l, -l + 1, \cdots, l$ while the spin quantum number $\mu$ takes values $-\lambda, -\lambda + 1, \cdots, \lambda$. For example, the isotropic chemical shift has $l = 0, \lambda = 1$, the homonuclear $J$ coupling has $l = 0, \lambda = 0$, the heteronuclear $J$ coupling has $l = 0, \lambda = 1$, the chemical shift anisotropy (CSA) and the heteronuclear dipolar coupling have $l = 2, \lambda = 1$, and the homonuclear dipolar coupling has $l = 2, \lambda = 2$. All terms with $l = 2$ and $m = 0$ vanish under magic angle spinning.

As presented in Ref.[29,30] the pulse sequence symmetry $RN_n^\nu$ leads to the following selection rule for the first order average Hamiltonian terms [31]

$$\mathcal{H}_{lm\lambda\mu}^{(1)} = 0 \quad \text{if} \quad mn - \mu \nu \neq \frac{N}{2} Z_\lambda$$

(2)

The symbol $Z_\lambda$ denotes any integer with the same parity as $\lambda$. If $\lambda$ is odd, then $Z_\lambda$ is any odd integer; if $\lambda$ is even, then $Z_\lambda$ is any even integer. This selection rule is more restrictive than that described earlier for $CN_n^\nu$ sequences [26,27].

Pulse sequences suitable for high–resolution MAS NMR of abundant spins are designed by selecting the symmetry numbers $N, n$ and $\nu$ such that (i) some terms of the form
\((l, m, \lambda, \mu) = (0, 0, 1, \mu)\) are symmetry–allowed, and (ii) all terms of the form \((2, m, \lambda, \mu)\), with \(m \neq 0\), are symmetry–forbidden. A sequence of this type generates an average Hamiltonian containing only isotropic chemical shifts and heteronuclear \(J\)–couplings to non–irradiated spins.

A list of suitable \(CN^\nu_n\) \((N \leq 10, n \leq 5 \text{ and } \nu \leq 5)\) and \(RN^\nu_n\) \((N \leq 20, n \leq 5 \text{ and } \nu \leq 10)\) symmetries is given in Table 1. \(RN^\nu_n\) symmetries and the \(CN^\nu_n\) symmetries with \(\nu \neq 0\) have an additional benefit in the case that the \(R\) element only involves phase shifts in integer multiples of \(\pi\) (this is called “amplitude modulation”). In this case, rf inhomogeneity may be incorporated in the selection rule, Eq. (2), as a term with \(l = m = 0\), \(\lambda = \text{even integer}\), and \(\mu = \pm 1\) [32]. The symmetries above are compensated for rf inhomogeneity, since the corresponding average Hamiltonian terms are symmetry forbidden. For the symmetries \(CN^0_n\) on the other hand, the basic \(C\) element may be locally compensated for rf inhomogeneity before insertion in the construction procedure. This is the case for the \(C3^0_1\) and \(C4^0_1\) sequences performed by Hafner and Spiess [24,25].

In this letter, we concentrate on the symmetry \(R18^0_2\), which benefits from rf compensation in the case of amplitude modulated \(R\) elements. The first order selection rules for \(R18^0_2\) are depicted by the space–spin selection (SSS) diagram [28] given in Fig. 1. The plotted levels correspond to a total value of \(mn - \mu \nu\). The superposition of \(mn\) and \(\mu \nu\) is split into two stages to assist visualisation. The “barrier” at the right hand side of the diagrams has holes separated by \(N\) units. The position of the holes depends on the parity of \(\lambda\). Symmetry–allowed pathways pass through the holes in the barrier. Figure 1a shows that homonuclear dipolar interactions with \(l = 2, \lambda = 2\) and \(m \neq 0\) are blocked by the barrier. Terms with \(l = 2, m = 0\) vanish under exact MAS. Figure 1b shows that CSA
interactions with \( l = 2, \lambda = 1, m \neq 0 \) are also blocked by the barrier. Figure 1c shows that terms with \( (l, m, \lambda, \mu) = (0, 0, 1, \pm 1) \) are symmetry–allowed. These correspond to isotropic chemical shift and heteronuclear \( J \)–coupling terms. This symmetry is therefore suitable for high resolution proton NMR spectroscopy in solids.

