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Simplifying DOSY spectra with selective TOCSY edited preparation

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Abstract

Diffusion-ordered NMR spectroscopy, while quite powerful, is limited by its inability to resolve signals that are severely overlapped in the proton spectrum. We present here a DOSY experiment that uses selective TOCSY as an editing/preparation period. With this method, well-resolved signals of the analytes are selectively excited and the magnetization subsequently transferred by isotropic mixing to resonances buried in the matrix background, which are then resolved by the ensuing DOSY sequence. Key to the success of our proposed method is the incorporation of a highly effective zero-quantum filter into the selective TOCSY preparation period, which prevents zero-quantum coherence from being carried into the DOSY part of the pulse sequence. Further improvement in spectral resolution can be obtained by expanding the proposed experiment into a 3D sequence and utilizing the homonuclear decoupling feature of the BASHD-TOCSY technique. Both pulse sequences were found to greatly simplify the DOSY spectrum of a 'dirty' sucrose/raffinose mixture, as the complex matrix background is no longer present to obscure or overlap with the signals of interests. Furthermore, complete resolution of the relevant signals was achieved with the 3D sequence.
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1. Introduction

Diffusion-ordered NMR spectroscopy (DOSY) [1,2] is a versatile and powerful NMR technique that is gaining importance in several frontiers of pharmaceutical research. It is a non-invasive analytical method for mixture analysis that does not require prior physical separation of the analytes. Instead, signals from different components are ordered along a second dimension based on their differential translational diffusion coefficients. Despite this potential, DOSY is limited by its inability to differentiate between signals from different components that are severely overlapped in the proton spectrum. Such signals, which appear in the DOSY spectrum at positions midway between the components, can complicate the data analysis considerably. This complication is particularly severe in cases where the components are structurally similar and/or significant matrix background is present.

There are at least two well-established solutions for improving the resolution of a DOSY spectrum. One approach seeks to achieve additional dispersion by spreading the signals over a third dimension. Several such 3D DOSY experiments have been developed by linking a diffusion pulse sequence to common 2D pulse sequences [3–8]. The second approach is to simplify the spectrum through spectral editing by exploiting a particular property of the spins under consideration [9,10]. For example, the gradient-modified spin-echo DOSY (GOSE-DOSY) achieves this by eliminating signals from coupled spin systems while leaving only the uncoupled resonances to represent the components of interest [9].

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Selective excitation has been shown to be a powerful tool for spectral simplification and in theory should be applicable to the DOSY experiment as well. The simplest approach is to replace the 90° preparation hard pulse in the original DOSY pulse sequence with a preparation period that selectively excites resonances in a relatively well-resolved region, e.g., all the anomeric protons in a mixture of sugars. In practice, however, such a selective DOSY experiment would be of very limited value, since it is rarely feasible to unambiguously identify a component of a mixture based on the chemical shift of a single resonance.

The selective 1D TOCSY sequence [11,12] has been utilized as an additional preparation period in such doubly selective experiments as the 1D TOCSY-NOESY sequence [11,13–16]. In this report, we propose to employ it as a *spectral editing* period for the DOSY experiment. In this method, well-resolved signals of the analytes are selectively excited and the magnetization subsequently transferred by isotropic mixing to resonances buried in the matrix background, which are then resolved by the ensuing DOSY sequence. Compared to the simple selective excitation scheme discussed above, the isotropic mixing period in our method reintroduces additional resonance lines that may be previously buried in the matrix background but key to the identification of certain components, while maintaining the overall spectral simplicity. Recent advances in the development of highly effective zero-quantum filters (ZQFs) have been incorporated into our method to minimize interference from zero-quantum coherence (ZQC).

2. Results and discussion

The pulse sequences considered in this work are shown in Fig. 1. The commonly used selective 1D TOCSY pulse sequence [11,12] is depicted in Fig. 1A, featuring the double pulsed field gradient spin echo (DPFGSE) for selective excitation [17]. Although in principle, other types of selective 1D pulse sequences can also be used, the selective 1D TOCSY is particularly

