# Detection and characterization of intermolecular multiple-quantum coherence NMR signals of *IS* (*I* = 1/2; *S* = 3/2) spin systems

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## A B S T R A C T

Intermolecular multiple-quantum coherences (iMQCs) have some intrinsic properties different from conventional single-quantum coherences in solution NMR. In this paper, we extended our study to heteronuclear iMQCs in *IS* (*I* = 1/2, *S* = 3/2) spin systems. A sample of sodium chloride (NaCl) water solution was taken as an example. Heteronuclear COSY revamped by asymmetric *Z*-gradient echo detection (CRAZED) experiments were performed. One- and two-dimensional heteronuclear iMQC spectra were obtained. The quantum-mechanical treatment was used to deduce the signal expressions. Magic angle experiments validate that the signals are indeed from intermolecular dipolar interaction and insensitive to the imperfection of radio-frequency (RF) flip angles. Both experimental results and theoretical analysis indicate that heteronuclear CRAZED experiment allows coherence transfer from spin-3/2 nuclei to spin-1/2, and vice verse. Furthermore, the dependences of iMQC signal intensities on RF pulse flip angles follow the same rules as those for heteronuclear *IS* (*I* = 1/2, *S* = 1/2 or 1) spin systems.

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## 1. Introduction

Quadrupolar spin probes are becoming increasingly important in a wide range of applications ranging from the NMR investigation of porous materials, (bio)polymers in liquid state to the diagnosis of pathology in humans via magnetic resonance imaging (MRI) [1–6]. Among these probes, the naturally existing spin-3/2 nuclei $^7$Li, $^{23}$Na, $^{39}$K, $^{87}$Rb, $^{35}$Cl, $^{81}$Br, and $^{131}$Xe constitute a significant class and attract much attention [7–13]. For example, due to the increasing importance of $^{23}$Na MRI and the need to discern different pools (e.g. intracellular vs. intercellular) of ions in biological systems, the relaxation and exchange processes involving $^{23}$Na nuclei have been studied [14,15].

Quadrupolar nuclei often result in spectral line broadening, thus concealing important spectral information. During the past decades, a lot of efforts have been taken to obtain high-resolution NMR spectra of quadrupolar spins. A number of variants and improvements of the original multiple-quantum magic-angle spinning (MQMAS) pulse sequence were proposed to efficiently reduce the quadrupolar broadening effects [16]. Subsequently, high-resolution heteronuclear correlation (HETCOR) NMR spectroscopy involving quadrupolar and spin-1/2 nuclei became available by combining MQMAS with cross-polarization (CP) or INEPT to allow magnetization transfer from quadrupolar to spin-1/2 nuclei or vice versa [17–19].

Intermolecular multiple-quantum coherences (iMQCs) have some intrinsic properties different from conventional single-quantum coherences (SQCs). They have found many applications after several years of rigorous study [20–29]. However, most of the iMQC studies focus on the iMQC signals of $^1$H–$^1$H spin system. As an important class of iMQC techniques, iMQCs involving other high natural abundant spin-1/2 or quadrupolar nuclei may find new applications. Recently, there has been increasing interest in the iMQC signals of these nuclei, such as $^{13}$C, $^{31}$P and $^2$H [30–33]. The iMQC signals of *IS* (*I* = 1, *S* = 1/2, 1) spin systems in liquid state have been observed and the dynamics of the iMQC signals has been studied [33,34]. High-resolution $^1$H NMR spectra in inhomogeneous fields were successfully retrieved via iMQCs between $^1$H and $^2$H nuclei [35]. These exciting works motivate us to further study the iMQCs in spin systems including spin-3/2 nuclei. Taking heteronuclear $^{23}$Na–$^1$H spin system as an example, the properties of iMQC signals of $^{23}$Na (spin-3/2) and $^1$H (spin-1/2) nuclei in heteronuclear CRAZED experiments are investigated. Theoretical expressions are deduced for the resulting signals. One- (1D) and two-dimensional (2D) experiments are performed to verify theoretical predictions. The results show that pure and optimal heteronuclear iMQC signals can be obtained with proper RF pulse flip angles, coherence selection gradients (CSGs) and phase cycling.

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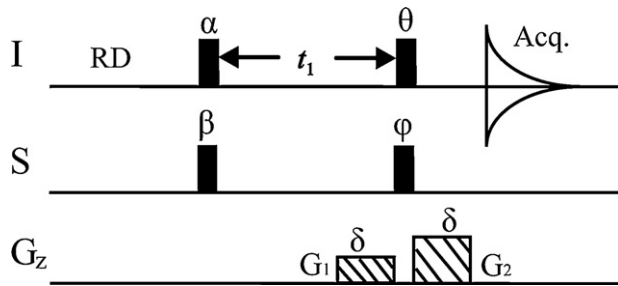*E-mail address:* shcai@xmu.edu.cn (S. Cai).

