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## Spatially encoded diffusion-ordered NMR spectroscopy of reaction mixtures in organic solvents

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Diffusion-ordered NMR spectroscopy (DOSY) is a powerful method for the analysis of mixtures. Classic DOSY methods require several minutes of acquisition, and we show here that DOSY experiments can be recorded in less than one second for the challenging case of solution mixtures in low-viscosity solvents. The proposed method relies on a spatial encoding of the diffusion dimension, for which convection-compensation and spectral-selection strategies are introduced. The method is illustrated with the analysis of a reaction mixture, for which more accurate estimates of the diffusion coefficients are obtained.

### Introduction

The analysis of chemical mixtures is a challenging task, for which nuclear magnetic resonance spectroscopy has many advantages. Diffusion-ordered NMR spectroscopy (DOSY) is a powerful analytical method that makes it possible to separate the spectra of compounds from a mixture according to their diffusion coefficient.<sup>1-3</sup> DOSY NMR has been widely used for the analysis of complex mixtures and provides information on molecular sizes<sup>4-7</sup> and shapes.<sup>4</sup> It can also be used to investigate molecular interactions,<sup>8</sup> as well as to characterize reactive intermediates.<sup>9-12</sup>

In DOSY, the diffusion information is obtained with a pseudo-2D experiments in which field-gradient pulses of increasing area (PFG)<sup>13</sup> are used to encode the effect of the random Brownian motion of particles as a signal decay. The most common approach to analyse DOSY data consists of an exponential fit of peak intensities or integrals  $I$  as a function of the diffusion-encoding gradient area ( $g\delta$ ), according to the Stejskal-Tanner equation,<sup>14</sup>

$$I = I_0 e^{-D\gamma^2 g^2 \delta^2 \Delta'} \quad (1)$$

where  $I_0$  is the reference intensity in the absence of diffusion weighting and  $I$ , in the presence of a gradient of strength  $g$  and duration  $\delta$ .  $D$  is the diffusion coefficient,  $\Delta'$  is the effective diffusion delay, and  $\gamma$  is the gyromagnetic ratio of the spin. This

analysis is only strictly valid if the concentrations of the components of the mixture remain constant during the experiment. For a mixture with a time-dependent composition, changes in concentrations during the DOSY experiments will result in over- (or under-) estimated diffusion coefficients for compounds that are consumed (or produced) over time. As a result, the standard experiment is not applicable as such to reaction mixtures, as it yields apparent diffusion coefficients that depend on the rate of the chemical transformation.

Several approaches have been introduced to account for changes in concentration in the processing of DOSY data. For example, Nilsson et al<sup>15</sup> proposed the use of a multivariate analysis, where time is used as a third dimension in a multiway decomposition, to simultaneously characterise both the concentration evolution and the diffusion coefficient during a chemical reaction. In the permuted-DOSY approach, a random permutation of the gradient intensities mitigates the influence of concentration changes on the estimated diffusion coefficients.<sup>16</sup>

Alternatively, several strategies are available to accelerate DOSY experiments, which can help reaction monitoring if the duration of the experiment can be made shorter than the characteristic time of the reaction. In the Oneshot pulse sequence,<sup>17</sup> coherence-selection and diffusion-encoding gradients are merged to reduce the number of required scans to one per increment. Schemes are also available for a joint reduced sampling of the indirect time and gradient dimensions.<sup>18, 19</sup> A significant acceleration of DOSY experiments is obtained with a spatial parallelisation (SPEN) of the diffusion dimension, introduced by Keeler and co-workers, which reduces the duration of the experiment to less than one second.<sup>20-22</sup> As shown by Frydman and co-workers, a single-scan 2D acquisition that separates the spectral and spatial dimension then helps to analyse more complex samples. We

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recently showed how the SPEN DOSY concept can also be generalised to higher-dimensional experiments.<sup>23</sup>

The SPEN DOSY experiment is in principle a good candidate to analyse mixtures with time-dependent compositions. The experiment in its current form, however, suffers from various sources of errors that limit its applicability. Specifically, its sensitivity to sample convection makes it unsuitable for the analysis of complex mixtures in important organic solvents such as dichloromethane or acetonitrile, and signal overlap because of spectral folding is also a limitation.