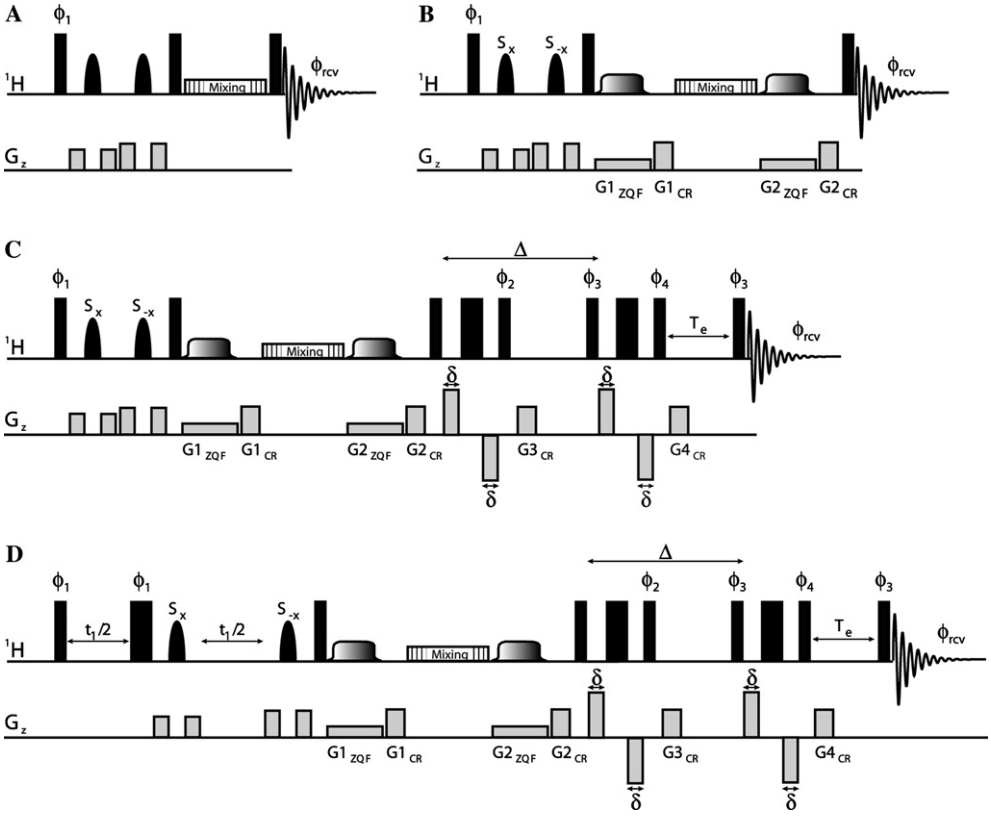

Fig. 1. Timing diagrams of the pulse sequences used in this study. Solid thin and thick bars designate hard 90° and 180° pulses, respectively. Solid and shaded icons represent selective 180° and frequency-swept inversion pulses for the ZQFs, respectively. All pulses have phase x unless noted otherwise. (A) The selective 1D TOCSY pulse sequence. Selective excitation of the target spin for the isotropic mixing period is achieved using the DPFGSE sequence. (B) The selective 1D TOCSY pulse sequence incorporating the ZQF. The basic phase cycling is $\phi_1 = \phi_{rcv} = x, -x$; this becomes the selective TOCSY edited preparation (STEP) function if acquisition is omitted. (C) The 2D STEP-DOSY pulse sequence. Δ is the diffusion delay, δ is the diffusion encoding/decoding gradient duration, and T_e is the eddy-current storage delay. $G3_{CR}$ and $G4_{CR}$ are crusher gradients to dephase coherences of greater than zero order. The basic phase cycle is $\phi_1 = x, -x$; $\phi_2 = 4(x), 4(-x)$; $\phi_3 = 8(x), 8(-x), 8(y), 8(-y)$; $\phi_4 = \phi_3 + 2(x), 2(-x)$; and $\phi_{rcv} = \phi_1 + \phi_2 + 2\phi_3 + \phi_4$. (D) The 3D STEP-DOSY pulse sequence. The basic phase cycling is the same as (C).

suitable as a spectral editing period of the DOSY experiment for several reasons. First, it generates *in-phase* coherence transfer, rendering subsequent manipulation of the magnetization straightforward. Second, highly efficient magnetization transfer can be achieved using a collection of available isotropic mixing sequences. The issue of RF inhomogeneity may be further addressed by the introduction of adiabatic mixing sequences [18].

However, the TOCSY experiment is plagued with the notorious ZQC, which often leads to deleterious anti-phase distortions to the line shapes of scalar coupled spins. This presents a particularly severe problem if the selective TOCSY sequence is to be used as a preparation period for the DOSY experiment, where ZQC has been shown to cause phase errors that lead to degradation in the quality of the DOSY spectra [2,19,20]. For this reason, most DOSY pulse sequences are designed to avoid the excitation of ZQC [19]; thus, it is imperative that the editing/preparation period do likewise.

