Compressed NMR: Combining *Compressive Sampling* and *Pure Shift* NMR Techniques

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ABSTRACT: Historically, the resolution of multidimensional NMR has been orders of magnitude lower than the intrinsic resolution that NMR spectrometers are capable of producing. The slowness of Nyquist sampling, as well as the existence of signals as multiplets instead of singlets have been two of the main reasons for this underperformance. Fortunately, two compressive techniques have appeared that can overcome these limitations. *Compressive sensing*, also known as *compressed sampling*, (CS), avoids the first limitation exploiting the compressibility of typical NMR spectra, thus allowing sampling at sub-Nyquist rates, and *pure shift* techniques eliminate the second issue "compressing" multiplets into singlets. This paper explores the possibilities and challenges presented by this combination (C*ompressed NMR*). First a description of the CS framework is given, followed by a description of the importance of combining it with the right *pure shift* experiment. Second, examples of compressed NMR spectra, and how they can be combined with covariance methods will be shown.

Introduction

Multidimensional Nuclear Magnetic Resonance (NMR) is unique among instrumental techniques in that the effective resolution that is typically obtained from the experiments is orders of magnitude lower than the instrument is capable of delivering. This is due in part to the fact that peaks usually occupy orders of magnitude more than the underlying spin physics requires, the latter being limited by the spin-spin relaxation time (T_2). Fortunately, the typical T_2 of a small or medium sized molecule, the subject of this publication, is long enough to produce peaks of just a few Hz wide, or less. Multidimensional NMR peaks are often far broader than this intrinsic limit due to two factors. The first is a practical matter; digitizing the indirect dimensions to very high digital resolution using classical methods is a time-consuming process that is generally not practical in a chemistry setting. Unfortunately, poor digitization leads to artificially broadened peaks. The second problem is that, in the presence of J coupling, the size of the multiplet limits the achievable resolution no matter how high the digital resolution is. Fortunately, solutions to both problems are now emerging, although they are not without problems. The first solution is a mathematical framework that shows how to reduce sampling times in cases where objects such as NMR spectra are sparse or compressible (near sparse). This framework has been named *compressive sampling*, as well as *compressed sensing*, (here referred to as *CS*).[1] The second, *pure shift* NMR, deals with the problem of reducing signals to their minimum expression; a singlet.[2,3] Although commonly used separately, these two techniques need be combined to obtain the best results; without *CS*, the potential resolution of *pure shift* experiments cannot be reached without expending many of hours of spectrometer time and, conversely, without *pure shift* techniques, *CS* cannot pass the limitations imposed by the presence of multiplets. This paper considers the opportunities and the challenges that the combination of such compressive techniques, (*Compressed NMR*) presents. Most of the experiments considered here have a *pure shift* character in only in one dimension. Fortunately, true pure shift spectra in which all dimensions are decoupled can be produced with the aid of covariance methods. The typical sample considered here contains small to medium sized molecules. In what follows, a short review of both compressive techniques (*CS* and *Pure Shift* NMR) will be given. A discussion of how these two techniques need to be combined to produce spectra with optimum resolution will be described. Without loss of generality, the manuscript is written from the point of view of an NMR service that caters for chemists. The work described has been carried out under automation using 600 and 700 MHz spectrometers with conventional, ambient-temperature probe-heads.

The Compressive (or Compressed) Sampling (CS) framework

The problem we address first is that the conventional sampling method is a slow process that requires sampling at a rate of twice the highest frequency present in the signal of interest (the *Nyquist rate*).[4] This poses a problem for multidimensional *pure shift* techniques because a high digital resolution is necessary to take full advantage of such techniques. For example, digitizing a 6 kHz bandwidth phase sensitive TOCSY down to 1.5 Hz/point requires sampling the signals 4096 times. This can take up to a dozen hours. Out of necessity, the number of increments is often limited to reduce the experiment time, for example acquiring the first 512 increments out of the ideal 4096 ones. While this reduces the total experiment time by a factor of eight, it also reduces the digital resolution to 12.0 Hz/point, a value insufficient to distinguish a multiplet from a singlet. An intuitive solution to the problem is to sample at sub-Nyquist rates. Unfortunately, this creates an underdetermined system that is not suitable for analysis by Fourier transformation. However, it has been known from research conducted in disciplines such as geophysics that, in some cases, signals sampled at sub-Nyquist rates can be recovered by means other than a Fourier transformation. The approach used in some of these