In this article, we show that spatially encoded DOSY can be used for the fast analysis of mixtures in low-viscosity solvents, using convection-compensation and spectral-selection schemes. The resulting experiment is used to monitor an organic reaction mixture, and SPEN DOSY is found to provide estimates of the diffusion coefficients that are less affected by changes of concentrations over time. In particular, an accurate diffusion coefficient is obtained for a transient intermediate. The reduced error in the diffusion measurement is found to translate into more accurate estimates of molecular weights for the components of the reacting mixture.

## Methods

### Sample preparation

Two samples were prepared for DOSY experiments on non-reacting mixtures. For the comparison of stimulated-echo (STE) SPEN DOSY and double-stimulated-echo (DSTE) SPEN DOSY, the mixture (M1) was composed of cyclododecane (1 mg), squalene (15  $\mu$ L) and adamantane (2 mg) solubilized in 600  $\mu$ L of  $\text{CD}_2\text{Cl}_2$ . For the comparison of DSTE SPEN DOSY with and without spectral selection, the mixture (M2) was composed of cyclododecane (1 mg), squalene (15  $\mu$ L), adamantane (2 mg) and 1,3-butadiene (5  $\mu$ L) solubilized in 600  $\mu$ L of  $\text{CD}_2\text{Cl}_2$ . For each sample a standard 5 mm tube was used.

### Reaction monitoring

The reaction analysed here is a di-amination reaction (M3). Two different initial stoichiometries were considered:

i/  $9.00 \cdot 10^{-4}$  mol of isobutyraldehyde (81  $\mu$ L) and  $9.26 \cdot 10^{-5}$  mol of p-phenylenediamine (10 mg);

ii/  $1.85 \cdot 10^{-4}$  mol of isobutyraldehyde (16  $\mu$ L) and  $9.26 \cdot 10^{-5}$  mol of p-phenylenediamine (10 mg).

In both cases, the reaction was carried out directly in a 5 mm NMR tube. A solution of isobutyraldehyde in 600  $\mu$ L of acetonitrile was prepared, and the sample was used to set the lock and shims. p-Phenylenediamine was added with a syringe, the NMR tube was inverted several times, then inserted into the NMR magnet. The measurements were started just after insertion of the sample.

### NMR spectroscopy

All the experiments were carried out on a Bruker spectrometer operating at a  $^1\text{H}$  Larmor frequency of 600.13 MHz, equipped with a 5 mm triple-axis gradient probe. For all the

experiments, the temperature was set at a nominal value of 283 K.

### Conventional DOSY

Conventional DOSY data were recorded using a double stimulated echo sequence with bipolar gradient pulses (dstebppg3s Bruker sequence with additional lock stabilisation gradients and spatial selective filter). The diffusion-encoding gradient values consisted of a linear ramp ranging from 0.0065 T/m to 0.455 T/m. The duration of the gradient pulses was 800  $\mu$ s. The diffusion delay was 120 ms for the experiments on the reacting mixture (M3), and 140 ms for the experiments on the unreacting mixtures (M1, M2). Each 2D data set was acquired with 16384 points in the direct dimension, a spectral width of 7000 Hz, an acquisition time of 1.4 s, a relaxation delay of 8 s and 8 gradient steps with a 16-step phase cycle, resulting in a total experiment duration of 22 min.

### SPEN DOSY experiment

For the SPEN experiments, the diffusion-encoding parameters were chosen so that the chirp pulse would sweep a region of 10 mm. For the unreacting mixtures (M1, M2), the chirp bandwidth was 74 000 Hz, the encoding gradient was 0.1696 T/m, the chirp duration was 1.5 ms, and the post-chirp gradient duration was 1.6 ms; the diffusion delay was 50 ms for SPEN STE and 84.5 ms for the DSTE experiment. The acquisition parameters were a 0.2881 T/m acquisition gradient strength with 128 gradients loops of 256 points each and a 1.1  $\mu$ s dwell time. This results in a spectral width of 1800 Hz.