Substantial efforts have been devoted to the development of ZQFs for the effective suppression of ZQC [21–25]. Very recently, Thrippleton and Keeler reported a highly efficient ZQF that utilizes a frequency-swept inversion pulse in combination with a simultaneously applied strong PFG [26,27]. Application of this ZQF to the selective 1D TOCSY-NOESY experiment [16] has been shown to lead to substantial improvement in the spectral quality. One of the most important features of this ZQF is that almost complete suppression of ZQC can be achieved in a *single* scan, making it ideal for the purpose of this work.

Fig. 1B shows the timing diagram of the 1D ZQF-TOCSY pulse sequence. The longitudinal TOCSY, as shown, allows convenient incorporation of the ZQF. Since the signal loss is dominated by longitudinal relaxation, the inclusion of the ZQFs only incurs a rather mild sensitivity penalty. Because the strong coupling Hamiltonian governing the isotropic mixing sequence causes an interchange between z-magnetization and ZQC, it is necessary to apply a ZQF both before and after the isotropic mixing period. To avoid accidental refocusing of the ZQC, different durations should be used for the two ZQFs [26]. Alternatively, orthogonal gradients, if available, could be used for the two ZQFs [25]. For the sake of simplicity, as well as to distinguish the selective 1D ZQF-TOCSY sequence of Fig. 1B from existing methods, we will refer to it as the selective TOCSY edited preparation (STEP) function hereinafter [16].

Fig. 1C shows the timing diagram of the 2D STEP-DOSY pulse sequence we propose. It was constructed by attaching the STEP function to the front of the BPPLED pulse sequence [28]. It should be noted that any high-resolution DOSY pulse sequence can be used, including those designed to compensate for convection currents [29]. While the merits of the BPPLED have been thoroughly described [2,19], it is worth noting for this discussion that the refocusing action of the 180° pulse in the middle of the bipolar gradient pulse pairs used for diffusion encoding prevents the creation of ZQC [19]; thus, the absence of ZQC during the subsequent diffusion delay is ensured. The 32-step phase cycle, which was obtained by simply combining the 2-step phase cycle for the STEP function and the 16-step BPPLED phase cycle, cancels secondary echoes as well as signals that arise from relaxation during STEP, Δ, and T_e. This ensures that only spatially encoded magnetization contributes to the observed signals. If signal averaging is unnecessary, the total phase cycle can be reduced to two steps by utilizing the ONE-SHOT DOSY sequence instead of the BPPLED [30].

To achieve even greater dispersion of overlapped resonances, the 2D STEP-DOSY can be easily expanded into a 3D experiment by inserting a t_1 evolution period. Fig. 1D shows the timing diagram of one such 3D STEP-DOSY pulse sequence utilizing the band-selective homonuclear decoupled TOCSY (BASHD-TOCSY) principle [31], in which the t_1 period is equally split on both sides of the first band-selective 180° pulse. In addition, a non-selective 180° pulse immediately follows the first half of the evolution period. In effect, the 'selected' protons experience a 360° pulse and all others experience a 180° pulse midway through t_1. This achieves homonuclear decoupling from those protons outside the inversion band of the 180° pulses, providing the highest possible resolution in F_1. Finally, only the 'selected' protons are refocused by the gradient echoes.

We have tested these pulse sequences on a mixture of sucrose [Glu($\alpha 1 \rightarrow 2$)Fru] and raffinose [Gal($\alpha 1 \rightarrow 6$)-Glu($\alpha 1 \rightarrow 2$)Fru]. To simulate a matrix background, low concentrations of 22 biologically relevant, small organic molecules were added. Fig. 2 shows its 1D ^{1}H spectrum, together with the pertinent molecular structures. The anomeric signals at ca. 5 ppm are well-resolved from the rest of the resonances, as indicated by the dashed rectangle. Note that only three anomeric signals are observed, since fructose has no anomeric protons, and those from the two glucose residues are slightly overlapped. The rest of the carbohydrate rings show severe overlap with each other and the 'matrix' background.

