Fast and flow compatible pseudo-3D diffusion NMR

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1. Materials and methods

Sample 1

A 25 mL solution was prepared from a 100 mM mixture of alcohols and L-valine. L-valine (293 mg), methanol (101 µL), ethanol (146 µL) and n-propanol (187 µL) were dissolved in approximately 24.5 mL of water (H_2O). The mixture was shaken thoroughly to ensure the solid particles were fully dissolved.

Sample 2 (synthesis of α-hydroxyphosphonate)

In a flat bottom flask (100 mL) a mixture of 4-nitrobenzaldehyde (2.64 g, 17.5 mmol) and triethylamine (244 µL, 1.75 mmol) in acetonitrile (23 mL) was stirred at room temperature. Prior to filling the flow system diethyl phosphonate (2 mL, 17.5 mmol) was added to the reaction mixture.

NMR spectrometer

NMR experiments were carried out with a spectrometer operating at a ^1H frequency of 500.13 MHz (Bruker, Avance III), equipped with an inverse-detection probe featuring triple-axis gradients. The experiments were conducted at a temperature of 298 K.

Flow tube

The experiments were performed with the use of a commercial flow tube (InsightMR, Bruker). The flow tube consists of a 5 mm NMR tube tip, connected to the output of the flow line with a 7 m long 0.5 mm I.D. PEEK capillary. A further 7 m capillary returns from the NMR tube tip to a sample collector. The length of the capillary is justified by the fact that we use an unshielded NMR magnet. A shielded magnet would allow for a shorter line. A Bruker InsightMR flow tube is easily inserted in the magnet guide, by sliding the end of the transfer line inside the spectrometer. The end of the transfer line consists of an NMR tube tip held by a plastic support shaped as a conventional spinner, and the diameter of the tube connected to it perfectly fits in the magnet bore.

Initially, the WET solvent suppression was set using only the solvent (water or acetonitrile) flowing through the system. Then, the system was filled with approximately 6 mL of solution at 1.5 mL/min with the outlet connected to the sample collector to prevent from any dilution of samples. After three minutes, the outlet was reconnected to the reactor and the NMR data acquisition was started. The online monitoring of the reaction was conducted at a flow rate of 1.5 mL/min in an air-conditioned room.

NMR parameters

A Solvent suppression was achieved using a WET block with four SEDUCE shaped pulses of 15.00 ms each, with nominal tip angles of 81.4°, 101.4°, 69.3° and 161°, four gradient pulses of amplitude of 0.504 T m^{-1}, 0.252 T m^{-1}, 0.126 T m^{-1} and 0.063 T m^{-1} and a duration of 2 ms, applied along the z axis.

The UF COSY parameters for desired spectral width optimization were as follows: the duration of the frequency-swept (smoothed chirp) pulse was 15 ms, and its bandwidth was 25 kHz. The strength of the spatial encoding gradient *Ge* was 7.6% along the x axis. The number of acquisition loops was set to 64. Here, two interleaved acquisitions and one scan for signal averaging were acquired. The bipolar gradients used during acquisition *Ga* were set to 80 % and -80 %.

The diffusion NMR parameters were optimized, using y-gradient axis with a maximum gradient strength of 48.2 G/cm for diffusion encoding in all experiments. The duration of the gradient pulse, δ was set for this mixture to 2000 µs for **sample 1** and 1700 µs for **sample 2**, the diffusion delay, Δ was 100 ms. The number of gradient increments was 8 from 10 % to 80 % of the maximum gradient strength.

Data processing and DOSY analysis

The data were processed using custom-made scripts in MATLAB adapted from the previous work.[1] Initially, every 2D UF spectrum in the diffusion-weighted array was processed individually. This included reordering the data into 2D matrices, in which the odd and even echoes (derived from the positive and negative gradients during acquisition) were processed separately. In the ultrafast (spatially encoded) dimension, the data were inverse-Fourier transformed and then apodised using a Gaussian window of the 3 mm width in the spatial dimension.[2] This was followed by zero-filling to 1024 points and a final Fourier transform. In the conventional dimension, the data were apodised using a sine window function, zero-filled to 1024 points, and then Fourier-transformed. The odd and even echoes were then recombined to increase the signal intensity. The DOSY analysis included defining the spectral regions of peaks using the first (lowest gradient strength) 2D spectrum. The peaks volumes were obtained for all diffusion increments and fitted to the Stejskal-Tanner equation.

