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High-Resolution NMR Spectra in Inhomogeneous Fields via IDEAL (Intermolecular Dipolar-Interaction Enhanced All Lines) Method

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High-resolution NMR is a powerful tool for analyzing molecular structures and dynamics. There are many circumstances where the spatial homogeneity of the magnetic fields is degraded, for instance, by magnetic susceptibilities of various tissues in biomedical in vivo spectroscopy, with ex situ analysis of rock samples for oil exploration, or in studies of porous resin beads in combinatorial chemistry. Distributions of inhomogeneous magnetic field and susceptibility produce spurious field gradients that broaden peaks. In this communication we report a new NMR detection scheme which we call IDEAL (intermolecular dipolar-interaction enhanced all lines) method, which can produce high-resolution NMR spectra in inhomogeneous fields, while maintaining quantitative relationships of chemical shifts, *J* coupling constants, multiplicity patterns, and relative peak areas.

A variety of techniques have been designed to extract NMR spectral information. One approach is to use the scalar and dipolar coupling interactions related to proximity within a molecule. Total coherence transfer echo,[1] intramolecular zero-quantum coherences,[2] constant-time spin-echo correlated spectroscopy,[3] proton-detected heteronuclear method,[4] and composite *z*-rotation pulses[5] have been used for obtaining high-resolution NMR spectra. More recently, high-resolution correlation spectra of disordered solids were obtained by INADEQUATE.[6] In 1D NMR spectroscopy, resonances are often identified by the use of chemical shifts, multiplet structures, coupling constants, and peak areas. However, none of the above techniques can retain all of the above quantities simultaneously. Another approach utilizes the dipolar interactions of the intermolecular spatial proximity. Intermolecular NOE caused by short-range dipolar interactions has been proposed,[7] but the signals from NOE are very weak. Recently, intermolecular zero-quantum coherences (iZQCs) caused by long-range dipolar interactions were shown to be an appealing method, since the signal with substantial and predictable intensities can be attained at high fields.[8] The main challenge in the method is to isolate the iZQC signals from the much stronger conventional single-quantum signals. In this study a novel approach is presented in an attempt to remedy the shortcomings of current techniques.

It has been reported that intermolecular double-quantum coherences (iDQCs) possess features similar to those of iZQCs.[9−11] Our previous works showed that there is no need to use additional phase cycling to obtain "pure" iDQC signals and their intensities are approximately 30% higher than those from iZQCs.[10] Therefore, a modification of iDQC sequence shown in Figure 1 was designed. To understand the essence of the sequence, we consider an *I* (solvent) and *S* (solute) spin systems of different resonance frequencies (where *I* and *S* are either homonuclear spins with chemical shifts, or heteronuclear spins), with the second RF pulse selective for the *I* spin only. The radiation damping effect can be neglected with proper adjustments.[12] The iDQC select gradients are applied just

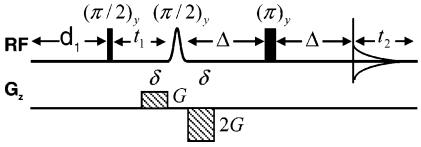

Figure 1. iDQC sequence for the study.