To demonstrate the efficiency of the ZQF, Fig. 3 compares the selective 1D TOCSY spectra of the anomeric protons obtained using the pulse sequence of Figs. 1A and B, respectively. In the case where no ZQ filtration is applied (upper panel), the anti-phase contributions caused by ZQC are evident. These anti-phase distortions are largely absent when two ZQFs with appropriately adjusted durations and gradient strengths are applied (lower panel).

Fig. 4 shows the DOSY spectra of the 'dirty' mixture of sucrose and raffinose. In the standard 2D DOSY

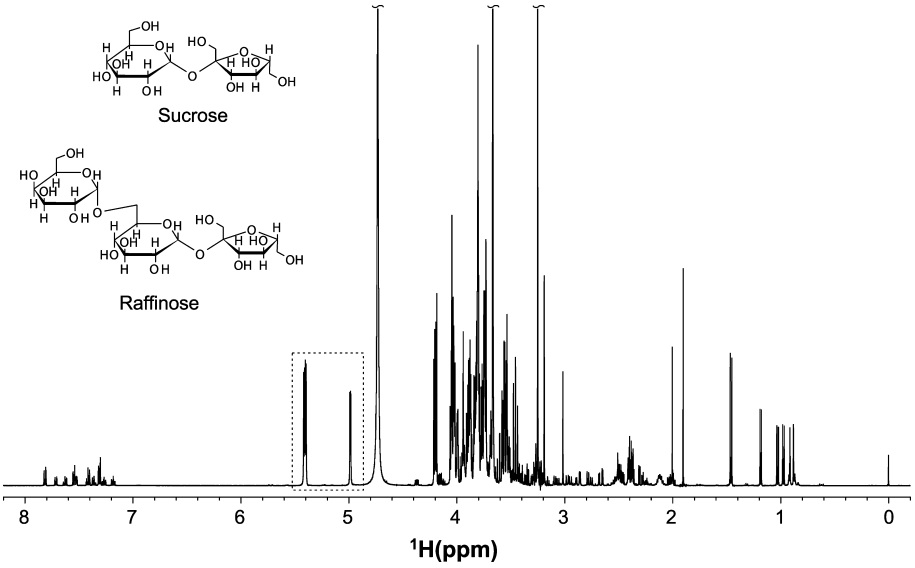

Fig. 2. The 1D ^{1}H spectrum of the 'dirty' sucrose/raffinose mixture and the molecular structures of the two sugars. Eight scans were collected with 8192 complex points for each and transformed with 4× zero-filling and no weighting. The anomeric protons are designated by the dashed rectangle.

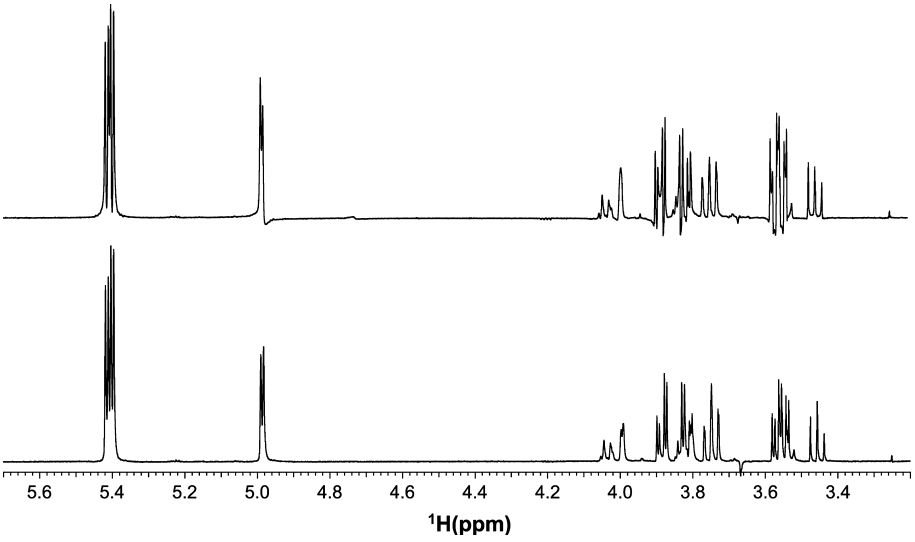

Fig. 3. Comparison of the selective 1D TOCSY spectra obtained without (top) and with (bottom) the zero-quantum filters. Sixteen scans were collected with 8192 complex points and transformed with 8× zero-filling and no weighting. The vertical scaling factor was adjusted such that the noise level is the same.

