



## Communication

High-resolution  $^{14}\text{N}$ -edited  $^1\text{H}$ - $^{13}\text{C}$  correlation NMR experiment to study biological solidsJean-Paul Amoureux<sup>a,\*</sup>, Julien Trébosc<sup>a</sup>, Bingwen Hu<sup>a</sup>, Nicholas Halpern-Manners<sup>b</sup>, Sasa Antonijevic<sup>c,d,\*</sup><sup>a</sup> *Unité de Catalyse et Chimie du Solide, UMR-CNRS 8181, Université de Lille 1, 59652 Villeneuve d'Ascq cedex, France*<sup>b</sup> *Department of Chemistry, University of California, Berkeley, CA 94720, USA*<sup>c</sup> *Department of Chemical Engineering, University of California, Berkeley, CA 94720, USA*<sup>d</sup> *Materials Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA*

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## ABSTRACT

It was recently shown that nuclear magnetic resonance (NMR) spectra of nitrogen-14 (spin  $I = 1$ ) can be obtained by indirect detection via spin  $S = 1/2$  nuclei in powders spinning at the magic angle. An increased number of solid-state NMR methods are now available to tailor sequences for specific purposes, e.g., hetero-nuclear dipolar recoupling or homo-nuclear dipolar decoupling schemes. Here, we combine the latest recoupling and decoupling techniques to obtain high-resolution  $^1\text{H}$ - $^{13}\text{C}$  through-space correlation spectra, where only the correlation peaks of those carbons close to nitrogen nuclei are observed. The experiment is demonstrated on a  $^{13}\text{C}$  enriched L-histidine. HCl·H<sub>2</sub>O powder sample.

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## 1. Introduction

Nitrogen is a nucleus of considerable chemical and biological importance. Despite the high isotopic abundance (99.63%) of nitrogen-14 (spin  $I = 1$ ), it has remained very difficult to study with nuclear magnetic resonance (NMR) spectroscopy. Thus, nitrogen NMR has been mostly limited to the less abundant isotope  $^{15}\text{N}$ , hence requiring isotopic enrichment. The main difficulty in observing  $^{14}\text{N}$  arises from the large quadrupole interaction, which results in broad NMR spectra of molecules in both liquid and solid states. In solutions, the broadening comes from very fast quadrupolar relaxation mechanisms. In solid-state samples, the large electric quadrupole moment results in spectra having a width of several MHz wide due to the first-order quadrupole interaction. The  $^{14}\text{N}$  MAS study of powdered solids has therefore been reduced to samples with quadrupole coupling constants of  $C_Q \sim 1$  MHz or less [1–5]. Tycko et al. [6–8] have demonstrated overtone NMR spectroscopy, where spectra are only influenced by the much smaller second-order quadrupole interaction. Because these transitions are only weakly allowed and require the use of a very large radio-frequency (rf) field, overtone methods result in poor sensitivity. Re-

cently, renewed interest in  $^{14}\text{N}$  NMR methodology led by Gan [9] as well as Cavadini et al. [10,11] has yielded a method for the indirect detection of  $^{14}\text{N}$  via a combination of scalar  $J$ -couplings and residual dipolar splittings (RDS). Using these new experiments it is possible to obtain two-dimensional (2D) spectra where  $^{14}\text{N}$  is observed in the indirect detection and the predominant broadening is through second-order quadrupolar interactions that are only a few kHz wide. More recently, Gan has shown that the combination of dipolar recoupling (instead of  $J$ -coupling) and HMQC (called  $D$ -HMQC) [12], is suitable for the efficient indirect detection of  $^{14}\text{N}$  via through-space dipolar couplings. As the dipolar coupling is much larger than both the  $J$ -coupling and RDS, Gan et al. obtained a 2D  $^1\text{H}$ - $^{14}\text{N}$  correlation NMR spectrum in just a few minutes using the rotary resonance recoupling ( $R^3$ )  $D$ -HMQC experiment [13]. Recently, it has been shown on a  $^{13}\text{C}$  enriched L-histidine.HCl·H<sub>2</sub>O sample that a 3D  $^1\text{H}$ - $^{13}\text{C}$ - $^{14}\text{N}$  correlation spectrum could also be obtained using the through-space dipolar interaction [14]. The efficiency of  $^{13}\text{C}$ - $^{14}\text{N}$ - $^{13}\text{C}$  transfer was very weak (4–5%) and the experiment lasted 85 h on a 18.8 T spectrometer. In order to decrease the experimental time it would be desirable to acquire one  $^1\text{H}$ - $^{14}\text{N}$  and two  $^1\text{H}$ - $^{13}\text{C}$  through-space 2D HETCOR spectra instead of running a 3D experiment: the first  $^1\text{H}$ - $^{13}\text{C}$  with cross-peaks related to all carbons, and the second where cross-peaks are only related to those carbons close to nitrogen atoms. A method to obtain  $^{14}\text{N}$ -edited  $^1\text{H}$ - $^{13}\text{C}$  spectra has already been proposed