2. Figures

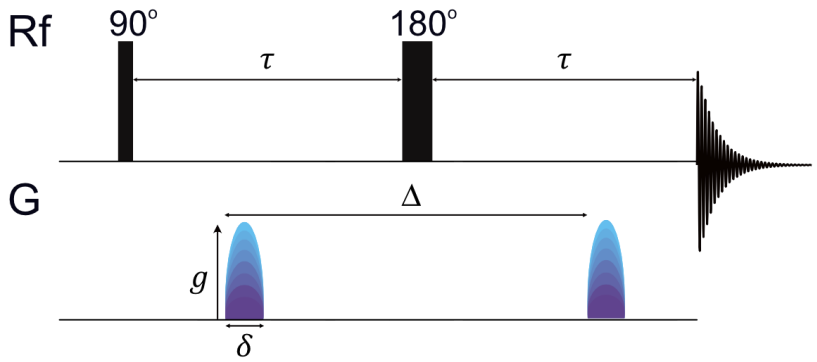

Figure S1. The scheme of the spin echo pulse sequence, where two gradient pulses of δ duration and g strength are applied with a time delay, Δ.

3. **Tables**

Peak number	Mean D x 10^{-10} $m^2.s^{-1}$ (triplica)	Mean D x 10^{-10} $m^2.s^{-1}$ (tripl., stop flow)	STD (triplica)	RMS (fitting)	Trueness, %
1. Ethanol (d)	12.13	12.90	0.11	0.24	5.97
2. n-Propanol (d)	11.14	12.01	0.34	0.12	7.30
3. Methanol (d)	14.68	17.97	1.65	0.79	18.32
4. n-Propanol (d)	11.22	11.43	0.18	0.44	1.77
5. Ethanol (d)	12.91	13.66	0.14	0.16	5.50
6. Valine (d)	8.46	8.67	0.19	0.20	2.38
7. Valine (d)	8.43	8.88	0.10	0.09	5.12
8. n-Propanol (d)	11.45	12.01	0.22	0.15	4.62
9. Ethanol (c)	11.09	12.91	0.33	0.73	14.09
10. n-Propanol (c)	10.93	12.06	0.15	0.34	9.37
11. Valine (c)	7.98	9.13	0.20	0.19	12.62
12. n-Propanol (c)	8.92	10.46	0.05	0.82	14.66
13. n-Propanol (c)	9.48	10.68	0.82	0.54	11.27
14. Ethanol (c)	11.44	12.63	0.47	0.57	9.43
15. n-Propanol (c)	10.53	11.60	0.31	0.48	9.23

Table S1. Results of the fitting of the diffusion decays in Fig. 2 to the ST model with the estimation of fitting errors and trueness. The trueness was estimated using diffusion coefficients obtained from data acquired under static conditions (i.e. stop flow) for diagonal (d) and cross (c) peaks.

	3 min		63 min		123 min	
Peak number	D x 10^{-10} $m^2.s^{-1}$	SNR	D x 10^{-10} $m^2.s^{-1}$	SNR	D x 10^{-10} $m^2.s^{-1}$	SNR
1	14.0±1.2	92	10.7±0.2	344	10.3±0.1	324
2	20.7±0.5	616	12.7±0.2	266	11.4±0.1	209
3	22.0±0.4	1566	16.6±0.4	342	16.9±0.5	289
4	15.7±0.7	213	10.9±0.1	972	10.3±0.1	922
5	20.0±0.5	109	13.6±0.4	33	12.4±0.4	27
6	21.1±0.6	173	12.7±1.1	29	11.0±1.5	15
7	*n.d.*	*n.d.*	11.7±0.1	98	9.9±0.1	92

Table S2. The results of fitting the diffusion decays from Fig. 3, corresponding to the different synthesis reaction times of α-hydroxyphosphonate, to the ST model are shown, along with the estimation of fitting errors and the signal-to-noise ratio of the highlighted peaks. *n.d.* : not detected; peak 7 is not present after three minutes of the reaction or present only at weak intensity, as it is the product peak.

4. References

1 C. Jacquemmoz and J. Dumez, *ChemPhysChem*, 2018, **19**, 3204–3210.

2 P. Giraudeau and S. Akoka, *Magn. Reson. Chem.*, 2011, **49**, 307–313.