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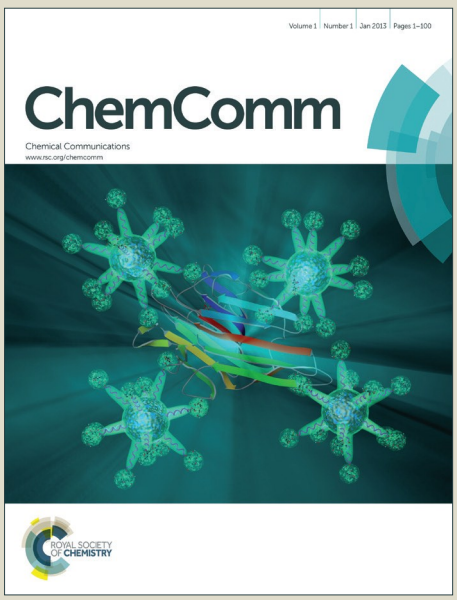

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Detection of quadrupolar nuclei by ultrafast 2D-NMR: exploring the case of deuterated analytes aligned in chiral oriented solvents

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Anisotropic ^{2}H ultrafast (ADUF) 2D-NMR spectroscopy to study analytes dissolved in chiral liquid crystals (CLC) is explored for the first time, and the analytical possibilities of this method are evaluated. We demonstrate that these unconventional sub-second 2D experiments are compatible with the basic gradient units (40-60 G.cm^{-1}) implemented on routine spectrometers, and allow recording ^{2}H signals of weakly aligned deuterated solutes in sub-second experimental times.

A major advantage of proton-decoupled (^{2}H-{^{1}H}) nD NMR spectroscopy in oriented media such as liquid crystals (LC's) is the access to anisotropic spectral data that are averaged to zero in liquids, such as the chemical shift anisotropy (^{2}H CSA) and the residual quadrupolar coupling (noted RQC(^{2}H) or $\Delta\nu_Q(^2H)$). These order-dependent data can provide key information on the molecular geometry, the conformational behavior and the dynamics of aligned analytes (solutes or mesophases itself) [1].

Compared to other nuclei with $I > 1/2$, deuterons possess a small quadrupolar moment ($Q_D = 2.86 \times 10^{-31}$ m^2) [2], thus limiting an excessive line broadening due to quadrupolar relaxation mechanisms. When dissolved into rather weakly orienting LC's such as polypeptide lyotropic systems, they produce ^{2}H quadrupolar doublets (QD) whose $|\Delta\nu_Q|$ magnitude ranges generally from 0 to 1000 Hz. Interestingly, since these aligning media are chiral (helical polymers), the spectral enantiodiscrimination of enantiotopic directions of prochiral molecules deuterated or enantiomers are possible on the basis of a difference of RQC's ($\Delta\nu_Q(^2H)^{R \text{ or } pro\text{-}R} \neq \Delta\nu_Q(^2H)^{S \text{ or } pro\text{-}S}$) [3].

Based on this strategy, various methodological developments (^{2}H nD NMR) and a large panel of applications (stereochemical analysis) have been proposed, including the detection of deuterium at natural abundance level (isotope fractionation analysis) [4].

Very recently, the first monitoring of chiral enzymatic transformations (the interconversion of L- and D-Alanine-d_3 enantiomers by the Alanine racemase) directly observed by anisotropic ^{2}H-NMR has been successfully pioneered [5]. The idea was to follow *in situ* and real-time the variation of peak intensity of QD's of each enantiomer during the bioprocess, and extract from the spectral fit the turnover numbers of the enzyme. An inherent drawback of this approach is the experimental time required to record spectral data for monitoring the time-dependent variations of all compounds in the mixture, in particular for extremely fast and/or multiple (cascade) chemical transformations for which the fast identification and quantification of ^{2}H signals of products (reactants, (un)stable intermediates, products, …) (chiral or not) require 2D-NMR experiments with sub-minute time resolutions or below.