For the reacting mixture (M3), the chirp bandwidth was 56 000 Hz, the encoding gradient was 0.1278 T/m, the chirp duration was 1.5 ms, and the post-chirp gradient duration was 1.6 ms; the diffusion delay was 150 ms. The acquisition parameters were a 0.1921 T/m acquisition gradient strength with 128 gradients loops of 256 points each and a 1  $\mu$ s dwell time. This results in a spectral width of 2000 Hz.

The gradient strength for coherence selection around the first chirp pulse, during the first stimulated echo, were  $a = 0.064$  T/m,  $a + c = 0.147$  T/m with a duration of 800  $\mu$ s. The gradient strength for coherence selection around the second chirp pulse were  $b = 0.128$  T/m,  $b + c = 0.211$  T/m with a duration of 800  $\mu$ s. The gradient strength for the spoiler during longitudinal storage was  $f = 0.3648$  T/m with a duration of 800  $\mu$ s.

During the second stimulated echo, gradient strength for coherence selection around the first chirp pulse were  $a = 0.089$  T/m,  $a + c = 0.160$  T/m with a duration of 800  $\mu$ s. The gradient strength for coherence selection around the second chirp pulse were  $b = 0.153$  T/m,  $b + c = 0.224$  T/m with a duration of 800  $\mu$ s. The gradient strength for the spectral selection scheme was 0.0585 T/m with a duration of 800  $\mu$ s. The gradient strength for the spoiler during longitudinal storage were  $f = 0.2752$  T/m and  $g = 0.3136$  T/m with a duration of 800  $\mu$ s.

### Data processing

Data from conventional DOSY experiments were processed with the Dynamics Center software (Bruker, Billerica, U.S.A.). For all SPEN DOSY experiments, the data were processed in

MATLAB (The Mathworks, Natick, U.S.A.) using home-written routines, adapted in part from the DOSY Toolbox<sup>24</sup>.

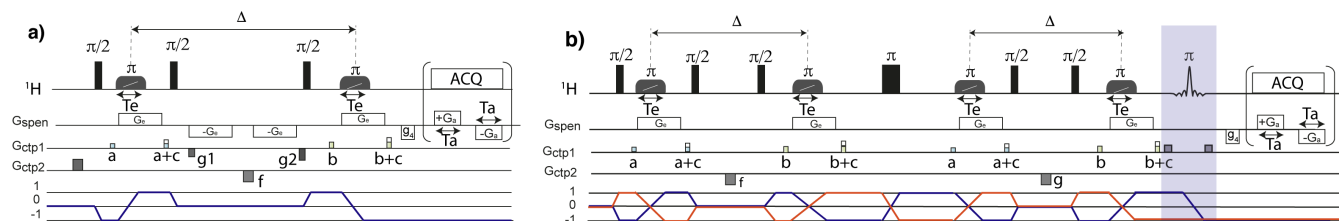


Figure 1 a) SPEN STE DOSY b) SPEN DSTE DOSY pulse sequences.  $\Delta$  is the time that elapses between the centres of the chirp pulses. The SPEN DSTE DOSY pulse sequence contains an optional spectral selection block, shown in a grey rectangle. The selected coherence transfer pathway is shown in red/blue for the sequence without/with spectral selection. Gradients  $a$  and  $b$  are crushers surrounding the refocusing  $\pi$  pulses; gradient  $c$  selects the anti-echo pathway for the stimulated echo; gradients  $g$  and  $f$  are a spoiler during longitudinal storage. (Gctp: gradient for coherence-transfer-pathway selection along x and y axis)

In short, the 2D SPEN data was read from Bruker files, then sorted and reshaped in order to get a 2D matrix. The data was multiplied by a sine function and zero-filled in the time dimension. Only the odd echoes were retained, and 2D Fourier transformation was performed. The spectra were processed in magnitude mode. For SPEN 2D DOSY, peak maxima were selected manually and the spatial profile for each peak was obtained as a row of the  $(z; \omega)$  data set. The spatial profiles were fitted with a Stejskal-Tanner equation for all resonances. The DOSY representation was obtained Gaussian line shapes with maxima corresponding to the calculated  $D$  value and linewidths set by the error of the fit.