(upper panel), the overlap of relevant signals with the 'matrix' background and with each other makes it almost impossible to unambiguously determine the number of significant components or their identities. However, the well-resolved anomeric region represents an ideal candidate for STEP. Using the pulse sequence of Fig. 1C, selective excitation of this region and subsequent magnetization transfer by isotropic mixing to the rest of the carbohydrate rings results in a much 'cleaner' DOSY spectrum (lower panel). The complex matrix background is efficiently eliminated, revealing relevant signals previously buried or obscured due to overlap. Furthermore, overlap between the components of interest is substantially reduced because the fructose residues are not excited, although this also results in a loss of useful spectral information.

Some overlap still exists between the relevant components due to the high similarity of their structures. If desired, this can be further resolved with the 3D STEP-DOSY experiment. The resolving capability of this sequence, constructed from the BASHD-TOCSY, is a result of two factors. First, as a band-selective experiment, the reduced spectral width in F_1 translates into a higher digital resolution when compared to non-selective methods with the same number of t_1 increments. Second, homonuclear decoupling collapses the multi-

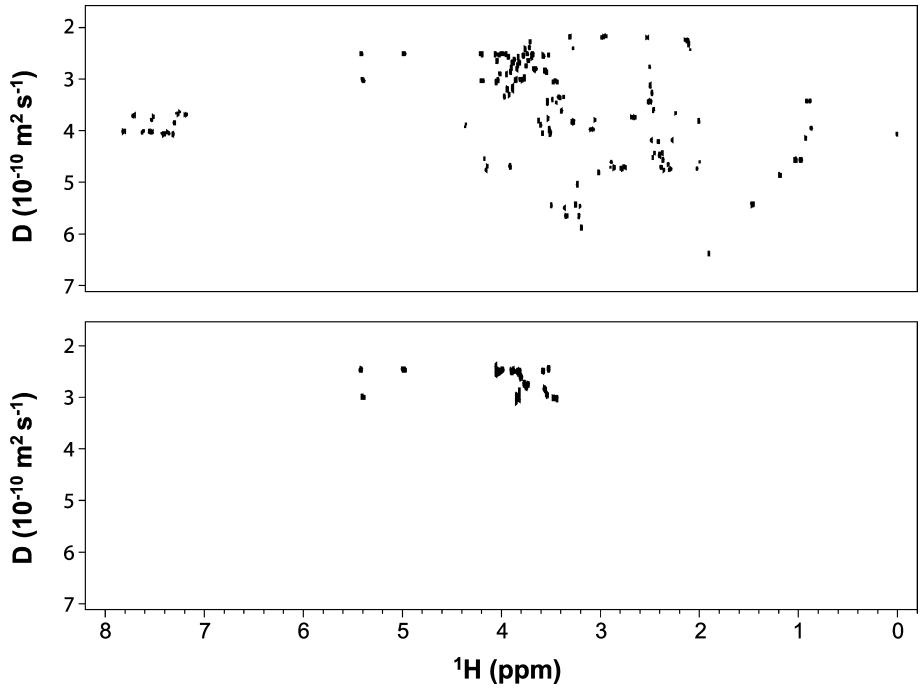

Fig. 4. Comparison of the regular 2D DOSY (top) and 2D STEP-DOSY (bottom) spectra of the 'dirty' sucrose/raffinose mixture.

plets to singlets in F_1, leading to further improvement in both spectral resolution and sensitivity. This is demonstrated in Fig. 5, which compares the 2D TOCSY spectra obtained with the band selective TOCSY and BASHD-TOCSY experiments, respectively. It is evident that the band-selective TOCSY (left panel) is not suffi-