Non-uniform acquisitions combined with covariance/compressed sensing processing [6] have been proposed to reduce the acquisition time of anisotropic NAD 2D-NMR experiments. Another appealing option is to rely on ultrafast (UF) 2D NMR, an approach capable of yielding arbitrary homo- or hetero-nuclear 2D correlations within a single scan when sensitivity allows it [7]. Within the last ten years, the performance of UF experiments has been greatly enhanced by numerous methodological developments, making UF NMR applicable to a wide range of analytical situations [8]. UF NMR has been applied to the real-time monitoring of fast chemical transformations [9], to the coupling with other techniques such as chromatography [10] or hyperpolarization [11], and also to the high-throughput quantitative analysis of complex samples [12].

The use UF 2D-NMR experiments in anisotropic environments has been described in 2012 [13] for extracting residual ^{13}C-^{1}H dipolar couplings (RDC's) from UF heteronuclear spectra. However, such approach has never been explored in the case of quadrupolar nuclei such as deuterium ($I = 1$) using aligned solvents.

In this communication, we report the first examples of anisotropic deuterium UF (ADUF) spectra of deuterated analytes dissolved into

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polypeptide lyotropic CLC's. We investigate the case of two isotopically enriched prochiral molecules of C_s symmetry, pentanol-d_{12} (**1**) and benzyl alcohol (**2**) enriched in ^{13}C and ^{2}H on the methylene prostereogenic group, both of those analytes possessing enantiotopic C-D directions. Although these chiral molecules possess rather few non-equivalent ^{2}H sites, (see **Figures** 2 and 3), they offer interesting model compounds to discuss the analytical possibilities of ADUF 2D-NMR in CLC's, and also to explore the case of spectrally detectable isotopologues.

The ADUF 2D pulse sequence shown in **Figure 1** follows the basic scheme of homonuclear 2D UF experiments, where the usual time encoding is replaced by a spatial encoding, formed by two chirp pulses applied together with a pair of opposite gradients [14]. This spatial encoding block is followed by a conventional mixing period and a detection block based on echo planar spectroscopic imaging (EPSI) [15]. The ^{2}H hard-pulse scheme is identical to the *Q*-COSY sequence developed for conventional ^{2}H experiments (QUOSY-type), and leading to magnitude-mode maps [2,3,16]. It is made of a ^{2}H 90°(x) pulse followed by a 180°(x) pulse, separated by a spatial encoding period of duration T_e. In contrast to conventional 2D *Q*-COSY experiment, the ADUF 2D scheme is a constant-time experiment, leading to the refocusing of all coupling patterns in the F_2 dimension. Note that in all UF experiments shown here, the spatially-encoded dimension is shown in F_2, while the dimension resulting from the Fourier Transform of the EPSI domain is shown in F_1. In the case of ^{2}H nuclei, this first consists in removing all $\Delta\nu_Q(^{2}H)$ in the F_2 dimension of the 2D map, concomitantly to the possible homonuclear scalar $^{n}J(^{2}H\text{-}^{2}H)$ and dipolar $^{n}D(^{2}H\text{-}^{2}H)$ couplings in the case of perdeuterated molecules. In other words, the expected ADUF 2D map is formally identical to that obtained for the conventional δ–resolved experiments (QUOSY-type), except that the spectral content of F_1 and F_2 are inverted compared to conventional spectra [16a] (see **ESI**). Consequently, the ADUF experiments can be considered as ^{2}H δ-resolved constant-time experiments.

Possible $^{n}J(^{2}H\text{-}^{1}H)$ and $^{n}D(^{2}H\text{-}^{1}H)$ heteronuclear couplings (generally < 2 Hz in PBLG mesophase) can be simply removed by implementing ^{1}H 180° hard pulses between the bipolar gradient pairs, in order to refocus such couplings during the spatial encoding and/or acquisition periods. These pairs of 180° pulses can also be associated with similar pulses on the heteronuclear X channel for further X-^{2}H heteronuclear decoupling. **Figure 1** shows such an optional block for a specific ^{13}C decoupling. Note that due to the smaller gyromagnetic value of ^{2}H nuclei compared to ^{1}H ($\gamma_{1H} = 6.515 \times \gamma_{2H}$), the magnitude of $^{n}J(^{2}H\text{-}^{13}C)$ and $^{n}D(^{2}H\text{-}^{13}C)$ couplings remains relatively weak (0 to 50 Hz), and simple 180° pulses are sufficient for an efficient decoupling. More complex decoupling schemes might be necessary according to the magnitude of ^{2}H-X couplings, in particular for X nuclei of high γ.

