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DIRECT MEASUREMENT OF TRANSVERSE RELAXATION TIME OF INTERMOLECULAR MULTIPLE QUANTUM COHERENCES IN NMR*

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A one-dimensional NMR method is presented for measuring the transverse relaxation time, $T_{2,n}$, of intermolecular multiple quantum coherences (IMQCs) of coherence order n in highly polarized spin systems. The pulse sequence proposed in this paper effectively suppresses the effects of radiation damping, molecular diffusion, inhomogeneity of magnetic field, and variations of dipolar correlation distance, all of which may affect quantitation of $T_{2,n}$. This pulse sequence can be used to measure not only IMQC transverse relaxation time $T_{2,n}(n > 1)$ quickly and directly, but also the conventional transverse relaxation time. Experimental results demonstrate that the quantitative relationship between $T_{2,n}(n \geq 1)$ and T_2 is $T_{2,n} \approx T_2/n$. These results will be helpful for understanding the fundamental properties and mechanisms of IMQCs.

Keywords: nuclear magnetic resonance, intermolecular multiple quantum coherences, transverse relaxation time, pulsed field gradient
PACC: 7620, 7660

I. INTRODUCTION

Relaxation properties of spin systems can provide useful information concerning rotational motion, transport properties, molecular structure, and molecular interactions. Since the information contained in the relaxation times of multiple-quantum coherences (MQCs) and single-quantum coherences (SQCs) is often complementary, there has been great interest recently in the relaxation times of MQCs. Multiple-quantum spectroscopy opens new perspectives for relaxation studies. There are mainly two kinds of relaxation times: longitudinal relaxation time, T_1, and transverse relaxation time T_2. The Carr-Purcell-Meiboom-Gill (CPMG) method is a most common method for measuring T_2,[1,2] since the method can effectively suppress the effects of diffusion, inhomogeneous broadening, and the effects of radiation damping in highly polarized spin systems.[3,4] However, the CPMG method can only be used to measure transverse relaxation times of SQCs. Since one cannot observe MQC signals directly, MQC transverse relaxation time of coherence order n, $T_{2,n}$, are mostly measured by means of two-dimensional NMR methods, which transfer MQC terms into SQC terms. The line width at the half height of a specific peak in the indirect dimension is usually used to determine $T_{2,n}$. However, this is a time-consuming and complicated method, prone to experimental errors. Some methods of one-dimensional NMR were designed to measure $T_{2,n}$ directly.[5−10] These methods are based on the following scheme: 1) MQC terms of a specific order is selectively produced in the prepared period; 2) the MQC terms are subjected to a free precession and an MQC relaxation attenuation during the evolution period; 3) the MQC terms are transferred into observable SQC terms during the mixing period; 4) the SQC signals detected during the detection period are modulated by the decayed MQCs; and 5) $T_{2,n}$ is determined by fitting an array of SQC signals, which are modulated by the evolution period τ of the MQCs.[6] In the past few years, the physical phenomena of intermolecular multiple-quantum coherences (IMQCs) in highly polarized spin systems have attracted great attention but have also aroused controversy. There are three theoretical pictures to explain the new experimental phenomena, including: 1) quantum-mechanical ma-

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trix treatment, i.e. IMQC theory;[11−13] 2) demagnetizing field treatment;[14] and 3) radiation damping treatment.[4,15] Though the three treatments differ significantly in their forms and there are still some theoretical issues remaining to be addressed, the effects of IMQCs and their potential application have caused great interest in the nuclear magnetic resonance (NMR) community. Warren and co-workers first reported a novel magnetic resonance imaging (MRI) method based on intermolecular zero-quantum coherence to obtain rat brain images at 9.4T.[16] Recently, we analysed the properties of IMQCs in detail. We also predicted and verified a series of new effects.[17−20] We obtained, for the first time, intermolecular double-quantum coherence (DQC) human brain images on a whole body 1.5T clinical scanner.[21] These results demonstrated that contrast mechanisms and properties of IMQC MRI are different from those of conventional SQC MRI as well as intramolecular MQC MRI. IMQC imaging may provide more sensitive and specific methods for function MRI.[16,21,22] The purpose of this paper is to design a new pulse sequence to measure IMQC $T_{2,n}$ directly and accurately. We also quantify properties of IMQC $T_{2,n}$ experimentally in a simple system.