cases, including NMR, was empirical, and thus it did not answer questions such as: "what kind of signal can be recovered from non-Nyquist sampling?" and "how should the signal be sampled?" or "what makes a signal recovery method adequate?" Recently, these questions have found answers from the pioneering work of Candès[5,6] and Donoho[7]. They have formalized a mathematical framework, *CS*, which gives some guidance regarding these questions. This group of theories demonstrates that not all objects or signals can be recovered from data sampled at sub-Nyquist rates, only those that are sparse or compressible in a particular representation (Fourier, wavelet, curvelet, etc.). In a rough way, the *CS* framework implies that the minimum number of measurements necessary is determined by the sparsity of the object rather than the nominal length of the signal. In particular, the framework shows that the time saving that can be realized depends on the sparsity (S) of the signal, (a definition of "sparsity" is provided in the Supplementary Information), the coherence of the sampling method (μ), and on the algorithm used to recover the signals. For example, if an algorithm that minimizes the ℓ1-norm is used, the number of increments (*m*) that has to be acquired to reconstruct an S-sparse signal is:

$$m \geq \mu^2 \cdot C \cdot S \cdot \log (ni) \qquad \text{Eq. 1}$$

where C is a constant, and *ni* is the number of increments that a Fourier transform would require if the data were sampled at the Nyquist rate.[6] Various non-Nyquist sampling methods were tried experimentally in several disciplines prior to the advent of *CS*; exponential, random, and spiral sampling schemes, among other functions, have been used in NMR and MRI where they are known collectively as non-uniform sampling.[8] However, the *CS* framework specifies that what makes a sampling method adequate is its incoherence in the sense that the more incoherently the signal is sampled (the lower μ), the larger the time savings (ni/m) would be, with $1 \leq \mu \leq \sqrt{ni}$. In fact, the largest savings are achieved when the sampling schedule is constructed from entries chosen from Gaussian or Bernouillan distributions with zero mean and variance $1/\sqrt{m}$. In these cases, the recovery guarantees provided by *CS* are:[9]

$$m \geq C \cdot S \cdot \log (ni/S) \qquad \text{Eq. 2}$$

Again Eq. 2 is valid for recovery algorithms that minimize the ℓ1-norm of the object to be reconstructed.

The implications for *compressed NMR* are substantial as *CS* facilitates increasing the digital resolution at logarithmic time cost, while traditional sampling/reconstruction methods require a linear increase in experimental times. For example, simplifying things, generating adequate digital resolution for the previous 6 kHz pure shift experiment (1.5 Hz/point), instead of the inadequate 12 Hz/point resolution requires an 800% increase in experiment time when using conventional

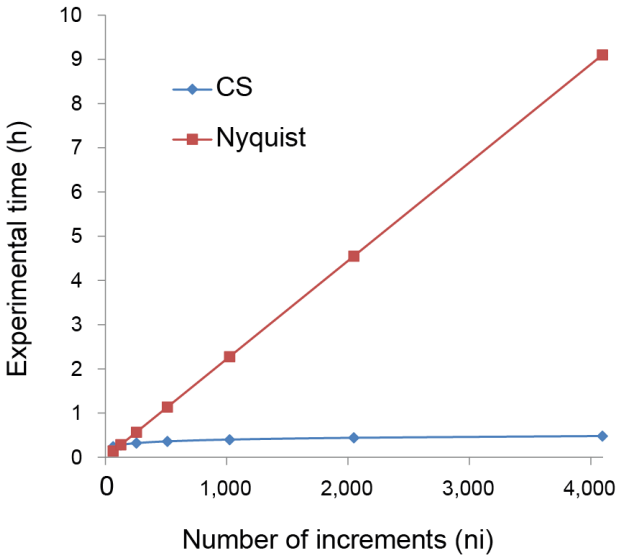

Figure 1. The chart plots the time that acquiring spectra at a particular digital resolution would require. Using classic Nyquist sampling (red squares) the time required scales linearly with the number of increments. Using CS, the same number of increments can be reconstructed from fewer, randomly distributed, data points, with a logarithmic time saving (blue diamonds), as shown in equations 1 and 2.