The anisotropic sample of **1** (**2**) was prepared using 100 mg of PBLG with a degree of polymerization of 534 (732), 100 (50) mg of solute, and 350 mg of $CHCl_3$ in a 5-mm o.d. tube (fire-sealed). Details concerning the anisotropic sample preparation can be found in references [2, 3]. The experiments were carried out at 303 K using a Bruker Avance HD spectrometer operating at 16.4 T, equipped with an inverse $^{1}H/^{13}C/^{15}N/^{2}H$ cryogenically cooled probe (107.5 MHz for ^{2}H) [17] and including a z-axis gradient.

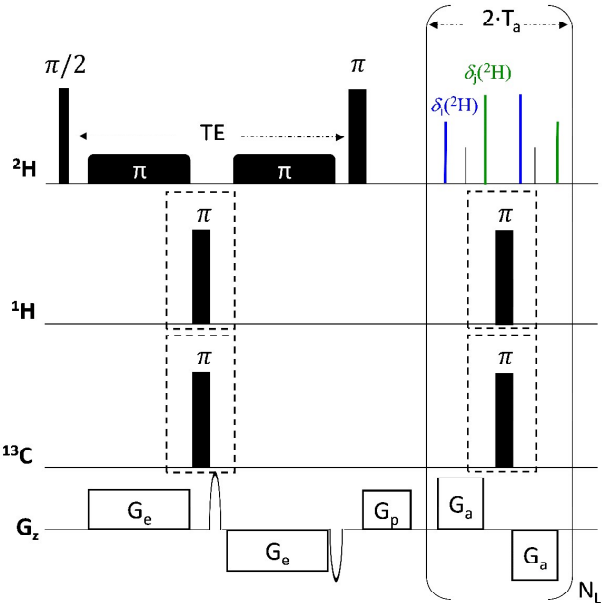

Fig. 1. Pulse scheme of the ultrafast δ-resolved constant-time pulse NMR sequence. The optional blocks for ^{13}C and ^{1}H decoupling during the spatial encoding and acquisition periods are shown in dashed boxes. TE is the duration of spatial encoding, T_a is the duration of acquisition gradients. N_L is the number of loops applied for the EPSI scheme, governing the resolution in the F_1 dimension. G_e and G_a correspond to the gradients applied during spatial encoding and acquisition, respectively. G_p is a pre-acquisition gradient adjusted to center the peaks of interest in the middle of the spectral window. Additional sine-shape gradients are used for the coherence pathway selection.

The ADUF 2D spectra were recorded with a single scan experiment. The following parameters were used for spatial-encoding: bipolar excitation gradient with gradients G_e of 20 ms and 9.7 $G.cm^{-1}$ each; 20 ms smoothed chirp pulses with a sweep range of 5 kHz. The acquisition gradient parameters were T_a = 716.8 µs and G_a = 58.5 $G.cm^{-1}$. For samples **1** and **2**, the number of loops N_L was set to 256 and 128, respectively. The ^{2}H π/2 pulse (87 µs / 38 W) was carefully calibrated to obtain an accurate 90°/180° excitation. The spatial encoding and acquisition parameters resulted in a spectral width of 1000 Hz which was sufficient to cover the spectral distribution of ^{2}H information in both dimensions. The ^{1}H and ^{13}C π pulses (21.3 µs / 180 W and 22.0 µs / 8.5 W, respectively) were also carefully calibrated to ensure an optimal refocusing of heteronuclear couplings. ^{1}H decoupling can be useful to remove possible residual $^{1}H\text{-}^{2}H$ couplings due to an imperfect perdeuteration of molecules (case of **1**) or eliminate any long-range $^{1}H\text{-}^{2}H$ couplings in the case of selectively deuterated solutes (case of **2**).