Ⅱ. PRINCIPLES AND METHODS

Since several effects such as molecular diffusion, radiation damping, inhomogeneity of magnetic field and variation of dipolar correlation distance may affect the measurement of IMQC $T_{2,n}$, these effects need to be effectively suppressed in order to warrant the accurate measurement of $T_{2,n}$. Therefore, we designed the pulse sequence shown in Fig.1.[1] In the following, we will explain why the pulse sequence can be used to measure $T_{2,n}$ directly and accurately.

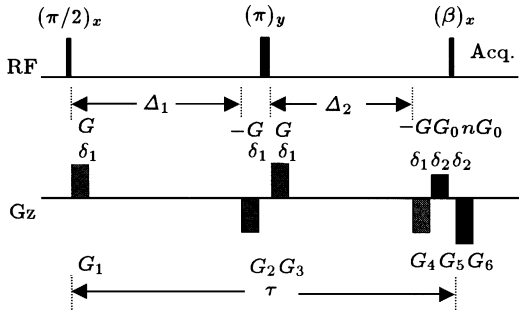


Fig.1. Pulse sequence for measuring IMQC $T_{2,n}$ directly.

According to the IMQC theory,[11,12] all orders of IMQC are produced after the first $(\pi/2)_x$ pulse is applied to a highly polarized nuclear spin system. The non-selective pulse $(\pi)_y$ is inserted at the middle of the evolution period, so Hahn echo is formed at the end of the evolution period. It means that the inhomogeneity of static magnetic field is effectively suppressed.

Similar to intramolecular MQCs, the attenuation of the nth-order IMQCs due to transverse relaxation satisfies a mono-exponential relationship during the evolution period. The $(\beta)_x$ pulse transfers the nth-order IMQCs, selected by the coherence-selection gradients G_5 and G_6, to observable SQCs. The signal intensity of the SQCs is modulated by the IMQC $T_{2,n}$ during the evolution period τ. Clearly, IMQC $T_{2,n}$ can be calculated from an array of signal intensities for different evolution period τ, which is similar to the method employed to measure intramolecular MQC $T_{2,n}$.

Now we discuss the effects of radiation damping. Radiation damping is characterized by a radiation damping decaying factor, $T_{\rm rd}$, which is defined as [15]

$$T_{\rm rd} = 2(\mu_0\gamma\eta Q M_0)^{-1}, \tag{1}$$

where μ_0 is the magnetic conductance in vacuum, γ the gyromagnetic ratio, η the filling factor of the sample in the detecting circuit; Q the quality factor of the resonant circuit; M_0 the thermal equilibrium magnetization per unit volume, which is proportional to the density of nuclear spin and the intensity of static magnetic field. It is known that a small value of $T_{\rm rd}$ will produce pronounced effects of radiation damping. In our sequence, effects of radiation damping are effectively suppressed by two pairs of z gradients of identical durations but opposite polarities, G_1, G_2 and G_3, G_4.[23] The first gradient G_1 or G_3 of each pair of the bipolar gradients dephases transverse coherences to suppress radiation damping while the second gradient G_2 or G_4 of each pair refocuses transverse coherences. Effects of radiation damping are further suppressed by decreasing the volume of the sample to decrease η and by deliberately detuning the probe to decrease Q. Although the bipolar gradients G_1, G_2 and G_3, G_4 can effectively suppress the radiation damping during the evolution period, effects of radiation damping during the detection period are still active. In order to reduce these effects, a small flip angle β pulse was used to decrease the transverse component of magnetization. Test results demonstrated that the effects of radiation damping during both evolution and detection periods were significantly suppressed when the above methods were applied. Therefore, effects of radiation damping

will be neglected in the following discussion.

Now we discuss how to remove confounding effects of molecular diffusion. To simplify discussion and notation, it is assumed that the attenuation due to molecular diffusion and relaxation follows a mono-exponential relationship. According to the IMQC theory, the signal at time t during the detection period can be written as [12]

$$M_n(\tau,t,G,G_0) = \mathrm{i}^{n-1} n M_0 \mathrm{e}^{-\mathrm{i}n\Omega\tau}\mathrm{e}^{-\mathrm{i}\Omega t}\frac{\mathrm{J}_n(\xi)}{\xi}\mathrm{e}^{-\tau/T_{2,n}} \cdot \mathrm{e}^{-t/T_2}\mathrm{e}^{-b_1 D_n} f(\delta_2, G_0, n), \quad (2)$$