So far, we have explored two variants of \( R18^9_2 \) symmetry. In the simplest version, denoted \( R18^9_2(I) \), we choose \( R = (180)_0 \), giving

\[
R18^9_2(I) = \{180, 90, 180, -90\}^9
\]  

where 9 repetitions of the bracketed elements span exactly 2 rotor periods. The nutation frequency of the rf field, \( \omega_{\text{nut}} \), for the above sequence is given by

\[
\omega_{\text{nut}}(I) = 4.5 \omega_r
\]  

where \( \omega_r / 2\pi \) is the spinning frequency in Hz. Note that this sequence simply consists of a set of 180° pulses, shifted in phase by 180° with respect to each other.

We have also explored the use of a composite pulse in order to improve local averaging of the homonuclear dipolar interactions. The sequence \( R18^9_2(II) \) is based on the composite pulse \( R = 90_{-45}90_{45}90_{-45} \) and \( R' = 90_{45}90_{-45}90_{45} \). The explicit \( R18^9_2 \) sequence is given by

\[
R18^9_2(II) = \{(90_{-45}90_{45}90_{-45})_0(90_{45}90_{-45}90_{45})_{-90}\}^9
= \{90_{45}90_{135}90_{45}90_{-135}90_{45}\}^9
\]  

where 9 repetitions of the bracketed elements span 2 rotor periods. The nutation frequency of the rf field, \( \omega_{\text{nut}} \), for this sequence is given by

\[
\omega_{\text{nut}}(II) = 6.75 \omega_r
\]
The sequence $R_{1892}^{9}(II)$ simply consists of a repetitive sequence of contiguous $90^\circ$ pulses, phase shifted by $90^\circ$ with respect to each other, as in the BLEW sequences [11]. The pulse sequences $R_{1892}^{9}(I)$ and $R_{1892}^{9}(II)$ are depicted in Fig. 2.

In the case of a heteronuclear $IS$ spin system, with $R_{1892}^{9}$ irradiation of the $I$–spins, the average Hamiltonian is

$$\mathcal{H}^{(1)} = \kappa (\omega^0_I I_x + 2\pi J I_x S_z) + \omega^0_S S_z$$

where the scaling factors $\kappa$ may be calculated using the formulae given in Ref.[30] and are given by $\kappa = 0.45$ for case (I) and $\kappa = 0.42$ for case (II). The rotating frame Larmor frequencies of spins $I$ and $S$ are denoted by $\omega^0_I$ and $\omega^0_S$. As indicated in Eq. (7), the effective field of both sequences is along the $x$–axis.

3. Experimental

3.1. Heteronuclear $J$–couplings in adamantane

Figure 3 shows $^{13}C$ spectra of adamantane acquired using the pulse scheme given in Fig. 2a.

After ramped cross–polarisation [33], the $^{13}C$ spectrum is acquired in the presence of repeating $R_{1892}^{9}$ sequences at the $^1H$ Larmor frequency. The spectrum in Fig. 3a was acquired with a simple $\pi$ pulse as the $R$ element, $R_{1892}^{9}(I)$. The $^1H$ rf nutation frequency was 90 kHz during the $R$ sequences. The spectrum in Fig. 3b was acquired with a composite $\pi$ pulse as the $R$ element, $R_{1892}^{9}(II)$. The $^1H$ rf nutation frequency was 135 kHz during the $R$ sequences. The $^1H$ reference frequency was set -1 kHz away from the centre of the $^1H$ spectrum taking into account the sign of the precession frequency [34].

The experiments were performed on a completely filled 3.2 mm rotor of adamantane at
a static magnetic field of 9.4 T, and a spinning frequency of 20 kHz. 512 transients were acquired with a recycle delay of 5 s.

The well–resolved heteronuclear $J$ splitting of both the CH$_2$ and CH peaks demonstrates the ability of $R18^g_{2}$ sequence to select heteronuclear $J$ couplings and to remove the masking effect of homonuclear dipolar couplings. A comparison of (a) and (b) reveals the superiority of the composite pulse $R$ element. The observed multiplet splittings in Fig. 2b are 78 Hz for the CH resonance and 74 Hz for the CH$_2$ resonance.