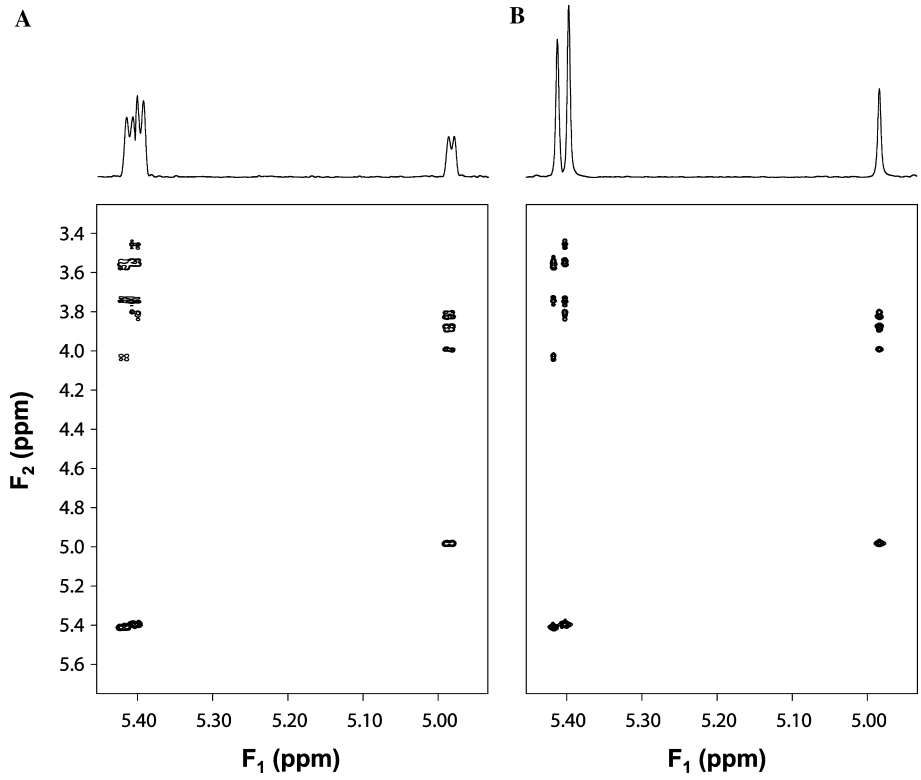

Fig. 5. Comparison of the 2D band-selective TOCSY (A) and BASHD-TOCSY (B) spectra with skyline projections for the 'dirty' sucrose/raffinose mixture. Two scans were acquired for each of the 64 t_1 increments for a total acquisition time of 7 min apiece.

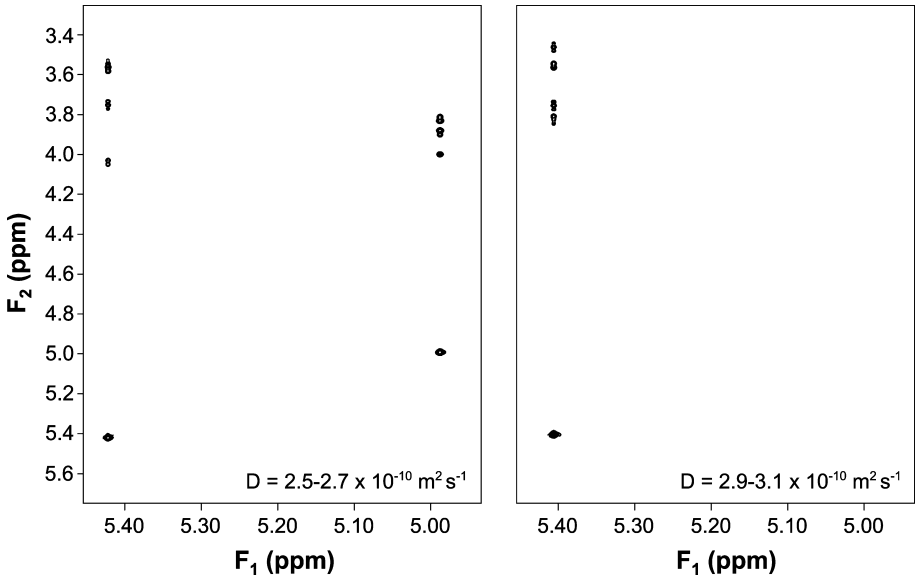

Fig. 6. Selected 2D projections from the 3D STEP-DOSY spectrum corresponding to diffusion coefficient ranges of $2.5–2.7 \times 10^{-10}$ m^2s^{-1} (left panel) and $2.9–3.1 \times 10^{-10}$ m^2s^{-1} (right panel). Sixteen scans were acquired for each of the 64 t_1 increments. Ten gradient increments were acquired over the range of 2.12–63.6 G/cm. The encoding/decoding gradient duration (δ) was 2.5 ms and the diffusion delay (Δ) was 0.025 s. The total acquisition time was 10 h.

cient to resolve the glucose residues even with 64 t_1 increments (and linear-predicted four times), whereas complete resolution is achieved with the BASHD-TOCSY (right panel). The results of the 3D STEP-DOSY are shown in Fig. 6. The two sugars have significantly different diffusion coefficients, and their respective 2D projections are displayed. Clearly, the 3D STEP-DOSY provides a highly effective tool for the unambiguous determination of the number of certain components in a mixture and their identities.