### Estimation of molecular weights

The diffusion coefficients  $D_x$  measured for sample M3 were converted into estimates of molecular weights  $MW_{est}$ , using the empirical relationships derived by Stalke<sup>6</sup> and co-workers:

$$\log(D_{x,norm}) = \log(D_x) - \log(D_{ref}) + \log(D_{ref,fix}) \quad (2)$$

and

$$MW_{est} = 10^{\frac{\log(D_{x,norm}) - \log(k)}{\alpha}} \quad (3)$$

where  $D_{ref}$  is the diffusion coefficient of an internal reference, chosen here to be the solvent (acetonitrile)<sup>25</sup>,  $\log(D_{ref,fix})$  is a tabulated value of the diffusion coefficient of the reference, and  $\log(k)$  and  $\alpha$  are empirical parameters determined by Stalke and co-workers by fitting a large set of diffusion data to Eq. 3. Here the parameters for “DSE” (dissipated spheres and ellipsoid) shapes were used.

## Results and discussion

### Spatially-encoded DOSY in low-viscosity solvents

In spatially encoded DOSY, the sequential acquisition of diffusion-attenuated NMR spectra for varying gradient areas is replaced by a parallel acquisition, in which different virtual slices of the sample tube experience different gradient areas. Following the work of Keeler and co-workers, as well as Frydman and co-workers,<sup>21, 22</sup> we recently reported a stimulated-echo-based (STE) SPEN

DOSY experiment for the sub-second acquisition of DOSY data, shown in Fig. 1a.<sup>23</sup>

While STE SPEN DOSY is appropriate for experiments in  $\text{D}_2\text{O}$ , a severe limitation becomes readily apparent for measurements carried out in low-viscosity solvents. Figure 2a shows the SPEN DOSY spectrum obtained from a mixture of three molecules that are frequently used as internal references in analyses of molecular weights with DOSY (M1: cyclododecane, squalene and adamantane) in deuterated dichloromethane  $\text{CD}_2\text{Cl}_2$  at 283 K. The large values of the estimated diffusion coefficients (Table 1), as well as the qualitatively incorrect shape of the diffusion decay curves (Figure S1) reveals that the measurement is affected by sample convection, which can be significant in a 5 mm NMR tube for a low-viscosity solvent such as dichloromethane.<sup>26</sup> In conventional DOSY experiments, the effect of convection may be mitigated by the use of two diffusion-encoding steps rather than one, with opposite coherence pathways.<sup>27</sup> For stimulated echoes, this reduces the signal intensity by a factor of 2 but provides more robust measurements. This double-diffusion-encoding approach was recently found to be also valid for spin-echo based spatially encoded DOSY<sup>28</sup>. Here we show that convection-compensation also works for stimulated-echo-based sequences (shown in Fig. 1b). Indeed the double stimulated-echo (DSTE) SPEN DOSY data (Fig. 2b) yields diffusion coefficients that are in very good agreement with those obtained with the conventional DSTE DOSY experiment (Table 1).

Note that all the results for conventional DOSY experiments are obtained here with a restricted sample length of 10 mm to limit systematic errors that originate from the non-linearity of the  $z$  magnetic-field gradient on our triple-axis gradient probe

A SPEN DOSY spectrum obtained with the DSTE approach is shown in Figure 2c, for a second mixture that additionally include 1,3-butadiene. The corresponding 1D  $^1\text{H}$  spectrum is shown in Figure 3. In this case, the reduced spectral width that can be accessed with the MRI-inspired acquisition employed in SPEN DOSY results in signal folding and overlap. As a result, inaccurate diffusion coefficient estimates are obtained from the single-exponential fit of

overlapped peaks. This is illustrated with the signal for cyclododecane at 1.38 ppm, which yields an overestimated diffusion coefficient because of the overlap with the folded signal of 1,3-butadiene. Using a spectral-selection scheme based on a band-selective refocusing pulse flanked by crusher gradients to suppress signals outside of the observed spectral region (figure 1b and 2d), significantly better results are obtained in the diffusion dimension. The cyclododecane signal at 1.38 ppm now yields an estimated diffusion coefficient (Table 1) that is in good agreement with the reference conventional DSTE DOSY on the same