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with the Saturation-Pulse Induced Dipolar Exchange with Recoupling (SPIDER) [15]. The SPIDER experiment is mainly suitable for slow spinning rates ( $\nu_R \approx 5$  kHz), which are not sufficient to cancel the  $^{13}\text{C}$  chemical shift anisotropy (CSA) on high-field spectrometers. We propose here a new magic angle spinning (MAS)  $^{14}\text{N}$ -edited method for  $^1\text{H}$ - $^{13}\text{C}$  through-space HETCOR spectra to obtain high-resolution in both dimensions. We combine latest hetero-recoupling (Simultaneous Frequency and Amplitude Modulation: SFAM<sub>2</sub>) [16,17] and homo-decoupling (Smooth Amplitude Modulation: SAM<sub>3</sub>) [18] techniques along with a filter based on  $^{13}\text{C}$ - $^{14}\text{N}$  D-HMQC experiment.

## 2. Pulse sequence

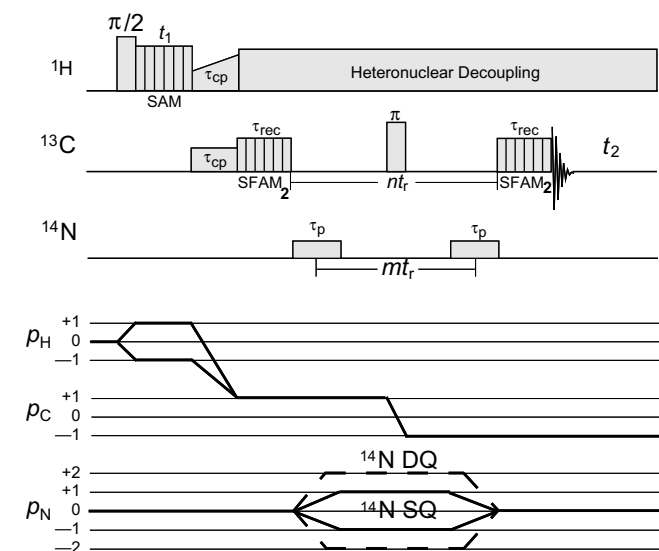
The pulse sequence and coherence transfer pathway diagrams proposed to obtain high-resolution  $^{14}\text{N}$ -edited  $^1\text{H}$ - $^{13}\text{C}$  2D correlation spectra of powdered samples under MAS and rotor-synchronization are shown in Fig. 1. The  $^1\text{H}$  coherences are excited and allowed to evolve during the  $t_1$  period while applying  $^1\text{H}$  homo-nuclear decoupling in order to obtain high-resolution spectra in the indirect dimension. We have decided to use the latest homo-nuclear decoupling technique SAM<sub>3</sub> (Smooth Amplitude Modulation with three modulation periods per rotor period), which leads to spectra with constant scaling factor and that are free from zero and image peaks, and RRF lines [18]. Both  $^1\text{H}$  coherences ( $\rho_{\text{H}} = \pm 1$ ) are allowed to contribute to the observed signal, resulting in amplitude modulation as a function of the  $^1\text{H}$  chemical shifts. After the  $t_1$  period,  $^1\text{H}$  coherences are transferred to the  $^{13}\text{C}$  nuclei by means of cross-polarization. This step is followed by the  $^{14}\text{N}$  D-HMQC filter in which hetero-

