Keywords: crown compounds · gold · luminescence · molecular switches · S ligands

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Sensitivity Enhancement in Transverse Relaxation Optimized NMR Spectroscopy**

Guang Zhu,* Xiangming Kong, Xianzhong Yan, and Konghong Sze

Continuing efforts to study ever larger biologically relevant proteins by NMR spectroscopy have resulted in many advances over the past 10 years; one notable development is the introduction of multidimensional heteronuclear techniques for proteins labeled with ^{13}C and ^{15}N. These techniques have greatly facilitated NMR studies of the structure and function of proteins with molecular weights up to 30 kD. However, their application to larger proteins is hampered by the decrease in the molecular tumbling rate.[1] This shortens the transverse relaxation time of the protein, which in turn

[*] Dr. G. Zhu, M.Sc. X. Kong, M.Sc. X. Yan, Dr. K. Sze
Department of Biochemistry
Hong Kong University of Science and Technology
Clear Water Bay, Kowloon (Hong Kong)
Fax: (+852) 2358-1552
E-mail: gzhu@ust.hk

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leads to larger spectral line widths and lower sensitivity. In a high magnetic field, dipole–dipole interactions and chemical shift anisotropy are the dominant factors in the relaxation of ^{1}H, ^{13}C, and ^{15}N. These two relaxation mechanisms can significantly interfere with one another,[2] a fact that must be taken into account in more precise measurements of protein dynamics[3] by NMR spectroscopy. Recently, a major advance in the study of large proteins (>30 kD) was made with the discovery that the interference between dipole–dipole interaction and chemical shift anisotropy can greatly reduce the transverse relaxation rates of ^{1}H and ^{15}N, and thus make the study of very large biomolecules possible.[4] This line-narrowing effect is utilized in transverse relaxation optimized spectroscopy (TROSY), in which only one component ($\omega_N+\pi^1J_{NH}$, $\omega_H-\pi^1J_{NH}$) of the four multiplets ($\omega_N\pm\pi^1J_{NH}$, $\omega_H\pm\pi^1J_{NH}$) of a ^{15}N–^{1}H moiety is observed. Theoretical calculations indicate that almost complete cancellation of the transverse relaxation of this component can be realized at a ^{1}H frequency near 1 GHz. The experimental results demonstrated a dramatic reduction in spectral line widths in a TROSY ^{15}N–^{1}H spectrum compared to those of an HSQC spectrum at 750 MHz.[4] Since only one component of the four multiplets is observed in the 2D ^{15}N–^{1}H TROSY experiment, the total intensity of the signal is reduced by 75%. However, the much narrower line widths in both dimensions make this experiment especially attractive compared to the traditional HSQC experiment for NMR studies of larger biomolecules.

We observed that the sensitivity of the TROSY experiment could be improved by a factor of $\sqrt{2}$ by simply changing the original phase cycles and the data-processing procedure. This method is similar to that applied in the sensitivity-enhanced HSQC, HMQC, and TOCSY experiments.[5] The pulse sequence of the sensitivity-enhanced TROSY experiment is shown in Figure 1. For each t_1 value, two transients are recorded with different radio frequency (rf) pulses and receiver phase cycles and are stored separately. The coherence transfer and evolution in the pulse sequence can be evaluated on the basis of the product operator formalism and the single-transition base operators[6] $S^{\pm}_{12}=\frac{1}{2}S^{\pm}+I_zS^{\pm}$ and $S^{\pm}_{34}=\frac{1}{2}S^{\pm}-I_zS^{\pm}$. The relaxation formalism is given in reference [4].