sample. For this mixture, a good resolution in the diffusion domain is obtained, with the signals of the four components clearly separated according to their molecular weight distribution:  $D_{\text{squalene}}$  (410 g.mol<sup>-1</sup>) >  $D_{\text{cyclododecane}}$  (162 g.mol<sup>-1</sup>) >  $D_{\text{adamantane}}$  (138 g.mol<sup>-1</sup>) >  $D_{\text{1,3-butadiene}}$  (54 g.mol<sup>-1</sup>). Note that the spectral-selection scheme only addresses the cases of overlap due to spectral folding; peaks that already overlap in the <sup>1</sup>H 1D spectra may be addressed with a multi-exponential fit if sufficient sensitivity is available.

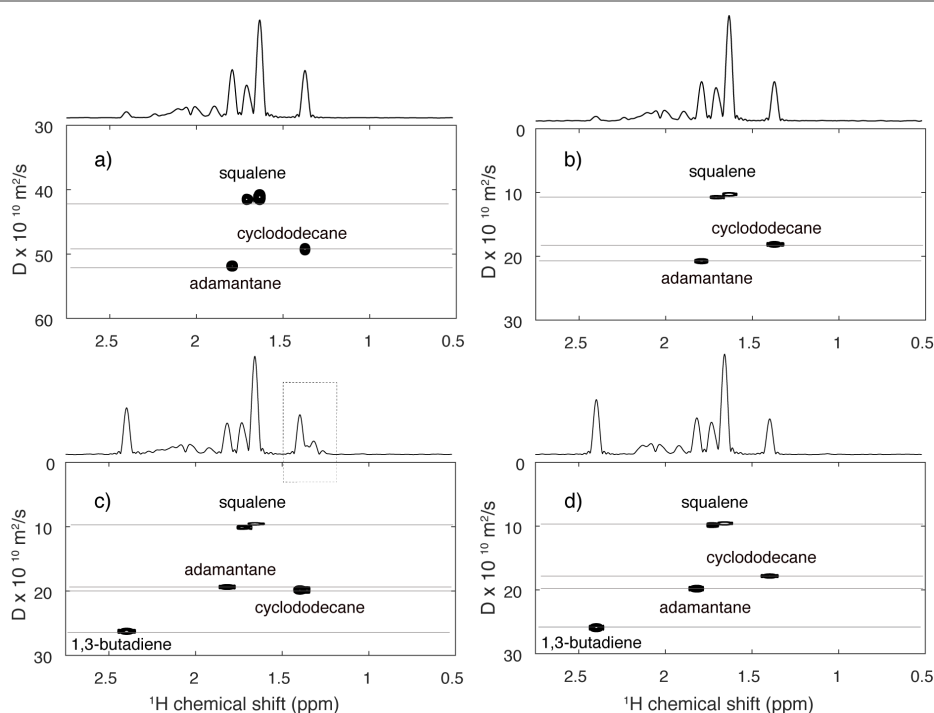


Figure 2 DOSY spectra of a mixture of cyclododecane, adamantane and squalene (a-b) and a mixture of cyclododecane, adamantane, squalene and 1,3-butadiene (c-d) in CD<sub>2</sub>Cl<sub>2</sub>. The spectra were recorded with SPEN STE (a) SPEN DSTE (b-c) and SPEN DSTE with spectrally selective filter (d) DOSY pulse sequences. The spectral dimension of the 2D data is shown above each DOSY display. Only resolved peaks were included in the DOSY processing. All the experiments were performed on a 600 MHz Bruker Avance spectrometer using a 5 mm triple-axis gradient probe

Table 1 Diffusion coefficients obtained from a mixture of cyclododecane, adamantane and squalene (M1) and a mixture of cyclododecane, adamantane, squalene and 1,3-butadiene (M2) using several DOSY pulse sequences.

compounds	$\delta$ (ppm)	Diffusion coefficient $\cdot 10^{10} \text{ m}^2 \text{ s}^{-1}$				
		SPEN STE	SPEN DSTE	Conv DSTE	SPEN DSTE	SS- SPEN DSTE
cyclododecane	1.38	49.2	18.1	17.3	20.8	17.7
squalene	1.64	41.2	10.1	9.8	9.5	9.4
squalene	1.71	41.5	10.6	9.1	10.0	10.1
adamantane	1.81	51.8	20.5	19.5	19.9	19.6