nuclear multiple quantum coherences are excited utilizing  $^{13}\text{C}$ - $^{14}\text{N}$  dipolar recoupling schemes. The important distinction between HMQC experiments involving  $^{14}\text{N}$  and  $^{15}\text{N}$  nuclei is that one can select either  $^{14}\text{N}$  single quantum (SQ) or double quantum (DQ) coherences. The  $^{14}\text{N}$  SQ coherences are utilized here as they lead to the greatest signal intensity. It is important that pulses applied on nitrogen nuclei are rotor synchronized to ensure complete removal of the first-order quadrupolar interaction as depicted on diagram, where  $m$  is an integer number and is aimed to be as small as possible, with  $m \geq 1$ . Depending upon the type of hetero-nuclear recoupling sequence ( $\gamma$ -encoded or not), it may also be necessary to rotor synchronize the two blocks of dipolar recoupling periods as shown on the diagram, where  $n$  is an integer number and  $n \geq m$ . The  $^{13}\text{C}$  coherences are acquired during the  $t_2$  period while hetero-nuclear  $^1\text{H}$  decoupling is applied during D-HMQC and acquisition times.

Hetero-nuclear dipolar recoupling between two types of nuclei can be achieved by applying specially designed pulses that rely on well-defined non-selective rotations on both nuclei. However, due to the large  $^{14}\text{N}$  quadrupole interaction, there are few ways to apply rf pulses that would result in non-selective rotations of  $^{14}\text{N}$  magnetization. Therefore, we have restricted our choice of recoupling schemes to those that would only manipulate  $^{13}\text{C}$  spins. The R<sup>3</sup> method, which has been used in previous  $^{14}\text{N}$  D-HMQC experiments, is one among many hetero-nuclear dipolar recoupling techniques [17]. It was first introduced by Levitt et al. [19,20] and serves to recover various anisotropic interactions while excluding others, depending on the R<sup>3</sup> parameter  $n_{\text{rec}}$  correlating rf field to spinning speed:  $n_{\text{rec}} = \nu_{\text{rf}}/\nu_R$ . The  $n_{\text{rec}} = 1/2$  condition, also known as HORROR [21], recouples only the homo-nuclear dipolar coupling. With  $n_{\text{rec}} = 1$ , the recoupling occurs for the CSA and both the homo- and hetero-nuclear dipolar interactions. For  $n_{\text{rec}} = 2$ , R<sup>3</sup> reintroduces the CSA and the hetero-nuclear dipolar interaction. We have very recently [17] compared several hetero-nuclear dipolar recoupling sequences to be used with indirectly detected MAS D-HMQC experiments between spin-1/2 and quadrupolar nuclei. In all cases, it has been noted that R<sup>3</sup> methods are less efficient due to the narrowness of their rf-matching curves. When homo-nuclear interactions are not negligible, as is the case in this work, the most interesting recoupling methods are the symmetry-based ( $R12_3^5$ ,  $R20_9^5$ ,  $SR4_7^2$ ) [17,22] sequences and simultaneous frequency and amplitude modulation (SFAM) [16,17] irradiation. With SFAM methods, the carrier frequency of the rf field is modulated cosinusoidally, while its amplitude is modulated sinusoidally. When there are few homo-nuclear interactions, it has been shown that the best efficiency for the hetero-nuclear dipolar recoupling is observed when the modulation frequency of this rf field is equal to  $\nu_R$ , leading to the SFAM<sub>1</sub> method [16]. However, SFAM<sub>1</sub> also recouples the homo-nuclear dipolar interactions, and thus should not be used when these are not negligible. In this case, the modulation frequency should be  $2\nu_R$ , leading to the SFAM<sub>2</sub> method [17]:

$$\Delta\nu_0(t) = \Delta\nu_0^{\text{max}} \cos(4\pi\nu_R t) \quad \nu_1(t) = \nu_1^{\text{max}} \sin(4\pi\nu_R t) \quad (1)$$

In both cases, the best efficiency is observed when the depth of the frequency modulation ( $\Delta\nu_0^{\text{max}}$ ) and the maximum amplitude of the rf field ( $\nu_1^{\text{max}}$ ) are of sufficient amplitude. The experimental comparisons were performed at  $\nu_R = 20$  kHz, and it was predicted that the advantage of SFAM<sub>2</sub> with respect to all other sequences increases with the spinning speed [17]. Indeed, SFAM<sub>2</sub> uses continuous modulations of frequency and amplitude, and is thus subjected to very little of the classical pulse-limitations (rise and fall times, phase glitches, etc.), which is not the case with the  $RN_n^m$  recoupling sequences. We have therefore decided to recouple the  $^{13}\text{C}$ - $^{14}\text{N}$  dipolar interaction with the SFAM<sub>2</sub> sequence. This sequence being  $\gamma$ -encoded, the two blocks of dipolar recoupling periods were rotor synchronized ( $nt_r$ ) as shown in Fig. 1.