where Ω is the frequency offset in the rotating frame, n the coherence order of IMQC, $\mathrm{J}_n(\xi)$ the nth-order Bessel function, $\xi = t\Delta_\mathrm{s}/\tau_\mathrm{d}$ the argument of the Bessel function, in which $\tau_\mathrm{d} = (\gamma\mu_0 M_0)^{-1}$ the dipolar demagnetization time, $\Delta_\mathrm{s} = [3(\hat{\boldsymbol{s}}\cdot\hat{\boldsymbol{z}})^2 - 1]/2$, $\hat{\boldsymbol{z}}$ the direction of the static magnetic field, $\hat{\boldsymbol{s}}$ the direction of coherence-selection gradients G_5 and G_6; $f(\delta_2, G_0, n)$ a function representing diffusion attenuation due to the gradients of G_5 and G_6 during evolution and detection periods. $\mathrm{e}^{-\tau/T_{2,n}}$ the attenuation due to $T_{2,n}$ during evolution period; $\mathrm{e}^{-b_1 D_n}$ the attenuation due to IMQC diffusion during evolution period, in which the diffusion weighting factor b_1 during evolution is given by[24]

$$b_1 = \gamma^2 G^2 \delta_1^2\left(\Delta_1 + \Delta_2 - \frac{2}{3}\delta_1\right), \quad (3)$$

where $\Delta_1 = \dfrac{\tau}{2} - \delta_1$ and $\Delta_2 = \dfrac{\tau}{2} - \delta_1 - \delta_2$. If δ_1 and δ_2 are kept constant, b_1 depends only on τ and G. Since Eq.(2) is a function in time domain, a Fourier transformation is needed to obtain an analytical expression in frequency domain. We have

$$I(\omega,\tau,G,G_0) = \int_0^{T_s} M_n(\tau,t,G,G_0)\mathrm{e}^{-\mathrm{j}\omega t}\mathrm{d}t, \quad (4)$$

where ω is the angular frequency and T_s the acquisition time. Experiments with an array of τ were performed when gradient amplitude G was set to G_a and $G_b = \sqrt{2}G_a$, respectively. If we define a function $E_n(\omega,\tau,G_a,G_b,G_0)$ as

$$E_n(\omega,\tau,G_a,G_b,G_0) = \frac{I^2(\omega,\tau,G_a,G_0)}{I(\omega,\tau,G_b,G_0)}, \quad (5)$$

with substitution of Eqs.(2), (3) and (4) into Eq.(5), we obtain

$$\begin{aligned} &E_n(\omega,\tau,G_a,G_b,G_0)\\ =&A(\omega,G_0)\\ &\cdot\frac{\left\{\exp\left[-\gamma G_a^2\delta_1^2\left(\tau-\frac{8}{3}\delta_1-\delta_2\right)D_n\right]\exp^{-\tau/T_{2,n}}\right\}}{\exp\left[-\gamma G_b^2\delta_1^2\left(\tau-\frac{8}{3}\delta_1-\delta_2\right)D_n\right]\exp^{-\tau/T_{2,n}}}\\ =&A(\omega,G_0)\mathrm{e}^{-\tau/T_{2,n}}, \end{aligned} \quad (6)$$

where $A(\omega,G_0)$ is a function of ω and G_0. Equation (6) contains no cross terms between molecular diffusion and IMQC $T_{2,n}$. Since $E_n(\omega,\tau,G_a,G_b,G_0)$ is independent of diffusion, it can be simplified into $E_n(\omega,\tau,G_0)$ which suggests an exponential decay with time constant $T_{2,n}$. On the other hand, substituting Eqs.(2) and (3) into Eq.(4), we deduce $I(\omega,\tau,G,G_0)$ to be an exponential function of τ, which can be written as

$$I(\omega,\tau,G,G_0) = B(\omega,G,G_0)\mathrm{e}^{-\tau/T(G)}, \quad (7)$$

where $B(\omega,G,G_0)$ is a function of ω, G, and G_0; and $T(G)$ is a time constant which characterizes an exponential attenuation of $I(\omega,\tau,G,G_0)$. Substituting Eq.(7) into Eq.(5), we have

$$\begin{aligned} &E_n(\omega,\tau,G_a,G_b,G_0)\\ =&\frac{[B(\omega,G_a,G_0)\mathrm{e}^{-\tau/T(G_a)}]^2}{B(\omega,G_b,G_0)\mathrm{e}^{-\tau/T(G_b)}}\\ =&C(\omega,G_a,G_b,G_0)\exp\left[-\tau\left(\frac{2}{T(G_a)}-\frac{1}{T(G_b)}\right)\right]. \end{aligned} \quad (8)$$

Since Eq. (6) is equivalent to Eq. (8), we have

$$\frac{1}{T_{2,n}} = \frac{2}{T(G_a)} - \frac{1}{T(G_b)}. \quad (9)$$

Since $T(G_a)$ and $T(G_b)$ can be calculated by fitting two arrays of experimental data of different τ values when the gradient amplitude G of G_1, G_2 and G_3, G_4 pairs is set to G_0 and $G_b = \sqrt{2}G_a$, respectively, Eq.(9) provides an analytical expression to calculate IMQC $T_{2,n}$.