All the ADUF 2D spectra were processed in magnitude mode: zero-filling, Gaussian spatial apodization in the spatially-encoded dimension F_2 [18] and conventional sinebell apodization in F_1, to obtain the most symmetrical ^{2}H lineshapes and to find an optimal compromise between resolution and sensitivity. All the spectra

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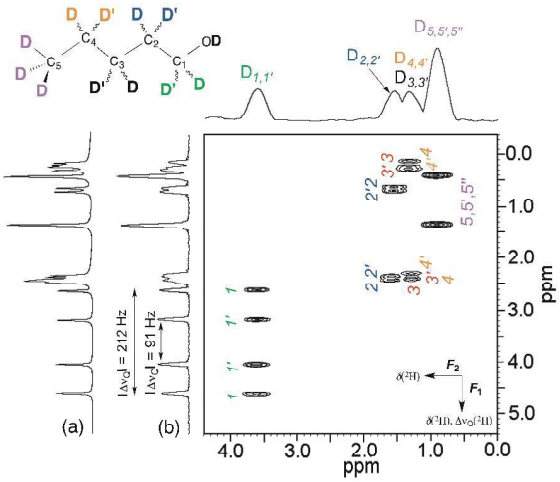

Fig. 2. (a) ^{2}H-{^{1}H} 1D spectrum of **1** in PBLG mesophase. (b) Single-scan ADUF-{^{1}H} 2D map recorded in *ca*. 400 ms, with the pulse sequence of **Figure 1**. The X/X' notation is arbitrarily defined.

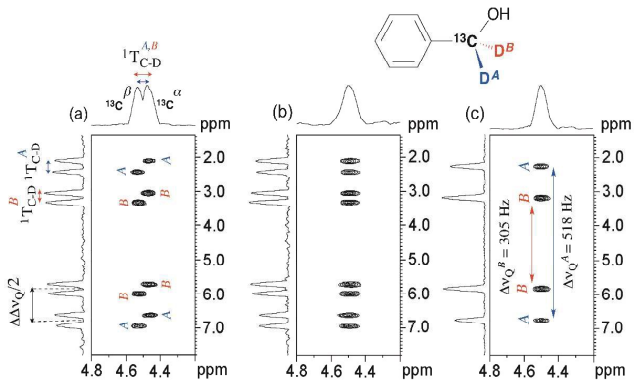

Fig. 3. Single-scan ADUF 2D ^{2}H-{^{1}H} maps of **2** in PBLG mesophase without ^{13}C decoupling (a), with ^{13}C decoupling in F_2 (b) and with ^{13}C decoupling in F_2 and F_1 (c), each of them recorded in *ca*. 220 ms. The *A*/*B* stereodescriptors shown on 2D maps are arbitrarily given. Note the increasing of S/N ratios (a factor of *ca.* 3) when the ^{13}C signal is decoupled in both dimensions (map c).

were analyzed using the Bruker program Topspin 3.2. The specific processing for ADUF spectra was performed using a home-written routine in Topspin. This processing program is available on a dedicated website, where a protocol is also provided to help users in the implementation of UF experiments [19]. The pulse sequence is available on demand. Other details are given in figure captions.

As a first example, we investigated the case of 1-pentanol-d_{12}. This prochiral flexible molecule of C_s symmetry possesses three homotopic C-D directions (methyl group) and four pairs of C-D enantiotopic directions associated to the four prostereogenic methylenes of the molecule. *A priori*, nine QD's are expected to be detected if all inequivalent C-D directions are spectrally discriminated in the CLC, disregarding the hydroxyl group. The ADUF-{^{1}H} 2D spectrum recorded in a single scan is shown in **Figure 2** along with the corresponding projections. Note that all $\Delta\nu_Q(^2H)$'s have been eliminated in F_2, and that no tilt is needed since this spatially-encoded dimension is constant-time. The F_2 dimension is therefore a "pure shift" dimension which reduces the useful spectral information to $\delta(^2H)^{aniso}$ only (*ca*. 500 Hz of width).