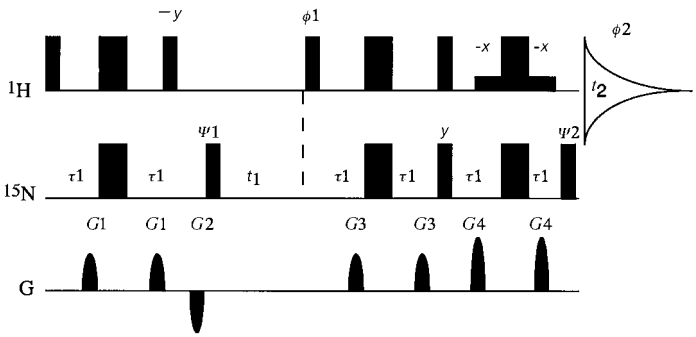

Figure 1. Pulse scheme of the sensitivity-enhanced ^{15}N–^{1}H TROSY correlation experiment. The narrow and wide bars represent nonselective 90° and 180° pulses, respectively. Pulses are applied along the x direction unless indicated otherwise. Because the water signal cannot be suppressed by presaturation owing to strong radiation damping at high magnetic field, solvent suppression was performed by the watergate scheme with an rf pulse of 2.1 ms at 110 Hz. The delay τ_1 corresponds to $1/(4\,^1J_{NH})=2.7$ ms. All gradients are applied along the z axis. The magnitudes of $G1$, $G2$, $G3$ and $G4$ are 12, 19, 14 and 21 G/cm with durations of 0.4, 1.0, 0.4, and 0.5 ms, respectively. Two transients were acquired and stored separately for each increment of t_1. The final absorption spectrum is obtained by the method described in the text. The first transient is obtained by using of the phase cycle $\psi1=y,\ x,\ -y,\ -x;\ \phi1=y;\ \psi2=x;\ \mathrm{rec}\,\phi2=x,\ -y,\ -x,\ y$. For the second transient, the phase cycle $\psi1=y,\ x,\ -y,\ -x;\ \phi1=-y;\ \psi2=-x;\ \mathrm{rec}\,\phi2=x,\ y,\ -x,\ -y$ is used. Note that the sign convention for the receiver phase may differ among the spectrometer manufacturers.[8]

For the first transient in the first step of the phase cycle (where $\psi1=y$, $\phi1=y$, $\psi2=x$, and $\mathrm{rec}\,\phi2=x$) the magnetization σ_1 before acquisition can be expressed by Equation (a).

$$\begin{aligned}\sigma_1=&\tfrac{1}{2}I^-[i\cos(\omega_s^{12}t_1)-\sin(\omega_s^{12}t_1)]\exp(-R_{12}t_1)\\&+\tfrac{1}{2}I^-[i\cos(\omega_s^{34}t_1)+\sin(\omega_s^{34}t_1)]\exp(-R_{34}t_1)\\&+I^-S_z[-i\cos(\omega_s^{12}t_1)+\sin(\omega_s^{12}t_1)]\exp(-R_{12}t_1)\\&+I^-S_z[i\cos(\omega_s^{34}t_1)+\sin(\omega_s^{34}t_1)]\exp(-R_{34}t_1)\end{aligned}\qquad(a)$$

Here R_{12} and R_{34} are the relaxation rates of the individual components of the S spin,[4] and ω_s^{12} and ω_s^{34} are $\omega_N+\pi^1J_{NH}$ and $\omega_N-\pi^1J_{NH}$, respectively. In the second step of the phase cycle (where $\psi1=x$, $\phi1=y$, $\psi2=x$, and $\mathrm{rec}\,\phi2=-y$) the magnetization σ_2 before detection is given by Equation (b).

$$\begin{aligned}\sigma_2=&\tfrac{1}{2}I^-[-\cos(\omega_s^{12}t_1)-i\sin(\omega_s^{12}t_1)]\exp(-R_{12}t_1)\\&+\tfrac{1}{2}I^-[\cos(\omega_s^{34}t_1)-i\sin(\omega_s^{34}t_1)]\exp(-R_{34}t_1)\\&+I^-S_z[\cos(\omega_s^{12}t_1)+i\sin(\omega_s^{12}t_1)]\exp(-R_{12}t_1)\\&+I^-S_z[\cos(\omega_s^{34}t_1)-i\sin(\omega_s^{34}t_1)]\exp(-R_{34}t_1)\end{aligned}\qquad(b)$$

The magnetization of the first transient in a four-step phase cycle is given by Equation (c). Similarly, the magnetization of the second transient can be expressed by Equation (d).