sampling, but only a 33% increase when *CS* is used (Eq. 1 and 3, and Figure 1):

$$100\ [\log (4096) / \log (512)]\ -100 = 33\% \qquad \text{Eq. 3}$$

In this paper the sampling method is based on a random distribution where large gaps are avoided by using a Poisson distribution.[10,11] In addition, we made the sampling denser at the beginning of the fid, where the signal is stronger, by using a cosine function.[10,11] This probably decreases the coherence of the sampling method (μ), increasing m, but increases the sensitivity of the experiment.[12] In fact, this might not be a problem as in many cases the minimum number of increments that need to be acquired is not determined by Eq. 1 or 2, but by the need to produce an adequate signal to noise ratio (SNR). Of course a laboratory that wishes to harness the potential of *Compressed NMR* systematically would be better off acquiring the most sensitive hardware possible. If, on the other hand, the available hardware is not especially sensitive or samples cannot be systematically concentrated, one has to sacrifice some time-savings in favour of sensitivity. Fortunately large time-savings can still be realized with regular hardware. Here it should be kept in mind that the SNR depends on the number of times the signal is measured, as well as on the amplitude of the signal in each of the measurements. In traditional Nyquist sampling this is the number of increments (ni) times the number of transients (nt) times two (for a phase sensitive experiment). In a *CS* experiment these are reduced by a factor of m/ni, so if measuring the signal 2 x m x nt times is not enough to produce a sufficient SNR, the recovery algorithm will fail to reli-

ably recover the signals. The case is similar to that posed by traditional Nyquist sampling. Take the example of the typical ^{1}H-^{13}C HSQC or F1-PSYCHE-TOCSY run with our spectrometers. We know that even when samples are relatively diluted, 512 increments with 2 transients per increment will recover all signals even when using traditional sampling, at least in most cases. Acquiring fewer increments increases the number of samples in which peaks are lost, as most samples are run under automation. This means that with our hardware, to guarantee the success of these experiments in an unsupervised, automated manner, the total number of measurements should be at least 2048 times. In the case of a 6 kHz *CS* F1-PSYCHE-TOCSY, a digital resolution of 1.5 Hz/point requires 4096 increments, of which random sampling has to acquire at least 512 to produce an adequate SNR to ensure reconstruction. In reality this number of measurements is likely to be higher when attempting to reach the maximum resolving power of the spectrometer, as relaxation losses increase with the t1 sampling time. The latter problem has been addressed in detail in reference [13]. This approach is a relatively safe way to ensure that most samples can be run blindly, and it is an approach that any laboratory can optimize to local needs. Of course, we can reduce experimental times ensuring that the limiting factors are Eq. 1 or 2, rather than the SNR, by avoiding dilute samples, using more sensitive hardware (if possible) or running more sensitive experiments. Here the sensitivity of the chosen *pure shift* experiment plays an important role in determining whether Eq. 1 or 2 rather than SNR will be the limiting factor.

Eq. 1 and 2, and the considerations of SNR discussed above, cautions against reports that advocate the use of a particular m/ni ratio for a particular type of experiment, as already pointed out by Kazimierczuk;[14] the m/ni ratio depends on the sparsity of the spectra, as well as on the sampling and reconstruction methods used, providing the SNR is sufficiently high to ensure that either Eq. 1 or 2 is the limiting factor. It is true, however, that for a given sample, experiments that produce sparser spectra (lower S), require a lower m/ni ratio than experiments that produce denser spectra (higher S).

Recovery algorithms

Sampling the signal is only part of the problem. The other part is reconstructing the signal from the incomplete, noise-contaminated measurements that randomly sampled pure shift techniques produce. Many algorithms can be used to reconstruct these data;[15–17] and many predate the development of the CS framework. Although the performance of these algorithms is important for classic multidimensional NMR, this is more so for *Compressed NMR*, because compressed NMR methods generate larger datasets than traditional ones, and often with a larger proportion of noise. Computationally efficient and noise tolerant algorithms are then a necessity. Another factor to be considered is the time saving that can be realized (ni/m) using a particular algorithm, as different algorithms require different numbers of minimum measurements (m) to ensure reconstruction. The following are some examples used within the *CS* framework:

Convex Relaxation.[18] The time savings that can be realized if SNR is not the limiting factor can be high. However, these methods are computationally complex. Some examples are Basis Pursuit,[19] Basis Pursuit De-Noising (BPDN) [19] and a modified BPDN.[20] Of particular importance for *compressed* NMR is the tolerance to noise of the last two. The minimum number of measurements necessary for Basis Pursuit is determined by Eq. 1.