3.2. High–resolution $^1$H NMR at high spinning frequencies

The two–dimensional pulse sequence in Fig. 2b was used to obtain high–resolution $^1$H NMR spectra. Since the effective field for the $R$ sequence is along the $x$–axis, repetitive $R$–sequences are applied directly to longitudinal $^1$H magnetisation. The final longitudinal magnetisation is measured by a $\pi/2$ read pulse followed by data acquisition. The phase of the $\pi/2$ pulse and the post–digitisation phase shift, $\phi_{dig}$, are both cycled according to $\phi = \phi_{dig} = M\pi/2$, where $M=0,1,2\cdots$ is the transient counter, in order to select signals passing through $z$–magnetisation before the final pulse.

A spectrum of a full 3.2 mm rotor of $^{15}$N–L–alanine obtained with the $R18^g_{2}$(II) sequence (Fig. 3) is shown in Fig. 4a. The experiment was performed at a static magnetic field of 9.4 T and a spinning frequency of 20 kHz. The $t_1$ interval was incremented in steps of 11.11 $\mu$s and 4 transients were acquired for each increment, separated by a 5 s waiting interval. 256 $t_1$ increments were acquired in total. The $^{15}$N–L–alanine spectrum shows resolved CH$_3$, CH and $^{15}$NH$_3^+$ proton peaks, with line widths of 125 Hz, 175 Hz and 180 Hz respectively.
Rapid sample spinning produces good intensity for the $^{15}\text{NH}_3^+$ protons, as observed before by Hafner and Spiess [24,25]. This spectrum is of similar quality to the published FSLG and PMLG data [20–22]. If the measured linewidths are divided by the product of the theoretical scaling factor $\kappa=0.42$ and the proton Larmor frequency, $|\omega^0/2\pi|=400$ MHz, we obtain scaled linewidths of 0.74 ppm, 1.04 ppm and 1.07 ppm for the CH$_3$, CH and $^{15}\text{NH}_3^+$ resonances, respectively. The measured separation of the CH$_3$ and the NH$_3^+$ peaks correspond to a scaling factor $\kappa=0.47$, in reasonable agreement with the theoretical value.

A $^1\text{H}$ spectrum of monoethyl fumarate obtained with the $R18^0_{2}(\text{II})$ sequence is shown in Fig. 4b. The experimental conditions were identical to those used in Fig. 4a. The spectrum shows resolved CH$_3$, CH$_2$, CH and COOH proton peaks, with linewidths of 147 Hz, 158 Hz, 139 Hz and 151 Hz respectively. All of the spectral peaks have appreciable intensity and the spectrum is comparable to published data for PMLG [21,22]. The CH$_2$ peak is relatively weak as is also observed with PMLG [21,22]. After correcting for the scaling factor, as above, the scaled linewidths are 0.87 ppm, 0.94 ppm, 0.83 ppm and 0.89 ppm for the CH$_3$, CH$_2$, CH and COOH proton resonances, respectively. The measured separation of the CH$_3$ and the COOH peaks corresponds to a scaling factor $\kappa=0.46$.

In both experiments, the $^1\text{H}$ reference frequency was set $+12$ kHz away from the centre of the $^1\text{H}$ spectrum taking into account the sign of the precession frequency [34]. As for most multiple pulse sequences, a moderate resonance offset was found to optimise the resolution.
4. Conclusions

We have demonstrated the symmetry–based design of pulse sequences for high resolution solid state $^1\text{H}$ NMR in the presence of fast magic angle spinning. We have explored two simple possibilities based on $R18_2^9$ symmetry, and showed that they perform well at reasonably high MAS frequencies. These sequences are easy to implement experimentally and are quite robust. As shown in Table I, there are numerous other possible symmetries and choices of $R$ element, including windowed versions which should allow direct detection of the $^1\text{H}$ NMR signal, and sequences suitable for work at very high MAS frequencies up to 50 kHz. Further work is necessary to analyse the performance of these sequences at high spinning frequencies and to compare them with existing methods such as the Hafner–Spiess synchronisation scheme [24,25]. Work is also in progress on further applications of the $R$–symmetries including the use of $R18_2^9$ in $^1\text{H}–^{13}\text{C}$ correlation spectroscopy. In this case, the use of fast MAS is particularly desirable, since it leads to simple $^{13}\text{C}$ spectra in the directly detected dimension.