This 2D map can be compared to the conventional anisotropic ^{2}H δ-resolved 2D experiment recorded with 128 t_1 increments and 8 scans in 17 min (see **Figures S1** and **S2** in **ESI**). Although the resolutions are lower than for the conventional 2D map (or 1D spectrum), the analysis of the ADUF spectrum shows that the discrimination of enantiotopic site pairs (visible for sites 1, 2 and 3) is similar to the one observed on the conventional spectrum acquired in 17 min. Still, the resolution in the F_1 dimension of the ADUF spectrum ($\Delta\nu_{1/2}(F_1)$ = 5.5 Hz) is limited by the number of loops that the gradient amplifier can support for the EPSI block, while this resolution could be improved in the conventional spectrum by increasing the number of t_1 increments –though at a time expense. The resolution in F_2 ($\Delta\nu_{1/2}(F_2)$ = 32 Hz) is a well-known limitation of UF experiments, inherent to the need to compromise between resolution, sensitivity and spectral widths [8a]. In the end, the maximum spectral width in F_2 is limited by the maximum amplitude of the acquisition gradients G_a.

Nevertheless, these first results are very promising and clearly indicate that: i) the detection of ^{2}H nuclei by UF approach within sub-second experimental times is possible for deuterated solutes, ii) the gradient power (G_z: 40-60 G.cm^{-1}) available on gradient units of routine spectrometers is sufficient to yield full-width 2D spectra in a single scan for nuclei with low gyromagnetic ratios –this would not have been possible at high field with ^{1}H due to the spectral width limitations of UF NMR; iii) the resolution in F_1 (a few Hz) allows the discrimination of enantiotopic sites up to differences of $|\Delta\Delta\nu_Q|/2 < 6$ Hz.

To further examine the spectral possibilities of ADUF 2D experiments, we focused our attention on another C_s symmetry solute, benzyl alcohol, isotopically enriched (^{2}H and ^{13}C) on the methylene group. Due to the presence of an abundant 100% ^{13}C nucleus, four QD's (instead of two for the ^{2}H-^{12}C isotopologue) are observed on the ^{2}H-{^{1}H} 1D spectrum (see **Figure S2**). The spectral difference between the two pairs of QDs corresponds to the difference of ^{2}H and ^{13}C total couplings ($|^1T_{C\text{-}D}{}^{A,B}| = |^1J_{C\text{-}D}{}^{A,B} + 2^1D_{C\text{-}D}{}^{A,B}|$) associated to the enantiotopic directions pro-*R*/pro-*S* but simply noted "*A*,*B*". From the 1D spectrum several choices for pairing the components are possible, leading to different $|^1T_{C\text{-}D}|^{A,B}$ values.

Figure 3a presents the single-scan ADUF 2D-{^{2}H} map of **2** in the PBLG mesophase recorded in 220 ms. In this second experiment, spectral resolutions of *ca.* 10 Hz (F_1) and 32 Hz (F_2) have been reached; the lower resolution in F_1 compared to **Figure 2** being explained by the lower number of EPSI loops. The two resonances observed in F_2 are not associated to independent ^{2}H peaks with distinct $\delta(^2H)$ (as for **1**), but originate from the total couplings, $^1T_{C\text{-}D}{}^{A}$ and $^1T_{C\text{-}D}{}^{B}$, the resulting doublet being centered on the $\delta(^2H)^{A,B}$ of the methylene group. Contrary to homonuclear couplings, the evolution of the heteronuclear ^{2}H-^{13}C total couplings is not eliminated by the csonstant-time chemical shift encoding. The presence of this doublet (due to the two energy levels of ^{13}C nuclei ($|\alpha>$ and $|\beta>$)) and the position of cross-peaks on the 2D map allow to easily assign the two components of each QD pair (associated to C-D^{A,B} directions), and then determine the magnitude of $^1T_{C\text{-}D}{}^{A}$ and

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$^1T_{C\text{-}D}{}^B$ to be equal to +29 and +35 Hz (on the 1D spectrum), respectively. Note that the moderate resolution in F_2 leads to detect one doublet with broad components instead of two resolved doublets.