Iterative Soft or Hard Thresholding Algorithms[21] are computationally faster than the convex optimization methods. This family of algorithms can recover even noisy signals provided that objects are sparse. Examples are *Expander Matching Pursuits (EMP)*,[22] *Sparse Matching Pursuit (SMP)*,[23] *Sequential Sparse Matching Pursuits*[24] and *Belief Propagation (BeP)*.[25] These are important for large datasets as they achieve almost near-linear recovery time. The time-savings can also be high; EMP and SMP require $m \geq C \cdot S \cdot \log(ni/S)$ while BeP requires $m \geq C \cdot S \cdot \log(ni)$ measurements.

Greedy Iterative Algorithms have the advantage of being computationally very fast in comparison with ℓ1-minimization, at least when dealing with high sparsity objects (low S). *Greedy* algorithms are potentially useful for *compressed NMR* because *pure shift* spectra tend to be large datasets. An early example of a *greedy* algorithm is *clean*[26,27] (implemented in Varian VNMRJ), but better performing methods are now available. Other early versions of a *greedy* algorithm, popular because of their computational speed, are Matching Pursuit[28], and derivatives such as Orthogonal Matching Pursuits (OMP)[29,30]. However, recovery becomes computationally demanding when sparsity is not high. This has driven the development of improved versions of OMP such as Regularized OMP,[31] Stagewise OMP (ROMP),[32] Compressive Sampling Matching Pursuits (CoSaMP),[33] Subspace Pursuits (SP),[34] Gradient Pursuits[35] and Orthogonal Multiple Matching Pursuit.[36] The time savings (ni/m) that can be realized are lower than those achievable using ℓ1-minimisation recovery algorithms, although this is less of a problem with the latest algorithms. For example, ROMP requires $m \geq C \cdot S \cdot \log^2(ni)$, StOMP $m \geq C \cdot ni \cdot \log(ni)$, CoSaMP $m \geq C \cdot S \cdot \log(ni)$ and SP $m \geq C \cdot S \cdot \log(ni/S)$. Furthermore, this may not be important for most NMR services where the time savings are limited by the need to produce adequate SNR.

Bregman Iterative Algorithms[37] work by iteratively solving a sequence of unconstrained sub-problems generated using Bregman iterative regularizations. These are very interesting because of their speed as they have been shown to reconstruct objects is just four to six iterations.

Non-Convex Minimization Algorithms recover signals from far fewer increments by replacing the ℓ_1-norm by ℓp-norms where $p < 1$.[38] They have been studied In the context of NMR by Kazimierczuk *et al.* who concluded that *iteratively re-*

weighted least squares with local ℓ_0–norm performs better than Iterative Soft Thresolding (*IST)*.[39]

Unfortunately, most of these algorithms are not available in commercial software, although some are available from particular research groups.[14] Currently, Jeol, Bruker TopSpin and MestreLabs all use some implementation of Iterative Soft Thresholding (IST), while Varian also offers a greedy algorithm, (*clean*), originally developed in radio astronomy.[26,40] Particular research groups, however, have been more adventurous exploring new algorithms.[30,40,41]

Details of the implementation of these algorithms are also of practical importance. All the examples shown later on were reconstructed using *clean*, precisely because it was, at the time, faster than the versions of *IST* we had. We did not notice any problems with time-savings when using *clean*, that should require higher m/ni ratios than *IST*, probably because the experiments were run in a fail-safe way that sacrifices some speed (ni/m) in favour of sensitivity. We have noticed though that the version of *IST* we currently use produces cleaner results than *clean*. Since the time of writing, vendors such as MestreLabs have optimized their implementation of the *IST* making it computationally competitive, so that is currently the method of choice for us.

One common problem that we continue to encounter is that we need computers with a 64-bit architecture, and software that supports it, with at least 8 Mb RAM to be able to open and process the large data files that *Compressed* NMR produces. The problem is important for NMR services that cater for a variety of customers using different hardware and software architectures.