Overall, the diffusion coefficients obtained with the SPEN DOSY display a systematic difference, compared to the ones obtained with conventional DOSY pulse sequences, of less than 5 % here. This may be accounted for

by residual effects of sample convection and gradient non-linearity, as well as imperfect coherence-transfer pathway (CTP) selection. Gradient-based CTP selection was used here to decrease the number of scans to one. In contrast, existing conventional convection-compensated pulse sequences rely on phase cycling for CTP selection, which requires several scans per gradient increment. The SPEN DSTE pulse sequence overall provides a significant acceleration of DOSY experiments in organic mixtures, with complete diffusion information obtained in less than 1 s. These results open up prospects for the monitoring of organic reactions and may help to characterize intermediate species as well as measure their diffusion coefficients.

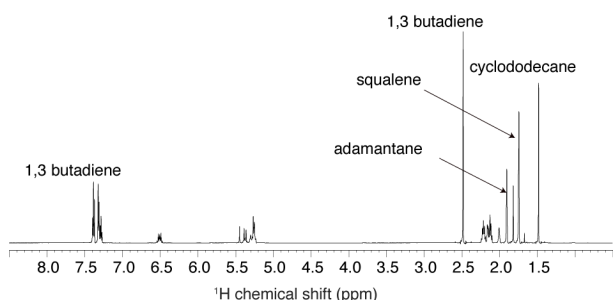


Figure 3 1D  $^1\text{H}$  NMR spectrum of a mixture of cyclododecane, adamantane, Squalene and 1,3-butadiene in  $\text{CD}_2\text{Cl}_2$ .

### Reaction monitoring

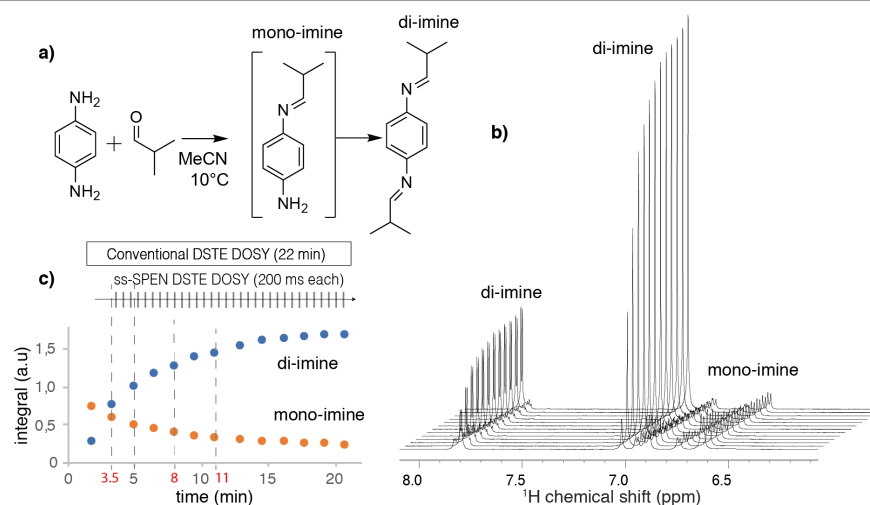


Figure 4 NMR monitoring of the reaction of isobutyraldehyde with 1,4-diaminobenzene in acetonitrile- $\text{d}_3$ . (a) Reaction scheme. (b) Time series of 1D  $^1\text{H}$  NMR spectra recorded during the reaction; the first spectrum was recorded 2 min after the start of the reaction, then a spectrum was recorded every 1.5 min; an expansion of the aromatic region is shown. (c) Time evolution of the peak areas generated using the  $^1\text{H}$  NMR data. The sampling scheme for the DOSY experiments is shown qualitatively. Dashed vertical lines indicates the times for which estimated diffusion coefficients are reported in Table 2.