$$\begin{aligned}M_1=&2[\sigma_1(d)-i\sigma_2(d)]\\=&-2I^-[-i\cos(\omega_s^{12}t_1)+\sin(\omega_s^{12}t_1)]\exp(-R_{12}t_1)\\&+4I^-S_z[-i\cos(\omega_s^{12}t_1)+\sin(\omega_s^{12}t_1)]\exp(-R_{12}t_1)\end{aligned}\qquad(c)$$

$$\begin{aligned}M_2=&-2I^-[i\cos(\omega_s^{12}t_1)+\sin(\omega_s^{12}t_1)]\exp(-R_{12}t_1)\\&+4I^-S_z[i\cos(\omega_s^{12}t_1)+\sin(\omega_s^{12}t_1)]\exp(-R_{12}t_1)\end{aligned}\qquad(d)$$

During the acquisition period, no decoupling is applied, and the detectable magnetization relaxes in a manner similar to that of ^{15}N in the t_1 domain. The detectable magnetization can be expressed by Equations (e) and (f).[4] Here R_{13} and R_{24} are the relaxation rates of the individual components of the I spin,[4] and ω_I^{13} and ω_I^{24} are $\omega_H+\pi^1J_{NH}$ and $\omega_H-\pi^1J_{NH}$, respectively. The signal intensities of the detectable magnetization of the two transients are given by Equations (g) and (h).

$$I^-\rightarrow A(\exp[i\omega_I^{13}-R_{13}]t_2+\exp[i\omega_I^{24}-R_{24}]t_2)\qquad(e)\text{-}$$

$$2I^-S_z\rightarrow A(\exp[i\omega_I^{13}-R_{13}]t_2-\exp[i\omega_I^{24}-R_{24}]t_2)\qquad(f)$$

$$M_1=-4[-i\cos(\omega_s^{12}t_1)+\sin(\omega_s^{12}t_1)]\exp(-R_{12}t_1)\exp(i\omega_I^{24}t_2-R_{24}t_2)\qquad(g)$$

$$M_2=-4[i\cos(\omega_s^{12}t_1)+\sin(\omega_s^{12}t_1)]\exp(-R_{12}t_1)\exp(i\omega_I^{24}t_2-R_{24}t_2)\qquad(h)$$

After data acquisition, the two transients for each t_1 value are added and subtracted, respectively, to form corresponding real and imaginary FIDs with a 90° shift added to one of the two resulting FIDs. The final pure absorption spectrum can be obtained by data processing according to the method of States et al.[7]

The effectiveness of the sensitivity-enhanced TROSY (enTROSY) experiment is demonstrated by ^{15}N–^{1}H correlation

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spectroscopy of ^{15}N-labeled calmodulin. Measurements were made at 15 °C on a Varian Inova 500 MHz NMR spectrometer, and the protein concentration was 1 mM in H_2O/D_2O (9/1) at pH 6.8. Figure 2 displays a small region of $^{15}N-^{1}H$ correlation spectra of calmodulin. Figure 2a shows the conventional HSQC spectrum obtained without the use of