Finally it is worth noting that references to *CS* in NMR papers are sometimes misleading. For example, it is common to read that "data has been reconstructed with *CS*", although *CS* is not an algorithm; or that "the *CS* algorithm has been used to reconstruct the data", when there are several families of them.

Pure shift NMR

The second problem we address is that the effective resolution in the spectrum is reduced when signals have multiplicity. This, recognized very early on, led to the development of decoupling. However, although heteronuclear decoupling was mastered relatively early, the homonuclear case remained stubbornly impractical until the development of techniques such as Zangger-Sterk,[42,43] PSYCHE,[44] and the re-development of ^{1}H constant-time[45–49] and BIRD decoupling.[50–53] Since then, it has become common to use the term *pure shift* as a synonym of homonuclear decoupling, yet strictly speaking, the term implies full decoupling. This is because all homonuclear and heteronuclear multiplicity have to be suppressed to produce truly *pure shift* signals (singlets).[54] Here we use the term in its strict sense. Examples of true multidimensional *pure shift* experiments are the F1-homodecoupled HETCOR,[55,56] the perfect-echo CLIP HSQC.[57]; and if germinal protons are not present, the real-time *pure shift* HSQC,[53] and the assembled RESET.[51] At times, however, it is important to keep one of the dimensions coupled to strike a balance between resolving power and the ability to analyze coupling patterns.[48] Examples are constant-time COSY,[48] F1-PSYCHE-TOCSY[58] and the regular HSQC. Fortunately these experiments can be converted into true *pure shift* two-dimensional experiments by exploiting covariance methods, as shown in Figures 2 and 4.[48,59–62]

As described previously, the sensitivity of the technique plays an important role in the probability of the recovery algorithm performing successfully; after all, signals that are not detected cannot be reconstructed. Amongst these techniques, the least sensitive is usually *BIRD*, as it discards 99% or more of the signal. The exceptions are *pure shift* ^{1}H-^{13}C pulse sequences where its application actually boosts the sensitivity of the experiment.[53] Among the others, *PSYCHE* is probably the best suited for general work, being the most robust, and, in general, the one that produces the best trade-off between sensitivity and tolerance of strong coupling. The Zangger-Sterk method should also be considered in cases where its sensitivity can be increased either by reducing the decoupling bandwidth or by increasing the bandwidth of its selective 180° pulse.[3,42,43,63]

In all of these cases the benefits of multidimensional techniques can be lost due to practicalities. As mentioned previously, achieving high digital resolution is a time-consuming process. This limitation is apparent even in two-dimensional experiments, but it becomes prohibitive when dealing with techniques such as the three dimensional *pure shift* HSQC.[51,57] The *CS* framework is then an ideal solution to harness the potential of these techniques. Without pure shift techniques, the *CS* framework cannot be used to reach the potential of the spectrometer, but without the *CS* framework, the time necessary to take full advantage of multidimensional pure shift spectra can become prohibitive. Finally, we note that CS techniques can be applied to any dimension, including the detected one.[64–66]

Putting it all together

Figures 2 and 3 illustrate the importance of combining *pure shift* and *CS* techniques. In this case, an organometallic chemist was making an optical device component. The chemist had taken the precaution of using mass spectrometry to determine the mass (or masses) of the compound (or compounds) present in the sample before analysing the NMR data. A single molecular ion peak was observed in the mass spectrum. High resolution ^{1}H-^{1}H TOCSY and ^{1}H-^{13}C HSQC were acquired using 512 increments and two transients per