The reaction was conducted in an NMR tube, in acetonitrile at 10 °C. 1D  $^1\text{H}$  NMR spectra were recorded at regular intervals over the reaction time, and characteristic resonances for the intermediate (mono-imine) and bis-imine product were identified (Figure 4b). The signal at 6.62 ppm was used to follow the mono-imine intermediate. Similarly, the bis-imine product could be followed by integration of its characteristic resonance at 7.01 ppm. In the reaction profile of this transformation, shown in Figure 4c, the transient formation of the mono-imine intermediate is apparent. The mono-imine then further reacts with a second aldehyde molecule to produce the bis-imine.

The total duration of a conventional DSTE DOSY experiment is of about 22 min in this context. This is because of the incremented gradient dimension together with a 16-step phase cycle. This duration is of the same order or magnitude as the reaction time for the transformation under study. As a result, the acquisition of diffusion information during the course of the reaction is impaired, as illustrated in Figure 5a with a conventional DSTE DOSY spectrum (the acquisition of which was started 1 min after the beginning of the reaction). Although a good

As an illustration of the possibility to analyse reacting mixtures, the reaction of isobutyraldehyde with 1,4-diaminobenzene<sup>29</sup> (Figure 4) in acetonitrile- $\text{d}_3$  was monitored by SPEN DSTE DOSY NMR experiment. The reaction yields a bis-imine and goes through a mono-imine intermediate. Depending on the initial stoichiometry, the mono-imine compound is either *i*) completely consumed (below the NMR detection limit) or *ii*) still detectable. This model reaction provides the possibility to both *ii*) tests the accuracy of a measurement on a transient species and *i*) record reference values of the diffusion coefficients (shown in Figure S3).

separation of the components is observed, erroneous values of the diffusion coefficients are obtained, as shown in Table 2. Specifically, the diffusion coefficient for the mono-imine is largely overestimated: the value obtained during the reaction is 50 % larger the one obtained at equilibrium ( $20.4$  vs  $13 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$ ).

The observed systematic error may also be appreciated from the diffusion decay curves (Figure S2), which are not suitably described by the Stejskal-Tanner equation. On the other hand, the product that evolves in the opposite direction displays an apparent diffusion coefficient slightly lower than expected (Table 2).

Table 2 Diffusion coefficients measured by conventional and SPEN DOSY on a reacting mixture in acetonitrile- $d_3$ . For the SPEN DOSY experiments, four-time points are given (corresponding to the dashed line in Figure 3c).

$\delta$ ppm	compound	Diffusion coefficient. $10^{10} \text{ m}^2 \cdot \text{s}^{-1}$				Conv DSTE started	
		SPEN DSTE DOSY at t (min)				t = 2 min	eq. <sup>a</sup>
7.01	bis-imine	11.4	12.7	12.6	12.3	10.1	11.3
6.62	mono-imine	13.4	13.7	13.3	13.1	20.4	13.0

<sup>a</sup>: chemical equilibrium

In a separate run, a time series of DOSY spectra was recorded using the SPEN DSTE experiment (Figure 4c). A representative spectrum is shown in Figure 5b. In this case, the inter-scan delay is set to 15 s and the complete

diffusion information for each spectral region is obtained in less than 200 ms, so that the estimated diffusion coefficient is much less affected by the variation of concentration. This is apparent in Table 2, with a good agreement between the diffusion coefficients obtained with SPEN DOSY “on the fly” and those obtained with the conventional experiment on an equilibrated sample.

Diffusion coefficients measured by DOSY are frequently used to estimate the hydrodynamic radii or the molecular weights of compounds in solution.<sup>3-6</sup> The consequences of erroneous measurements of diffusion coefficients for time-dependent concentrations are well illustrated here by an attempt to estimate molecular weights for the reacting mixture, using conventional DOSY and SPEN DOSY data. The external-calibration-curve (ECC) method of Stalke and co-workers was used, as it requires a single internal reference that can be the solvent.<sup>6,25</sup>