5. Acknowledgements

This research was supported by the Swedish Natural Science Foundation and by the Göran Gustafsson Foundation for Research in the Natural Sciences and Medicine.
Table I

$CN_n^\nu$ and $RN_n^\nu$ symmetries for the observation of isotropic chemical shifts and heteronuclear $J$ couplings in the presence of fast MAS. All $CN_n^\nu$ sequences with $\nu \neq 0$ select isotropic chemical shift terms $(l, m, \lambda, \mu)=(0,0,1,0)$. All $RN_n^\nu$ sequences select isotropic chemical shift terms $(l, m, \lambda, \mu)=(0,0,1,\pm 1)$.

| n=1  | C3\textsuperscript{0} C4\textsuperscript{0} C5\textsuperscript{0} C6\textsuperscript{1} C7\textsuperscript{0} C8\textsuperscript{1} C9\textsuperscript{0} C10\textsuperscript{0} C10\textsuperscript{1} C10\textsuperscript{5}  
| | R6\textsuperscript{3} R8\textsuperscript{4} R10\textsuperscript{5} R12\textsuperscript{6} R14\textsuperscript{7} R16\textsuperscript{8} R18\textsuperscript{0} R20\textsuperscript{10}  |
| n=2  | C3\textsuperscript{2} C5\textsuperscript{2} C6\textsuperscript{2} C7\textsuperscript{0} C9\textsuperscript{0} C9\textsuperscript{2} C10\textsuperscript{2}  
| | R6\textsuperscript{3} R10\textsuperscript{5} R14\textsuperscript{7} R18\textsuperscript{2}  |
| n=3  | C4\textsuperscript{3} C5\textsuperscript{3} C7\textsuperscript{0} C8\textsuperscript{0} C8\textsuperscript{4} C9\textsuperscript{1} C9\textsuperscript{3} C9\textsuperscript{4} C10\textsuperscript{0} C10\textsuperscript{0} C10\textsuperscript{0} C10\textsuperscript{1} C10\textsuperscript{5}  
| | R8\textsuperscript{3} R10\textsuperscript{3} R14\textsuperscript{3} R16\textsuperscript{3} R20\textsuperscript{10}  |
| n=4  | C3\textsuperscript{4} C5\textsuperscript{4} C6\textsuperscript{4} C7\textsuperscript{4} C9\textsuperscript{4} C9\textsuperscript{4} C10\textsuperscript{5}  
| | R6\textsuperscript{4} R10\textsuperscript{4} R14\textsuperscript{4} R18\textsuperscript{4}  |
| n=5  | C3\textsuperscript{5} C4\textsuperscript{5} C6\textsuperscript{5} C6\textsuperscript{5} C7\textsuperscript{5} C8\textsuperscript{5} C8\textsuperscript{5} C9\textsuperscript{5} C9\textsuperscript{3} C3\textsuperscript{5}  
| | R6\textsuperscript{5} R8\textsuperscript{5} R12\textsuperscript{5} R14\textsuperscript{5} R16\textsuperscript{5} R18\textsuperscript{5}  |
REFERENCES


31. We employ an indexing of the Magnus expansion starting at one.

32. M.Carravetta, A.Brinkmann, M.H.Levitt, to be published.


Figure Captions

Figure 1: Space-spin selection diagram for the sequence $R18_2^9$. (a) Suppression of the homonuclear dipolar interactions. (b) Suppression of CSA. (b) Selection of isotropic chemical shifts and heteronuclear scalar couplings with quantum numbers $(m, \mu) = (0, \pm 1)$. The mirror pathways arising from the negative $m$ values have been suppressed for simplicity.

Figure 2: Pulse sequences employing $R18_2^9$ used for (a) observing $^1H–^{13}C$ $J$ couplings and (b) isotropic $^1H$ chemical shifts, in the case of organic solids.

Figure 3: Experimental $^{13}C$ spectra of adamantane obtained by the pulse sequence given in Fig. 1a using (a) $R18_2^9$(I) and (b) $R18_2^9$(II). The experimental details are given in the text.

Figure 4: Experimental proton spectra obtained by the pulse sequence given in Fig. 1b on (a) monoethyl fumarate and (b) $^{15}N$–L–alanine. The $R18_2^9$(II) sequence was used. The experimental details are given in the text. The projection of the two-dimensional spectrum onto the $\omega_1$–axis is shown. The displayed spectrum is the region with $\omega_1 > 0$: the mirror image with $\omega_1 < 0$ is not shown. No apodisation function was used and the data were zero filled to 1024 points in both cases. A baseline correction was used in (b).