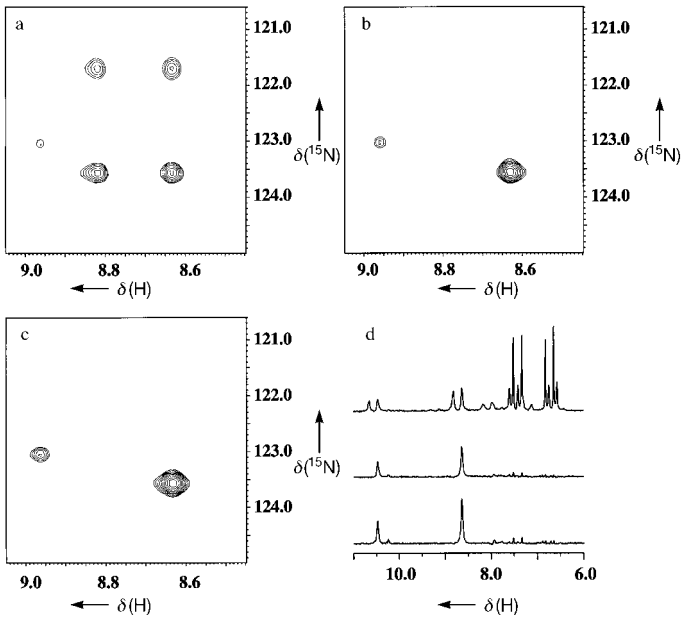

Figure 2. Contour plots of $^{15}N-^{1}H$ correlation spectra of ^{15}N-labeled calmodulin. a) Conventional HSQC spectrum, obtained without decoupling during the t_1 and t_2 periods. b) Spectrum recorded in a conventional TROSY experiment.[4] c) Spectrum recorded in a sensitivity-enhanced TROSY experiment (see text). d) One-dimensional cross sections from the spectra a–c at $\delta(^{15}N) = 123.6$ (from top to bottom). The peaks between 6 and 8 ppm in the HSQC cross section correspond to the cross-peak multiplets at the ^{15}N frequency ($\omega_N - \pi^1 J_{NH}$), which is not observed by TROSY experiments. Spectra b and c, which were recorded and processed with the same parameters, have been scaled to the same noise level. The spacing factor between two consecutive contour lines is 1.2.

decoupling during the t_1 and t_2 periods. It is notable that even at 500 MHz there are significant differences in line width between the four individual multiplets. Figures 2b and 2c are taken from spectra recorded in conventional and sensitivity-enhanced TROSY experiments, respectively. Comparison of Figures 2b and 2c, as well as all other correlation peaks (not shown here), shows that a uniform enhancement in sensitivity of all peaks by a factor of $\sqrt{2}$ was achieved without introducing any artifacts.

The introduction of the TROSY experiment makes NMR spectroscopy a promising technique for studying the structure and function of larger biomolecules. We have improved the sensitivity of the original 2D TROSY experiment by a factor of $\sqrt{2}$ by using different phase cycling and data-processing schemes. This improvement will doubtless have widespread practical application in high-field NMR studies of large proteins.

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[8] Note added in proof: A reviewer's comments alerted us to a difference between Varian and Bruker spectrometers, which requires that the *y*-axis receiver phases be inverted. It is also necessary to invert the *y*-axis pulse phases. In the pulse sequence of Figure 1, the particular phase cycling means that only the phase of the second 90° ^{1}H pulse needs to be considered. For optimal sensitivity, the phase of this pulse should be $-y$ for Varian and $+y$ for Bruker. If this phase is inverted then the "steady-state" enhancement, described by Pervushin et al. (*J. Am. Chem. Soc.* **1998**, *120*, 6394–6400) after this manuscript was submitted, will be lost. The sensitivity enhancement presented in this work is independent of the phase of this pulse and a $\sqrt{2}$ enhancement is gained over the corresponding TROSY experiment that has the same phase for this pulse.

Directed Positioning of Organometallic Fragments Inside a Calix[4]arene Cavity

Catherine Wieser-Jeunesse, Dominique Matt,* and André De Cian

A major attraction of cone-shaped calix[4]arenes concerns the presence of a macrocyclic cavity defined by four symmetrically sited phenoxy rings.[1] To date, exploitation of such organized structures has mostly relied on converging π systems on the inner side that facilitate weak binding of various substrates,[2] including certain metal cations.[3] Surprisingly, despite increasing interest in the application of calixarenes as ligands in transition metal chemistry,[4] the

[*] Dr. D. Matt, Dr. C. Wieser-Jeunesse
Université Louis Pasteur, UMR 7513 CNRS
Groupe de Chimie Inorganique Moléculaire
1 rue Blaise Pascal, F-67008 Strasbourg Cedex (France)
Fax: (+33) 3-88-617852
E-mail: dmatt@chimie.u-strasbg.fr
Dr. A. De Cian
Université Louis Pasteur, UMR 7513 CNRS
Laboratoire de Cristallochimie et Chimie Structurale
4 rue Blaise Pascal, F-67008 Strasbourg Cedex (France)

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