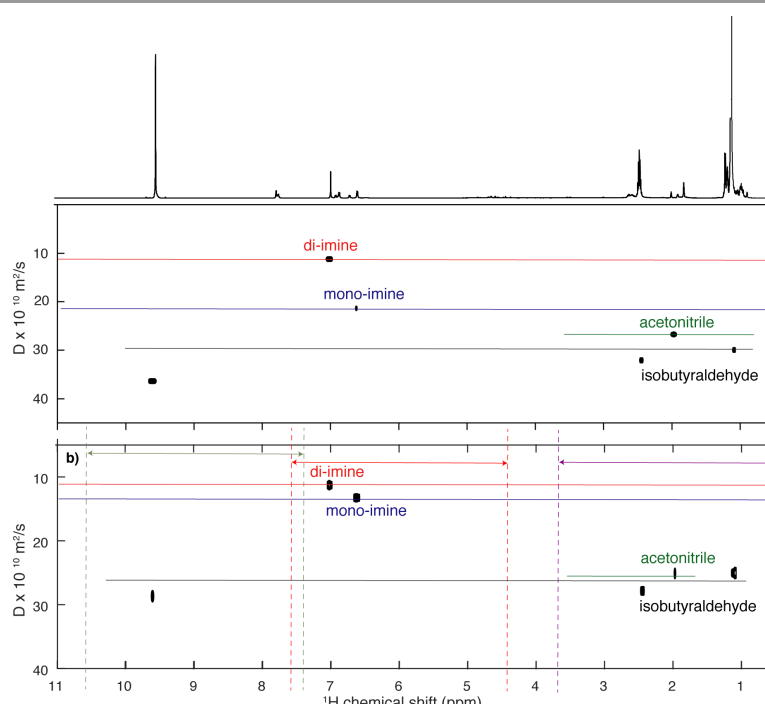


Figure 5 DOSY spectra of a reaction mixture of isobutyraldehyde with 1,4-diaminobenzene in acetonitrile- $d_3$ . (a) Conventional DSTE DOSY spectrum recorded over 22 min from the beginning of the reaction. (b) Concatenation of 3 spectrally selective SPEN DSTE DOSY spectra recorded at  $t = 3.5$  min. A spectrum was obtained every 15 s, and each spectrum was recorded in less than 200 ms. A  $^1\text{H}$  1D spectrum of the mixture is shown above the DOSY displays. Only resolved peaks were included in the DOSY processing.

Table 3 Estimated molecular weights obtained on the reaction mixture M3 with external-calibration curves, using acetonitrile as an internal reference.

$\delta$ ppm	compound	SPEN DSTE DOSY			Conv DSTE started at						
		t (3.5 min)			t (2 min)		eq. <sup>a</sup>				
		D	MW	$\Delta$	D	MW	%	D	MW	$\Delta$	
		$\cdot 10^{10}$	$\text{g} \cdot \text{mol}^{-1}$	%	$\cdot 10^{10}$	$\text{g} \cdot \text{mol}^{-1}$		$\cdot 10^{10}$	$\text{g} \cdot \text{mol}^{-1}$	%	
7.0	bis-imine	11.4	244	11	10.1	314	31	11.3	243	11	
6.6	mono-imine	13.4	185	12	20.4	96	69	13.0	192	16	
1.9	acetonitrile	25.1	-	-	25.8	-	-	24.8	-	-	

$\Delta$ : difference in MW

Table 3 shows estimated molecular weights obtained from several data sets, for the mono-imine (MW = 162  $\text{g} \cdot \text{mol}^{-1}$ ) and bis-imine (MW = 216  $\text{g} \cdot \text{mol}^{-1}$ ) compounds. While the conventional DOSY data yields estimates that are erroneous by 50% or more, with SPEN DOSY data the estimated molecular weights are within 20% of the known values. These results are due to the fact that the use of an internal reference makes it possible to compensate for some sources of error (such as gradient mis-calibration), but cannot compensate for the change in concentration of the analysed compounds during the reaction. While the model reaction analysed here serves as a validation, the possibility to obtain a sensible estimate of the molecular

weight of an intermediate would be particularly useful for the mechanistic study of a novel reaction.

## Conclusions

In summary, we have shown that the acquisition of diffusion-ordered NMR spectra can be accelerated significantly for experiments carried out in low-viscosity solvents, which include important organic solvents such as chloroform, dichloromethane or acetonitrile. This study sheds light on the great potential of SPEN DOSY to follow chemical transformations and to obtain diffusion information from reaction intermediates.

## Conflicts of interest

“There are no conflicts to declare”.

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