before and following the second RF pulse to minimize the diffusion-related signal loss. When effects of relaxation, diffusion, *J* coupling, and radiation damping are neglected, the intermolecular cross-peak M^S_{obs} between *I* and *S* spins can be represented by[11] $M^S_{obs} = (1/3)\gamma\mu_0 M_0{}^I t_2 M_0{}^S\ e^{i(\omega_I+\omega_S)t_1}\ e^{i(\omega_S)t_2}$, where t_1 and t_2 are the time intervals of the evolution and detection periods, $M_0{}^I$ and $M_0{}^S$ are the equilibrium magnetization densities of the *I* and *S* spins, ω_I and ω_S are the angular frequency offset of the *I* and *S* spins in the absence of field inhomogeneity, respectively, γ is the gyromagnetic ratio, and μ_0 is the magnetic permeability constant. The expression indicates that the intensity for the cross-peak between the solvent and solutes is proportional to the product, $M_0{}^I M_0{}^S$. If $\Delta B(x,y,z)$ is the width of the spatially dependent field inhomogeneity, the resonance frequency for the *S* spins in the F2 dimension ranges between $\omega_{SQC}(x,y,z) = \omega_S \pm {}^1/_2\gamma\ \Delta B(x,y,z)$. Since the spins on two molecules coupled by long-range dipolar interactions are physically close to each other and should experience the same magnetic field over the distance between the two spins, the frequency in the F1 dimension ranges between $\omega_{DQC}(x,y,z) = (\omega_I + \omega_S) \pm \gamma\ \Delta B(x,y,z)$. If the spectrometer reference frequency coincides with the resonant frequency of the *I* spin, i.e., $\omega_I = 0$, the intermolecular cross-peaks between *I* and *S* spins will be centered at (ω_S, ω_S) with separate streaks along the specific direction $\phi = \arctan 2$ due to the field inhomogeneity. It means that the frequency ranges of the streaks in the F1 dimension will be twice those in the F2 dimension. It is noted that the possible diagonals' peak at (ω_S, ω_S) due to COSY signal is completely suppressed by the asymmetry gradient pair, and the second RF pulse is selective for the *I* spin only. Since the detected signal requires a time on the order of $\tau_d = (\gamma\mu_0 M_0{}^I)^{-1}$ to appear and the signal decays very rapidly in the inhomogeneous field, an π RF pulse is applied to refocus the signal at $2\Delta + 2t_1$ after the second pulse. Although the line ranges of the streaks are susceptible to inhomogeneity in both F1 and F2 dimensions, a projection of the cross-peaks along the special axis perpendicular to ϕ gives a 1D high-resolution spectrum without inhomogeneous broadening. Since the spatial correlation via dipolar field of the solvent affects all the spins of the solutes equally, the relative areas and chemical shifts from iDQCs are the same for all resonances as for those in the routine 1D spectrum. On the other hand, the correlation of spatial distribution of field inhomogeneity is independent of *J* couplings, so that the spins of the solute evolve under *J* couplings in both F1 and F2 dimensions. Therefore, the trace in the F2 dimension has the same multiplicity patterns with the scale factor $1 + \cot\phi = 1.5$ of the *J*'s.

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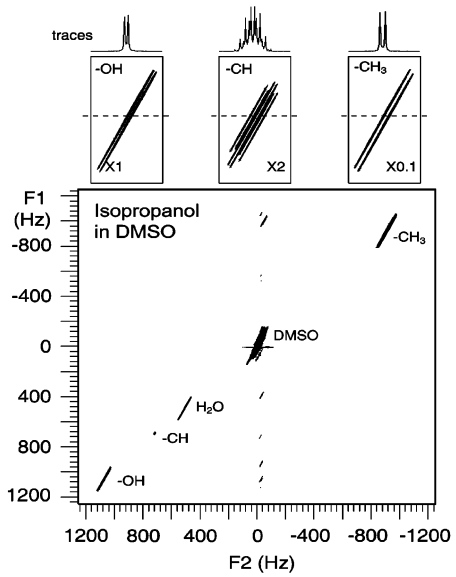

Figure 2. 2D iDQC spectrum in an inhomogeneous field. The −OH, −CH, and $-CH_3$ regions are expanded in both vertical and horizontal directions. The 1D spectra are the traces along the dashed line. Total acquisition time is about 3.5 h.

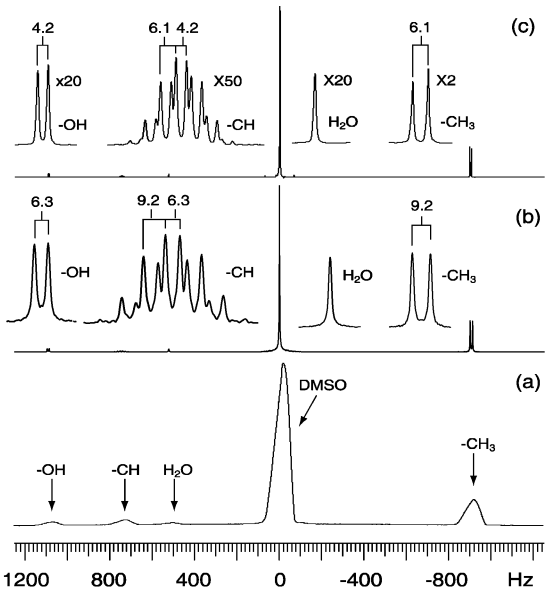

Figure 3. (a) Conventional 1D ^{1}H spectrum in the inhomogeneous field used in Figure 2, (b) accumulated projection of the sheared spectrum shown in Figure 2, and (c) single-pulse spectrum in a well-shimmed field. Insets are magnified in both vertical and horizontal directions.