**Fig. 1.** Heteronuclear CRAZED pulse sequence for investigating different coherence order iMQCs between spin-1/2 and spin-3/2 nuclei.

## 2. Theoretical formalism

The pulse sequence shown in Fig. 1 was adopted to detect the iMQC signals between spin-1/2 and spin-3/2 nuclei. For the sake of simplicity, the RF pulses are assumed to apply along the $y$-axis. The CSGs are applied along the $z$-axis. The desired coherence order is determined by the area ratio of the two CSGs immediately before and after the second pair of RF pulses. The amplitudes of the two CSGs are $G_1$ and $G_2$ respectively, and their durations are $\delta$. We consider a homogeneous heteronuclear $IS$ ($I = 1/2$, $S = 3/2$) spin system in liquid state, where no $J$ coupling exists. Since the tumbling motion of molecules is rapid and all orientations are equally probable, the quadrupolar interaction is averaged to zero in a NMR timescale. So the quadrupolar interaction does not need to consider [35]. The effects of background inhomogeneous field, relaxation, diffusion and radiation damping are all ignored. Since the iMQC signals of spin-3/2 nuclei in such a heteronuclear system have already been studied [33], herein we focus on the properties of iMQC signals of spin-1/2 nuclei. Channel $I$ is for $I$ spin and channel $S$ is for $S$ spin. For easy comparison, we use the same notations as previous ones [33]. After dropping unimportant factors [36], we can deduce the evolution of $I_{zi}S_{zj}$ under the pulse sequence using the reduced density operator, where $I_{zi}$ represents the $z$ component of the $i$th $I$ spin operator, $S_{zj}$ represents the $z$ component of the $j$th $S$ spin operator.

After the first pair of RF pulses $\alpha$ and $\beta$, the initial two-spin term $I_{zi}S_{zj}$ in the reduced density operator becomes

$$\sigma(t_1^-) = \sum_{i=1}^{N}\sum_{j=1}^{M}\left\{\left[I_{zi}\cos\alpha + \frac{1}{2}(I_i^+ + I_i^-)\sin\alpha\right]\left[S_{zj}\cos\beta + \frac{1}{2}(S_j^+ + S_j^-)\sin\beta\right]\right\}$$

$$= \sum_{i=1}^{N}\sum_{j=1}^{M}\begin{bmatrix} I_{zi}S_{zj}\cos\alpha\cos\beta + \frac{1}{2}I_i^+S_{zj}\sin\alpha\cos\beta + \frac{1}{2}I_i^-S_{zj}\sin\alpha\cos\beta \\ + \frac{1}{2}I_{zi}S_j^+\cos\alpha\sin\beta + \frac{1}{2}I_{zi}S_j^-\cos\alpha\sin\beta \\ + \frac{1}{4}(I_i^+S_j^+ + I_i^-S_j^- + I_i^-S_j^+ + I_i^+S_j^-)\sin\alpha\sin\beta \end{bmatrix}$$

$$(1)$$

where $N$ and $M$ are the total molecular numbers of $I$ and $S$ spin, respectively. Under the effects of chemical shifts and pulsed field gradient (PFG) during the $t_1$ period, the spin density operator before the second pair of RF pulses becomes

$$\sigma(t_1^+) = \sum_{i=1}^{N}\sum_{j=1}^{M}\begin{cases} I_{zi}S_{zj}\cos\alpha\cos\beta + \frac{1}{2}I_i^+S_{zj}e^{-i\phi_1(z_i)}e^{-i\omega_I t_1}\sin\alpha\cos\beta \\ + \frac{1}{2}I_i^-S_{zj}e^{i\phi_1(z_i)}e^{i\omega_I t_1}\sin\alpha\cos\beta \\ + \frac{1}{2}S_j^+I_{zi}e^{-i\phi_1(z_j)}e^{-i\omega_S t_1}\cos\alpha\sin\beta \\ + \frac{1}{2}S_j^-I_{zi}e^{i\phi_1(z_j)}e^{i\omega_S t_1}\cos\alpha\sin\beta \\ + \frac{1}{4}I_i^+S_j^+e^{-i[\phi_1(z_i)+\phi_1(z_j)]}e^{-i(\omega_I+\omega_S)t_1}\sin\alpha\sin\beta \\ + \frac{1}{4}I_i^-S_j^-e^{i[\phi_1(z_i)+\phi_1(z_j)]}e^{i(\omega_I+\omega_S)t_1}\sin\alpha\sin\beta \\ + \frac{1}{4}I_i^-S_j^+e^{-i[-\phi_1(z_i)+\phi_1(z_j)]}e^{-i(-\omega_I+\omega_S)t_1}\sin\alpha\sin\beta \\ + \frac{1}{4}I_i^+S_j^-e^{-i[\phi_1(z_i)-\phi_1(z_j)]}e^{-i(\omega_I-\omega_S)t_1}\sin\alpha\sin\beta \end{cases}$$