3. Conclusions

We have proposed two novel pulse sequences that use selective TOCSY as a means to edit DOSY spectra. Both sequences utilize DPFGSE to excite well-resolved signals and isotropic mixing to transfer the magnetization to resonances buried in the complex matrix background. A key element to the proposed STEP-DOSY sequences is the zero-quantum filter, which prevents zero-quantum coherence generated during isotropic mixing from being carried into the diffusion sequence. The results shown here demonstrate that greatly simplified DOSY spectra are obtained because the complex matrix background is not present to obscure or overlap with the relevant signals. The 3D STEP-DOSY sequence enables further dispersion of signals from the relevant compounds and benefits from both band selection and homonuclear decoupling in the F_1 dimension. Although the results shown here are for the DOSY experiment, the selective TOCSY edited preparation function affords a general technique for spectral simplification and its application to other types of experiments is currently under investigation.

4. Experimental

Spectra were recorded for a mixture of sucrose (100 mM) and raffinose (100 mM) in D_2O, which also contained 0.1% NaN_3, 1 mM TSP, and 22 small organic molecules ranging in concentration from 10 to 20 mM. All spectra were acquired at 25.0 °C on a Varian INOVA 500 MHz spectrometer equipped with a Performa II gradient amplifier, a programmable pulse modulator in the X channel, and a 3 mm ID HX probe. The internal temperature and the gradient strength of the probe were calibrated with ethylene glycol [32] and 99.9% D_2O ($D = 19.0 \times 10^{-10}$ m^2s^{-1} at 25.0 °C) [33], respectively. All pulses have phase x unless noted otherwise. All gradient pulses were applied along the z-axis with no shaping. All shaped pulses were generated using the program Pandora's Box [34] available as part of the Varian NMR software.

Selective excitation of the anomeric region was achieved with REBURP pulses (bw = 250 Hz, pw = 19.5 ms, B_1(rms) = 0.0909 kHz) [35]. The isotropic mixing period was 135 ms using the DIPSI-3 sequence [36] and a 6.25 kHz B_1 field, which generated optimal magnetization transfer to the entire carbohydrate ring. Zero-quantum suppression was accomplished with two ZQFs, both of which used the constant-adiabaticity WURST waveform [37] covering a 20 kHz bandwidth

and a gradient of 2 G/cm. The duration of the first sweep was 29 ms and the second was 31 ms.

For the 2D DOSY, 16 gradient increments (64 scans each) were acquired over the range of 2.12–53.0 G/cm. The encoding/decoding gradient duration (δ) was 2.0 ms and the diffusion delay (Δ) was 0.07 s. The resulting FIDs were zero-filled eight times and weighted with a mild Lorentzian-to-Gaussian window function (lb $= -0.61$ Hz, gf $= 0.4$) prior to Fourier transformation. Diffusion coefficients and standard errors were obtained for each and every signal in the spectrum by fitting the attenuation of the peak intensity to the Stejskal–Tanner equation [38],

$$S = S_0 \exp[-D\gamma^2 g^2 \delta^2 (\Delta - \delta/3 - \tau/2)], \quad (1)$$

where S_0 is the signal intensity at zero gradient strength, D is the diffusion coefficient, γ is the magnetogyric ratio, g is the encoding gradient strength, δ is the duration of the encoding gradient, Δ is the diffusion delay, and τ is the delay between the first two 90° pulses. 2D DOSY spectra were then constructed by extending the 1D spectrum with a diffusion dimension, where the diffusion peaks are centered at their calculated diffusion coefficients and given a Gaussian lineshape with a width corresponding to the standard error. Each 2D contour plot contained 16 k × 1 k data points. All aspects of the DOSY processing were done with the standard Varian software package.

Acquisition parameters for the 2D TOCSY and 3D STEP-DOSY include a 1 s relaxation delay, 64 t_1 increments and 1024 complex points. The number of scans and the total acquisition times are reported in the figure legends. All spectra were transformed after linear-predicting four times in F_1, zero-filling to 2048 × 2048 complex points, and weighting with unshifted Gaussian window functions in both dimensions. Diffusion coefficients were calculated by the same fitting routine described above except using the attenuation of the crosspeak volume. 2D slices were then constructed by grouping the crosspeaks according to their calculated diffusion coefficients.

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