**Fig. 1.** Pulse sequence and coherence transfer pathways for the  $^1\text{H}$ - $^{13}\text{C}$  CP HETCOR correlation NMR experiments implementing  $^{14}\text{N}$ -editing via dipolar driven D-HMQC sequence. During the  $^{14}\text{N}$  editing period it is possible to selectively choose single-quantum (SQ) (solid lines) or double-quantum (DQ) (dashed lines)  $^{14}\text{N}$  coherences. Homo-nuclear  $^1\text{H}$  decoupling sequences can be used during  $t_1$ , e.g., Smooth Amplitude Modulation (SAM) [18], in order to obtain high-resolution  $^1\text{H}$  spectra in the indirect dimension. Recoupling of dipolar interactions between  $^{13}\text{C}$  and  $^{14}\text{N}$  nuclei during the excitation and reconversion periods of D-HMQC can be achieved by Simultaneous Frequency and Amplitude Modulated (SFAM<sub>2</sub>) pulses applied on  $^{13}\text{C}$  nuclei [17]. The time between two blocks of SFAM<sub>2</sub> pulses should be equal to a multiple of the number of rotor periods ( $nt_r$ ). It is also important to adjust the delay between the centers of the two nitrogen pulses to be equal to a multiple numbers of rotor periods ( $mt_r$ ) with  $n \geq m$ . Efficient hetero-nuclear decoupling is required to prevent  $^1\text{H}$ - $^{13}\text{C}$  coherences to be created.