$$(2)$$

where $\phi_1(z_i) = \gamma_I G_1\delta z_i$ and $\phi_1(z_j) = \gamma_S G_1\delta z_j$ are the dephasing angles of the $i$th $I$ spin and the $j$th $S$ spin at positions $z_i$ and $z_j$ due to the first PFG, and $\gamma_I$ and $\gamma_S$ are the gyromagnetic ratios of $I$ and $S$ spins, respectively. $\omega_I$ and $\omega_S$ are the frequency offsets of $I$ and $S$ spins in the rotating frame. After the second pair of pulses, there are no subsequent pulses, so we only need to consider $I_i^-S_{zj}$ terms that contribute to the observable signals of $I$ spin. In addition, only terms that do not depend on the absolute position in the sample retain after spatial averaging. Thus after the RF pulses $\theta$ and $\varphi$ and the second PFG, the terms that will finally be transformed into observable signals are (see Supplemental material for more detailed deduction):

$$\sigma^I(t_1, t_2^-) = \begin{cases} \sum_{i=1}^{N}\sum_{j=1}^{M} -\frac{1}{4}I_i^-S_{zj}(\cos\alpha\sin\beta\sin\theta\sin\varphi)e^{i\gamma_S G_1\delta(z_i-z_j)}e^{-i\omega_S t_1} \\ (+iSQC) \\ \sum_{i=1}^{N}\sum_{j=1}^{M} -\frac{1}{4}I_i^-S_{zj}\left(\cos\alpha\sin\beta\sin\theta\sin\varphi\right)e^{-i\gamma_S G_1\delta(z_i-z_j)}e^{i\omega_S t_1} \\ (-iSQC) \\ \sum_{i=1}^{N}\sum_{j=1}^{M} +\frac{1}{4}I_i^-S_{zj}\left(\sin\alpha\sin\beta\sin^2\frac{\theta}{2}\sin\varphi\right)e^{i\gamma_S G_1\delta(z_i-z_j)}e^{-i(\omega_I+\omega_S)t_1} \\ (+iDQC) \\ \sum_{i=1}^{N}\sum_{j=1}^{M} -\frac{1}{4}I_i^-S_{zj}\left(\sin\alpha\sin\beta\cos^2\frac{\theta}{2}\sin\varphi\right)e^{-i\gamma_S G_1\delta(z_i-z_j)}e^{i(\omega_I+\omega_S)t_1} \\ (-iDQC) \\ \sum_{i=1}^{N}\sum_{j=1}^{M} -\frac{1}{4}I_i^-S_{zj}\left(\sin\alpha\sin\beta\sin^2\frac{\theta}{2}\sin\varphi\right)e^{-i\gamma_S G_1\delta(z_i-z_j)}e^{-i(\omega_I-\omega_S)t_1} \\ (+iZQC) \\ \sum_{i=1}^{N}\sum_{j=1}^{M} +\frac{1}{4}I_i^-S_{zj}\left(\sin\alpha\sin\beta\cos^2\frac{\theta}{2}\sin\varphi\right)e^{i\gamma_S G_1\delta(z_i-z_j)}e^{-i(-\omega_I+\omega_S)t_1} \\ (-iZQC) \end{cases}$$

$$(3)$$

The CSG strength ratios for +iSQC, −iSQC, +iDQC, −iDQC, +iZQC, −iZQC are $G_1/G_2 = \gamma_I/\gamma_S$, $-\gamma_I/\gamma_S$, $\gamma_I/(\gamma_S+\gamma_I)$, $-\gamma_I/(\gamma_S+\gamma_I)$, $-\gamma_I/(\gamma_S-\gamma_I)$ and $\gamma_I/(\gamma_S-\gamma_I)$ respectively.

During $t_2$ period, the operators evolve under the effects of chemical shift and intermolecular dipolar coupling (in the form of $2D_{ij}I_{zi}S_{zj}$, where $D_{ij}$ is the dipolar coupling constant between the $I_i$ spin and the $S_j$ spin). The intermolecular dipolar coupling "removes" the $S_{zj}$ term, leaving single-quantum terms $I_i^-$ for detection. The evolution of spin density operator $I_i^-S_{zj}$ under the operator $I_{zi}S_{zj}$ is [37]:

$$e^{-i2D_{ij}I_{zi}S_{zj}t}I_i^-S_{zj}e^{i2D_{ij}I_{zi}S_{zj}t}$$

$$= \begin{bmatrix} I_i^-S_{zj}E_S\left(\pm\frac{3}{2}\right)\cos(3D_{ij}t) + \frac{3}{2}iI_i^-E_S\left(\pm\frac{3}{2}\right)\sin(3D_{ij}t) \\ +I_i^-S_{zj}E_S\left(\pm\frac{1}{2}\right)\cos(D_{ij}t) + \frac{1}{2}iI_i^-E_S\left(\pm\frac{1}{2}\right)\sin(D_{ij}t) \end{bmatrix}$$

$$(4)$$

where $E_S(\pm 1/2) = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$, and $E_S(\pm 3/2) = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$.