Interestingly, the data contained on the ADUF 2D spectrum of **2** can be modulated according to the ^{13}C decoupling blocks implemented in the T_e and T_a periods of the initial pulse sequence (see **Figure 1**). On the one hand, the ^{13}C decoupling during the spatial collapses the doublet into a single resonance centred now on $\delta(^2H)^{pro\text{-}R} \approx \delta(^2H)^{pro\text{-}S}$ ($CSA(^2H)^{pro\text{-}R} \approx CSA(^2H)^{pro\text{-}S}$) in F_2 (see **Figure 3b**). On the other hand, the ^{13}C-^2H total coupling can also be eliminated by implementing ^{13}C 180° pulses between gradients of the EPSI block, simplifying the spectral information to two QDs in F_1. Applying the ^{13}C decoupling in both dimensions leads to the map shown in **Figure 3c** where the magnitude of QD can be determined unambiguously ($\Delta\nu_Q(^2H)^A$ = +305 Hz and $\Delta\nu_Q(^2H)^B$ = +518 Hz). The positive sign is coherent with the $^1T_{C\text{-}D}{}^{A,B}$ values measured, and considering that $^1J_{C\text{-}D}{}^{A,B}$ = +22 Hz (the ratio "$\Delta\nu_Q(^2H)/^1D_{C\text{-}D}$" = 70-80 for sp3 carbon atoms.

Conclusions

In the present work, we have demonstrated the experimental feasibility and analytical possibilities of anisotropic UF 2D-NMR experiments in the case of quadrupolar nuclei such as deuterons. Practically, ADUF experiments suit the study of weakly aligned deuterated solutes because the small magnitudes of RQC's(^2H) lead to a distribution of resonances on moderate spectral widths (< 1000 Hz), that are rather well-adapted to the technical limitations of UF experiments. Consequently, these original experiments can be performed on routine NMR spectrometers equipped with basic gradient units, while γ_{1H} is 6.5 times lower than γ_{2H}. As shown, recording all relevant anisotropic information (of perdeuterated analytes) is possible within sub-second experiment times, while the heteronuclear information (if detectable) can be modulated according to the decoupling scheme applied in both dimensions.

These pioneering findings open a vast array of prospects such as: i) the ADUF experiments for which the ^2H chemical shifts would be refocused in the direct dimension (F_1), similarly to the *Q*-resolved 2D experiments; ii) the replacement of constant-time scheme by a real-time scheme [20] to produce maps where the ^2H autocorrelations would distribute perpendicularly to the main diagonal as in a conventional ^2H *Q*-COSY 2D maps, iii) the development of algorithms to process the UF spectra in phase-sensitive mode, thus improving the resolution. While the samples studied in this paper were compatible with the acquisition of full-width spectra in a single scan, the sensitivity and the spectral widths may be increased even further, if needed, by relying on hybrid experiments recently described, which combine a few UF scans to increase the analytical performance at a reasonable time cost [21]. Such hybrid experiments would also pave the way to the acquisition of fast 3D spectra to reduce peak overlap even further [22].

No doubt that the ultimate challenge of ADUF experiments is sensitivity. Here, the sensitivity of a single-scan ADUF spectrum was found *ca*. six times lower than the one of a single-scan 1D ^2H spectrum. This is a well-known limitation of UF NMR [8a]. Detailed SNR measurements (see ESI) show that the acquisition of a single-scan ADUF spectrum with our hardware requires at least 15 mg of ^2H-labeled compound in the NMR tube. While this limit of detection can be lowered by an order of magnitude by signal averaging, the detection of ^2H nuclei at natural abundance level [4] will require more sensitive techniques, such as hyperpolarization methods that can be efficiently coupled to UF 2D NMR [11].