To test the proposed method, we measured a mixture of 2-propanol and dimethyl sulfoxide (DMSO). It was intentionally deshimmed to produce a line width of ∼105 Hz. In the 2D experiment, data were acquired with 1024 increments, with two scans per increment, 2.5 kHz in both F1 and F2 dimensions, $d_1 = 5$ s, and $\Delta =$ 40 ms. The coherence-selection gradient with strength G of 0.2 T/m and duration δ of 1.2 ms was applied. Figure 2 shows that intermolecular cross-peaks extend along the ϕ direction. The trace indicates that the J multiplets are narrow and well resolved. To obtain a projection spectrum which is similar to a conventional 1D one, a rotation of ϕ around the centers of individual J multiplets was performed. After this shearing procedure, a projection along the new F1 was made, resulting in a spectrum with suppressed inhomogeneous broadening. This projection of the 2D spectra (Figure 3b) has much higher resolution than the original 1D spectrum shown in Figure 3a. The line width is reduced from 105 to 2 Hz, remarkably similar to the conventional high-resolution ^{1}H spectrum (Figure 3c).

The IDEAL sequence ensures that solute-solvent cross-peaks are obtained while solute-solute cross-peaks are effectively suppressed. Unlike other methods, this technique simply requires that the molecules containing two or more spin populations be intermingled on a microscopic scale which provides spatial correlation via an intermolecular dipolar field. In a 600 MHz spectrometer, the ^{1}H signal from iDQCs between the solvent and the solute is about one-tenth of the equilibrium proton magnetization, which is much larger than those from NOEs between the solvent and the solute.[7] Therefore, the method can be applied to a wider range of samples than the techniques which rely on J coupling or NOEs. The 1.5 times change in the scale factor of J couplings may help to obtain refined multiplet patterns in many cases (i.e., weakly coupled systems). Strong coupling influences both the transition intensities and the observed splits, often rendering spectral interpretation more difficult. The rescaling factor for the J constant introduced by the IDEAL can result in more complicated multiplet patterns. To overcome these difficulties in strongly coupled systems, it is desirable to have an unchanged scale for the J constant. Decreased sampling width in F1 dimension and scan number per increment can shorten acquisition time. Potential approaches for improvement will be discussed elsewhere in a full paper. Although the method will fail with extremely large field inhomogeneity discussed in ref 5, it works in the case of moderate inhomogeneous fields even if the solvent peak partly overlaps some of the solute resonances. Our results suggest that the method works well for samples such as a mixture of tyrosine and glutaminic acid in which there are overlapped solvent/solute lines. Similar to routine NMR methods, there are complications in studying larger molecules. Further work will be done to demonstrate the ranges of the field inhomogeneity and the size of the solute molecule over which the method can be applied.

In conclusion, we have outlined a novel method to obtain 1D high-resolution NMR in inhomogeneous fields. Chemical shifts, J couplings, multiplicity patterns, and relative spectral areas are mostly retained. It has significant advantages over its iZQC counterpart,[8] and it is useful for in vivo or in situ high-resolution NMR studies on catalytic reactions and combinatorial chemistry.

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Supporting Information Available: Additional data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Weitekamp, D. P.; Garbow, J. R.; Murdoch, J. B.; Pines, A. *J. Am. Chem. Soc.* **1981**, *103*, 3578−3579.
(2) Hall, L. D.; Norwood, T. J. *J. Chem. Soc. Chem. Commun.* **1986**, 44−46.
(3) Hall, L. D.; Norwood, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 7579−7581.
(4) Bendel, P.; van Zijl, P. C. M. *J. Magn. Reson.* **1994**, *110*, 130−135.
(5) Meriles, C. A.; Sakellariou, D.; Heise, H.; Moule, A. J.; Pines, A. *Science* **2001**, *293*, 82−85.
(6) Sakellariou, D.; Brown, S. P.; Lesage, A.; Hediger, S.; Bardet, M.; Meriles, C. A.; Pines, A.; Emsley, L. *J. Am. Chem. Soc.* **2003**, *125*, 4376−4380.
(7) Balbath, J. J.; Conradi, M. S.; Cistola, D. P.; Tang, C. G.; Garbow, J. R.; Hutton, W. C. *Chem. Phys. Lett.* **1997**, *277*, 367−374.
(8) (a) Vathyam, S.; Lee, S.; Warren, W. S. *Science* **1996**, *272*, 92−96. (b) Lin, Y. Y.; Ahn, S.; Murali, N.; Brey, W.; Bowers, C. R.; Warren, W. S. *Phys. Rev. Lett.* **2000**, *85*, 3732−3735.
(9) Mori, S.; Hurd, R. E.; van Zijl, P. C. M. *Magn. Reson. Med.* **1997**, *37*, 360−340.
(10) Zhong, J.; Chen, Z.; Kwok, E. *Magn. Reson. Med.* **2000**, *43*, 335−341.
(11) Chen, Z.; Chen, Z. W.; Zhong, J. *J. Chem. Phys.* **2001**, *115*, 10769−10779.
(12) Sklenar, V. *J. Magn. Reson., Ser. A* **1995**, *114*, 132−135.

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