Provided the area of the coherence selection field gradient G_5 is fixed for the pulse sequence shown in Fig.1, the dipolar correlation distance remains constant.[16] Therefore, the area of G_5 was maintained constant for measurements of IMQCs of different coherence orders presented in this paper.

Ⅲ. RESULTS AND DISCUSSION

NMR experiments were carried out on a Varian Unity+ 500 spectrometer, which is equipped with a

self-shielded z-gradient coil and a 5mm HCN triple-resonance RF coil of 1.5cm effective length. For all experiments in this paper, the gradient duration δ_1 of G_1, G_2, G_3, and G_4 was 2 ms, the gradient duration δ_2 of G_5 and G_6 was 3 ms, the gradient amplitude of G_5 related to dipolar correlation distance was 0.065 T/m. Gradient strengths were calibrated with a gradient profile experiment. Firstly, experimental data of an array of τ were acquired when the gradient amplitude of G_1, G_2, G_3, and G_4 was set to G_a, then Eq.(7) was used to fit $T(G_a)$. Secondly, experimental data of an array of τ with $G_b = \sqrt{2}G_a$ were used to fit $T(G_b)$. Finally, the IMQC $T_{2,n}$ of a specific coherence order n was obtained from Eq.(9). Three samples made of 80% H_2O+20% D_2O were used in this work: sample a, with long relaxation time; sample b, intermediate relaxation time, with a bit of $CuSO_4$ added to the sample to shorten transverse relaxation time; and sample c, short relaxation time, with more $CuSO_4$. In order to test the validity of Eq.(9), the method proposed herein and the CPMG method were used to measure SQC transverse relaxation times, $T_{2,1}$ and T_2 respectively. Experimental data and fitting curves are shown in Fig.2, and the calculated results of $T_{2,1}$ and T_2 are listed in Table 1.