Notes and references

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1 (*a*) P. Lesot, *Encyclopedia of Magnetic Resonance* (eMagRes), 2013, **2**, 315; (*b*) C. Aroulanda, O. Lafon and P. Lesot, P. *J. Phys. Chem. B*. 2009, **113**, 10628; (*b*) K. Tabayashi and K. J. Akaska, *Liquid Crystals*, 1999, **26**, 127.
2 P. Lesot and J. Courtieu, *Prog. Nucl. Magn. Reson., Spectrosc*., 2009, **55**, 128.
3 (*a*) P. Lesot, C. Aroulanda, H. Zimmerman and Z. Luz, *Chem. Soc. Rev*., 2015, **44**, 2330; (*b*) M. Sarfati, P. Lesot, D. Merlet and J. Courtieu. *Chem. Commun*. 2000, 2069.
4 (*a*) V. Baillif, R. J. Robins, S. Le Feunten, P. Lesot and I. Billault, *J. Biol. Chem*., 2009, **284**, 10783; (*b*) P. Berdagué, P. Lesot, J. Jacob, V.-J. Terwilliger and C. Lemilbeau*, Geochim. Cosmochim. Acta*, 2016, **173**, 337.
5 M. Chan-Huot, P. Lesot, P. Pelupessy, L. Duma, G. Bodenhausen, P. Duchambon, M. D. Toney, U. V. Reddy and N. Suryaprakash, *Anal. Chem.,* 2013, **85**, 4694.
6 (*a*) O. Lafon, B. Hu, J.-P. Amoureux and P. Lesot, *Chem. Eur. J.*, 2011, **17**, 6716; (*b*) K. Kazimierczuk, O. Lafon and P. Lesot, *Analyst,* 2014*,* **139**, 2702.
7 L. Frydman, A. Lupulescu and T. Scherf, *J. Am. Chem. Soc.,* 2003, **125**, 9204.
8 (*a*) P. Giraudeau and L. Frydman, *Annu. Rev. Anal. Chem*., 2014, **7**, 129.
9 A. Herrera, E. Fernández-Valle, R. Martínez-Álvarez, D. Molero-Vílchez, Z .D. Pardo-Botero and E. Sáez-Barajas, *Magn. Reson. Chem*., 2015, 2015, **53**, 952.
10 L. H. K. Queiroz Jr, D. P. K. Queiroz, L. Dhooghe, A. G. Ferreira and P. Giraudeau, *Analyst*, **201**, 137, 2357.
11 J. N. Dumez, J. Milani, B. Vuichoud, A. Bornet, J. Lalande-Martin, I. Tea, M. Yon, M. Maucourt, C. Deborde, A. Moing, L. Frydman, G. Bodenhausen, S. Jannin and P. Giraudeau, *Analyst*, 2015, **140**, 5860.
12 T. Jézéquel, C. Deborde, M. Maucourt, V. Zhendre, A. Moing and P. Giraudeau, *Metabolomics,* 2015*,* **11**, 1231.
13 P. Giraudeau, T. Montag, B. Charrier and C.M. Thiele, *Magn. Reson. Chem.,* 2012, **50**, S53.
14 P. Pelupessy, *J. Am. Chem. Soc.,* 2003, **125**, 12345.
15 P. Mansfield, *Magn. Reson. Med.* 1987, **1**, 370.
16 (*a*) D. Merlet, B. Ancian, J. Courtieu and P. Lesot, *J. Am. Chem. Soc*. 1999, **121**, 5249.
17 H. Kovacs and D. Moskau, M. Spraul, *Prog. NMR Spectrosc.*, 2005, **45**, 131.
18 P. Giraudeau and S. Akoka, *Magn. Reson. Chem.,* 2011, **49**, 307.
19 http://www.univ-nantes.fr/giraudeau-p
20 Y. Shrot, B. Shapira and L. Frydman, *J. Magn. Reson.,* 2004, **171**, 163.
21 S. Akoka and P. Giraudeau, *Magn. Reson. Chem*., 2015, **53**, 986.
22 (a) R. Boisseau, B. Charrier, S. Massou, J. C. Portais, S. Akoka and P. Giraudeau, *Anal. Chem.,* 2013, **85**, 9751; (b) O. Lafon and P. Lesot, *Chem. Phys. Lett.*, 2005*,* **404**, 90.

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