### 3. Experimental

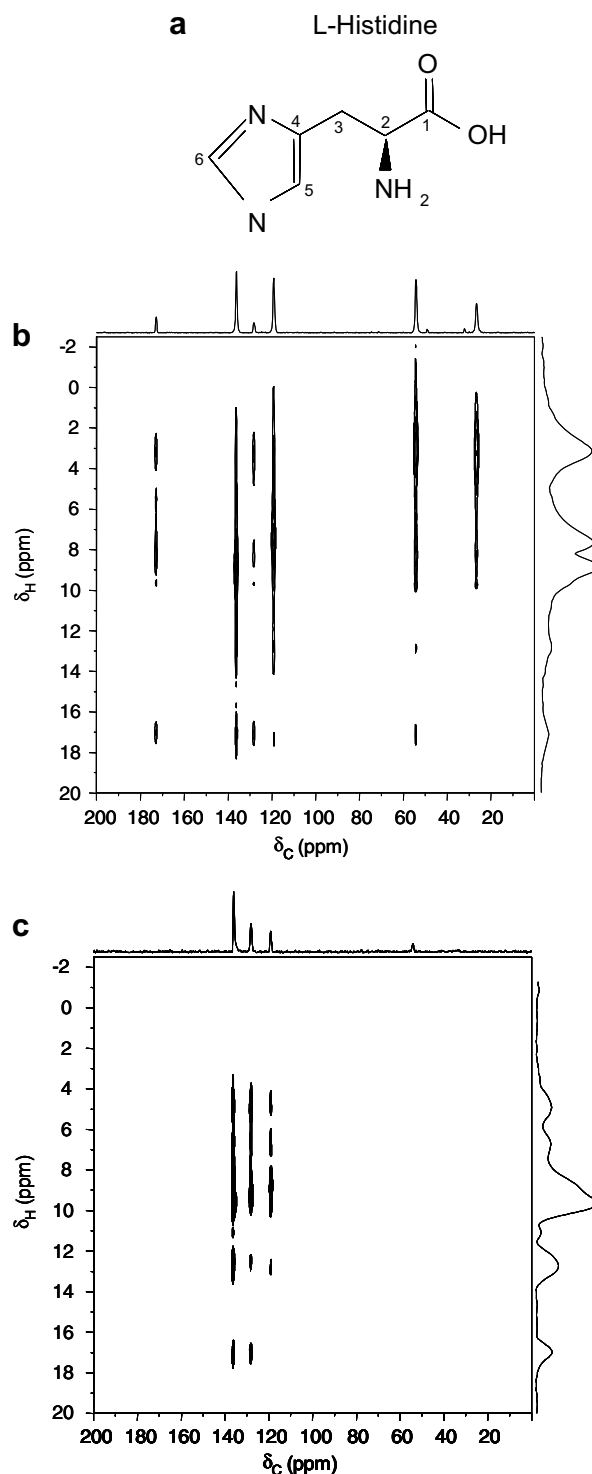
Our test sample, L-histidine·HCl·H<sub>2</sub>O (98% <sup>13</sup>C enriched), was purchased from Cortecnet and used without further purification. It has three different nitrogen sites (Fig. 2a), which are all connected to at least one <sup>1</sup>H and one <sup>13</sup>C. Nitrogen N<sub>11</sub> connects with three <sup>1</sup>H and one carbon (C<sub>2</sub>), while N<sub>12</sub> and N<sub>13</sub> each connects to one <sup>1</sup>H and two carbons: C<sub>4</sub>/C<sub>6</sub>, and C<sub>5</sub>/C<sub>6</sub>, respectively. The samples were packed in 3.2 mm zirconia rotors and spun at  $\nu_R = 17.5$  kHz in a Bruker triple resonance MAS probe at 18.8 T magnetic field (<sup>1</sup>H, <sup>13</sup>C and <sup>14</sup>N Larmor frequencies of 800, 201 and 58 MHz, respectively). Spectra were recorded using a Bruker Avance II console. Cross-polarization (CP) was used with  $\nu_{1,1H} = 70$  kHz and  $\nu_{1,13C} = 52.5$  kHz. The SFAM<sub>2</sub> scheme was used for <sup>13</sup>C–<sup>14</sup>N recoupling with a carbon rf peak amplitude of  $\nu_{1,13C}^{peak} = 40$  kHz and the offset modulated in extent of 10 kHz. The <sup>1</sup>H homo-nuclear SAM decoupling scheme was used with three rf periods for the cosine amplitude modulation, with constant phase, during a single rotor period (SAM<sub>3</sub>), varying the proton rf amplitude up to  $\nu_{1,1H}^{peak} = 70$  kHz. The rf-carrier was able to be fixed in the middle of the proton spectrum due to the lack of zero-frequency and image peaks and first-order RRF lines [18]. The experimental scaling factor was close to its optimal theoretical value:  $\kappa_{opt} \approx 0.70$  [23]. Small Phase Incremental ALternation (SPINAL-64) [24] proton decoupling scheme was used with  $\nu_{1,1H} = 80$  kHz and pulse widths of 5.7  $\mu$ s. With a 1 kW amplifier, the <sup>14</sup>N pulses had a modest amplitude of  $\nu_{1,14N} = 30$  kHz, calibrated by direct detection of NH<sub>4</sub>Cl. The chemical shifts of <sup>1</sup>H, and <sup>13</sup>C are referenced relative to TMS, which was also used to calibrate the rf power levels. Typically 35 mg of material were used to obtain the spectra shown in this work.

### 4. Results

2D <sup>1</sup>H–<sup>13</sup>C HETCOR spectra of L-histidine, with homo-nuclear decoupling, are shown in Fig. 2, after <sup>1</sup>H rescaling. Total correlation between <sup>1</sup>H and <sup>13</sup>C is obtained using the standard CP-HETCOR sequence and all the carbon atoms are observed in Fig. 2b as expected. Using sequence in Fig. 1, with the SAM<sub>3</sub> decoupling during  $t_1$ , we obtain one spectrum that displays only <sup>13</sup>C resonances that are in close proximity to <sup>14</sup>N nuclei (Fig. 2c). The weak efficiency of the <sup>13</sup>C–<sup>14</sup>N–<sup>13</sup>C transfer is observable by comparing Fig. 2b and c. Indeed, the S/N ratio is much lower in Fig. 2c than in Fig. 2b, in spite of 32 more transients. One observes: (i) that CH<sub>2</sub> + CH<sup>(3)</sup> peak observed at c.a. 1.5 ppm [25] in Fig. 2b has disappeared in Fig. 2c, (ii) that the two peaks corresponding to CH<sup>(1)</sup> + NH<sub>3</sub><sup>+</sup> + CH<sup>(2)</sup> in Fig. 2b (6–9 ppm) simplify into a single NH<sub>3</sub><sup>+</sup> peak in Fig. 2c (9 ppm), and (iii) that NH<sup>(1)</sup> ( $\approx 16$  ppm) and NH<sup>(2)</sup> ( $\approx 12$  ppm) peaks [25] are emphasized in Fig. 2c with respect to Fig. 2b. Spectra shown in Fig. 2 are only slightly more resolved along the F<sub>1</sub> dimension than those displayed without homo-nuclear decoupling (not shown). Indeed, they have been recorded at  $\nu_R = 17.5$  kHz, and the resolution gain is expected to be more pronounced at higher spinning rates (c.a. 60–70 kHz) as shown recently [18]. However, faster spinning speed would require larger <sup>1</sup>H decoupling rf amplitude that are not available on our probe. Indeed, we noticed that a minimum ratio  $\nu_{1,1H}/\nu_R \approx 5$  is necessary to prevent <sup>1</sup>H–<sup>13</sup>C coherence built up during SFAM<sub>2</sub> recoupling periods that leads to signal decrease through spin diffusion on the proton side, in addition to lower resolution on <sup>13</sup>C spectrum.