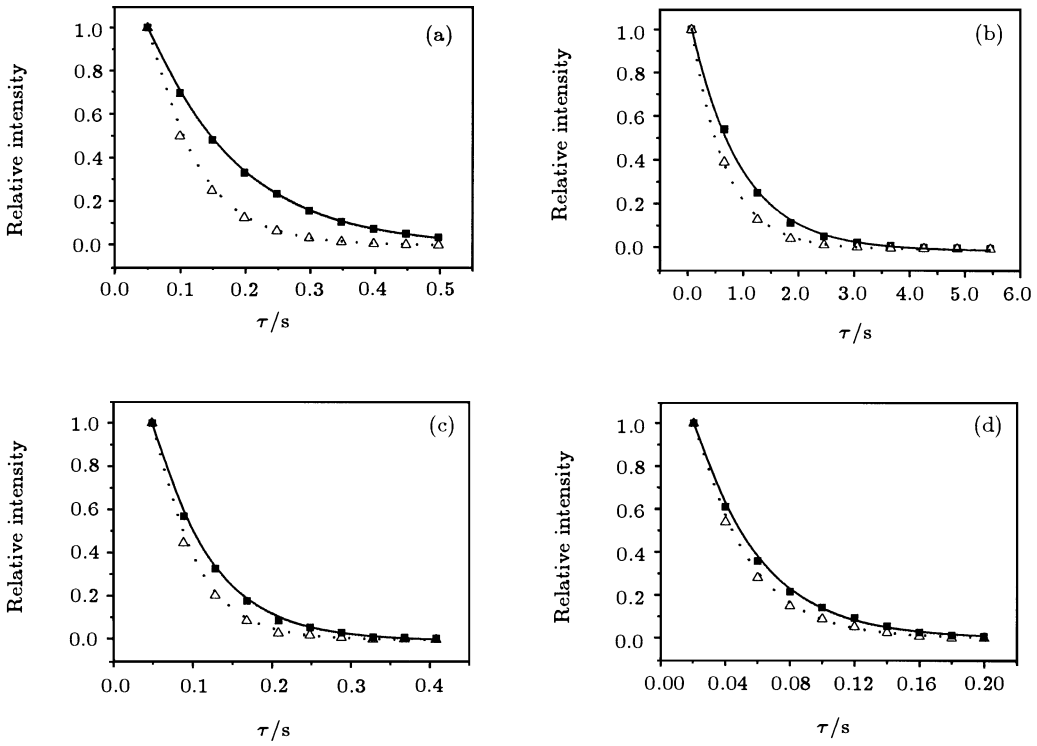


Fig.2. Experimental data and their exponential curves for n=1. The symbol "■" represents the experimental results when $G = G_a$, the symbol "△" represents the experimental results when $G = G_b$, the solid line is the fitting curve for the experimental data of $G = G_a$, and dot line is the fitting curve for the experimental data of $G = G_b$. (a) Sample a with G_a=0.108T·m^{-1}, (b) sample a with G_a=0.0337T·m^{-1}, (c) sample b with G_a=0.108T·m^{-1}, and (d) sample c with G_a=0.108T·m^{-1}.

Table 1. SQC transverse relaxation times $T_{2,1}$ and T_2.

Sample	G_a/T·m^{-1}	$[T(G_a)]^{-1}$/s^{-1}	$[T(G_b)]^{-1}$/s^{-1}	$T_{2,1}^{-1}$/s^{-1}	T_2^{-1}/s^{-1}
a	0.108	6.71	12.50	0.9±0.1	0.65±0.02
a	0.033	1.14	1.62	0.66±0.09	0.65±0.02
b	0.108	14.1	20.2	8.0±0.4	8.1±0.1
c	0.108	24.9	31.2	18.6±0.9	18.1±0.1

The results listed in table 1 show that the discrepancies between $T_{2,1}$ and T_2 values are quite small for samples b and c. For sample a, $T_{2,1}$ is almost equal to T_2 with G_a=0.033T·m^{-1}, but there is obvious deviation between $T_{2,1}$ and T_2 when G_a=0.108T·m^{-1}. We postulate that it is related to the longer T_2 of sample a. When a larger gradient amplitude such as G_a=0.108T·m^{-1} was used, attenuation due to molecular diffusion is predominant while attenuation due to relaxation is a minor component for the signal decay. From the experimental results listed in table 1, one can find that the ratio of $[T(G_b)]^{-1}$ over $[T(G_a)]^{-1}$ in this case approaches 2. This provides positive evidence to support our view. When the smaller gradient amplitude such as G_a=0.033T·m^{-1} was used, attenuation due to molecular diffusion became less important while attenuation due to relaxation became predominant. In the latter case, the measured results show that $T_{2,1} \approx T_2$. Measurements of other similar samples also show the same reasonable trend. However, it is worth noting that gradient amplitude G_a should not be too small, or pronounced effects of radiation damping may affect the measurement accuracy of $T_{2,1}$. In addition, data in table 1 suggest that the CPMG method results in smaller standard measured errors than the new method does. The reasons are as follows. For the CPMG method, one array of experimental data is used to fit a T_2 value. For the method proposed herein, two arrays of experimental data and difference calculations are needed to obtain a T_2 value. Clearly, a difference error is introduced in difference calculation. Moreover, there are six gradients in the pulse sequence shown in Fig.1, so unstable gradients including amplitude, rising time and falling time, may cause additional measurement errors.

Table 2. Measured results of IMQC $T_{2,n}$.

n	G_a/T·m^{-1}	$T(G_a)^{-1}$/s^{-1}	$T(G_b)^{-1}$/s^{-1}	$T_{2,n}^{-1}$/s^{-1}
1	0.108	14.1	20.2	8.0±0.4
2	0.108	31.9	47.1	17±2
3	0.108	45.0	65.5	25±3
4	0.075	47.5	58.2	37±6

Even though the method proposed herein may generate large errors for measuring a SQC transverse relaxation time, it can obtain satisfactory results if appropriate parameters are used. This conclusion has been verified with the results in table 1. The most important advantage of the new pulse sequence is that it can be used to measure IMQC $T_{2,n}(n > 1)$ quickly and directly. As an example, the experimental results of IMQC $T_{2,n}$ with different orders for the sample b are listed in table 2. Clearly, they approximately satisfy the following relationship:

$$T_{2,n} \approx \frac{T_{2,1}}{n}. \tag{10}$$

Equation (10) is a specific property of IMQCs, which is different from intramolecular MQCs.[5,6] We use a DQC as an example to concisely analyse the relationship. An intermolecular DQC can be expressed by raising and lowering operator $I_1^+ I_2^+$ where I_1^+ and I_2^+ are two individual spins on different molecules. Since I_1^+ and I_2^+ are a pair of remote spins, the dipolar interaction between them is very weak, and correlation between them is very small. If the two spins I_1^+ and I_2^+ belong to the same type of molecule such as water molecules in this paper, each isolated I_1^+ or I_2^+ has the identical T_2. The attenuation of operator $I_1^+ I_2^+$ due to transverse relaxation is approximately expressed as $e^{-\tau/T_2}$ $e^{-\tau/T_2}$=$e^{-2\tau/T_2}$, that is, the intermolecular DQC $T_{2,2}$ is equal to 1/2 of the SQC T_2. In general, the $T_{2,n}$ of the nth IMQC is equal to n^{-1} of the SQC T_2. However, intramolecular MQCs result from interactions of different spins on the same molecule. For example, with $I_1^+ I_2^+$ standing for intramolecular DQC, since I_1^+ and I_2^+ are two individual spins on the same molecule, there are strong interactions such as dipolar interaction and J scalar coupling between the two spins. Therefore, the transverse relaxation process of $I_1^+ I_2^+$ needs to be considered with their entire behaviour as a coupled spin system, not as two isolated spins. Several previous reports have provided some complicated expressions for transverse relaxation times in coupled spin systems,[5–9,25] but a detailed discussion of intramolecular MQC relaxation is beyond the scope of this paper.

Direct measurement of IMQC $T_{2,n}$ is useful for exploring the properties and mechanisms of IMQC relaxations in highly polarized spin systems. A more detailed theoretical formalism and further experimental results of IMQC $T_{2,n}$ will be presented in a separate paper.

References

[1] Carr H Y and Purcell E M 1954 *Phys. Rev.* **94** 630

[2] Meiboom S and Gill D 1958 *Rev. Sci. Instrum.* **29** 6881

[3] Mao X A, Guo J X and Ye C H 1994 *Chem. Phys. Lett.* **227** 65

[4] Mao X A and Ye C H 1997 *Concepts Magn. Reson.* **9** 173

[5] Yang J C, Wu Q Y and Ye C H 1987 *Chin. Phys.* **7** 905

[6] Ye C H and Xu P 1990 *Sci. China* A **34** 430

[7] Yang D W and Ye C H 1991 *Chem. Phys. Lett.* **183** 309

[8] Yang D W and Ye CH 1991 *Acta Phys. Sin.* **40** 1533 (in Chinese)

[9] Yang D W and Ye C H 1992 *Sci. China* A **35** 842

[10] Jung K J, Cannon P J and Katz J 1997 *J. Magn. Reson.* **124** 393

[11] Warren W S, Richter W, Andreotti A H and Farmer II B T 1993 *Science* **262** 2005

[12] Lee S, Richter W, Vathyam S and Warren W S 1996 *J. Chem. Phys.* **105** 874

[13] Lin Y Y, Listza N, Ahn S and Warren W S 2000 *Science* **290** 118

[14] Levitt M H 1996 *Concepts Magn. Reson.* **8** 77

[15] Mao X A 1998 *Radiation Damping Effects in NMR* (Beijing: Science Press) (in Chinese)

[16] Warren W S, Ahn S, Mescher M, Garwood M, Ugurbil K, Richter W, Rizi R R, Hopkins J and Leigh J S 1998 *Science* **281** 247

[17] Chen Z, Kennedy S D and Zhong J 1999 *Chem. Phys. Lett.* **313** 217

[18] Chen Z, Lin G X and Zhong J 2001 *Chem. Phys. Lett.* **333** 96

[19] Chen Z, Chen Z W and Zhong J 2001 *Chem. Phys. Lett.* **333** 126

[20] Chen Z and Zhong J 2001 *J. Chem. Phys.* **114** 5642

[21] Zhong J, Chen Z and Kwok E 2000 *Magn. Reson. Med.* **43** 335

[22] Zhong J, Kwok E and Chen Z 2001 *Magn. Reson. Med.* **45** 356

[23] Sklenár V 1995 *J. Magn. Reson.* A **114** 132

[24] Wong E C, Cox R W and Song A B 1995 *Magn. Reson. Med.* **34** 139

[25] Ernst R R, Bodenhausen G and Wokaun A 1987 *Principles of Nuclear Magnetic Resonance in One and Two Dimensions* (Oxford: Oxford University Press) p 274