### 5. Conclusion

We have demonstrated a solid-state NMR 2D experiment to obtain <sup>1</sup>H–<sup>13</sup>C correlation spectra for only those carbons that are in



**Fig. 2.** (a) Molecular formula of L-histidine, and two-dimensional <sup>1</sup>H–<sup>13</sup>C, (b) CP HETCOR and (c) <sup>14</sup>N-edited CP HETCOR NMR spectrum of polycrystalline L-histidine fully <sup>13</sup>C enriched. SAM<sub>3</sub> <sup>1</sup>H homo-nuclear decoupling scheme was applied during  $t_1$  to record both spectra. Spectra (b and c) are acquired using a pulse sequence that selects pure SQ <sup>14</sup>N coherences during the D-HMQC step. Spectra are the result of averaging (b) 2 and (c) 64 transients for each of 30  $t_1$  increments with  $\Delta t_1 = t_r = 57.1$   $\mu$ s, with a relaxation interval of 5 s. The total experimental time has been of 10.6 min (b) and 340 min (c). The SFAM<sub>2</sub> recoupling intervals during excitation and reconversion were  $\tau_{rec} = 8t_r = 457$   $\mu$ s, while the lengths of the two <sup>14</sup>N pulses were  $\tau_p = 30$   $\mu$ s. The rotor synchronization is achieved with  $n = 2$  and  $m = 1$ .  $B_0 = 18.8$  T with  $\nu_R = 17.5$  kHz. <sup>1</sup>H–<sup>13</sup>C CP-MAS: contact time = 500  $\mu$ s,  $\nu_{1,1H} = 67.5$  kHz,  $\nu_{1,13C} = 50$  kHz. <sup>1</sup>H decoupling:  $\nu_{1,1H} = 80$  kHz. <sup>13</sup>C  $\pi$  and  $\pi/2$  pulses:  $\nu_{1,13C} = 50$  kHz.

close proximity to nitrogen-14 nuclei. The selectivity with which  $^1\text{H}$ - $^{13}\text{C}$  cross-peaks are observed can be controlled by a selective (differing)  $^1\text{H}$ - $^{13}\text{C}$  cross-polarization step. It must be noted that this experiment does not require a very large magnetic field, a perfectly adjusted magic angle or a perfectly stabilized spinning speed, as with previous  $^1\text{H}$ - $^{14}\text{N}$  and  $^{13}\text{C}$ - $^{14}\text{N}$  HMQC experiments [9–14]. Indeed, the different  $^{14}\text{N}$  magnetizations are utilized, instead of being observed as previously. The sensitivity of the experiment depends upon the  $D$ -HMQC editing step and this will depend upon the  $^{13}\text{C}$  refocused line-widths and  $^{14}\text{N}$  excitation and re-conversion efficiencies. It has been observed that in amino acids and peptides the overall HMQC efficiency of the excitation and re-conversion transfers to and from  $^{14}\text{N}$  is presently only around 5%, which is certainly the main limitation of the method. Spectrum shown in Fig. 2c has been recorded in 340 min, on 18.8 T spectrometer, with a  $^{13}\text{C}$  enriched sample. This means that the method is more efficient than the previous 3D  $^1\text{H}$ - $^{13}\text{C}$ - $^{14}\text{N}$  version [14], but still does not allow studying biologically relevant compounds on a routine basis without any isotopic enrichment. Further methodological developments, such as the use of hyper-adiabatic pulses [26], are still needed to enhance the sensitivity of the  $^{13}\text{C}$ - $^{14}\text{N}$ - $^{13}\text{C}$  transfer.

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