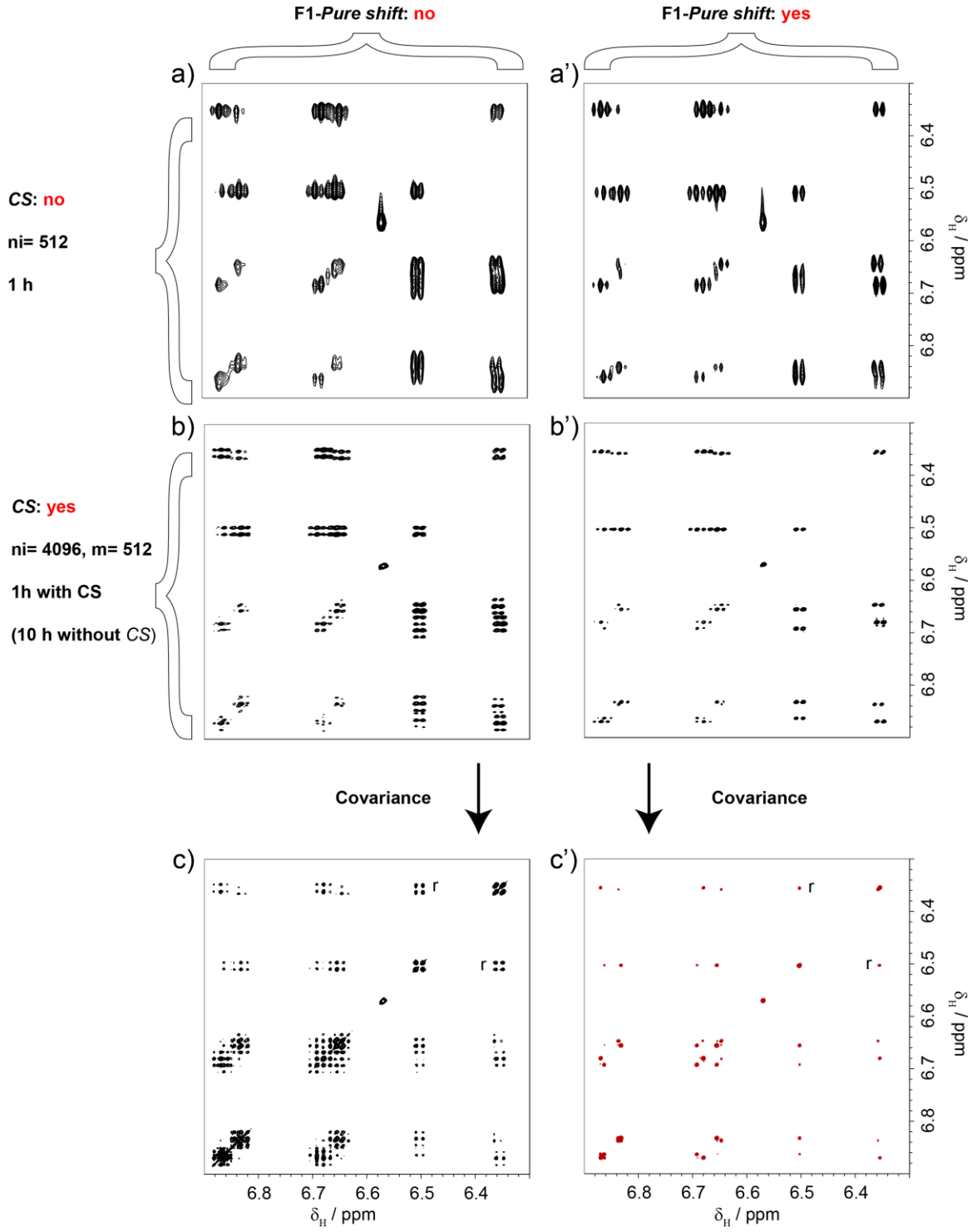

Figure 2. Aromatic region of a typical ^{1}H-^{1}H TOCSY spectra acquired using Nyquist sampling (a). It was processed using a double Fourier transform. The digital resolution is 12 Hz/point. The sample contains two isomers, but this cannot be seen in (a). Two techniques can be applied to reveal the presence of the isomers, but they have to be used in conjunction. The first one exploits the *CS* framework to increase the digital resolution at no time cost. This is done in (b) where the digital resolution has been increased to 1.5 Hz/point. The resulting spectrum is higher digital resolution than the one depicted in (a), but the presence of the isomers is difficult to see. In c) the covariance spectrum of b) has been calculated, but this does nothing other than to create a relay peak (marked *r*). The second technique has the potential to reveal the presence of the isomers but with just one hour it is not possible to distinguish a multiplet from a singlet, so the problem remains unsolved (a'). In contrast, the combination of F1-*pure shift* techniques with the *CS* framework b') enables us to harness the potential of the spectrometer and to reveal what appears to be a mixture of isomers. Note that b') is not a true *pure shift* spectrum, as singlets only feature in one of the dimensions; however, a true *pure shift* spectrum can be produced by calculating the covariance spectrum of b') as in c'). The presence of the isomers is clear now. Note that b') represents a good trade-off between resolution and the ability to measure coupling constants. All experiments took one hour to acquire.

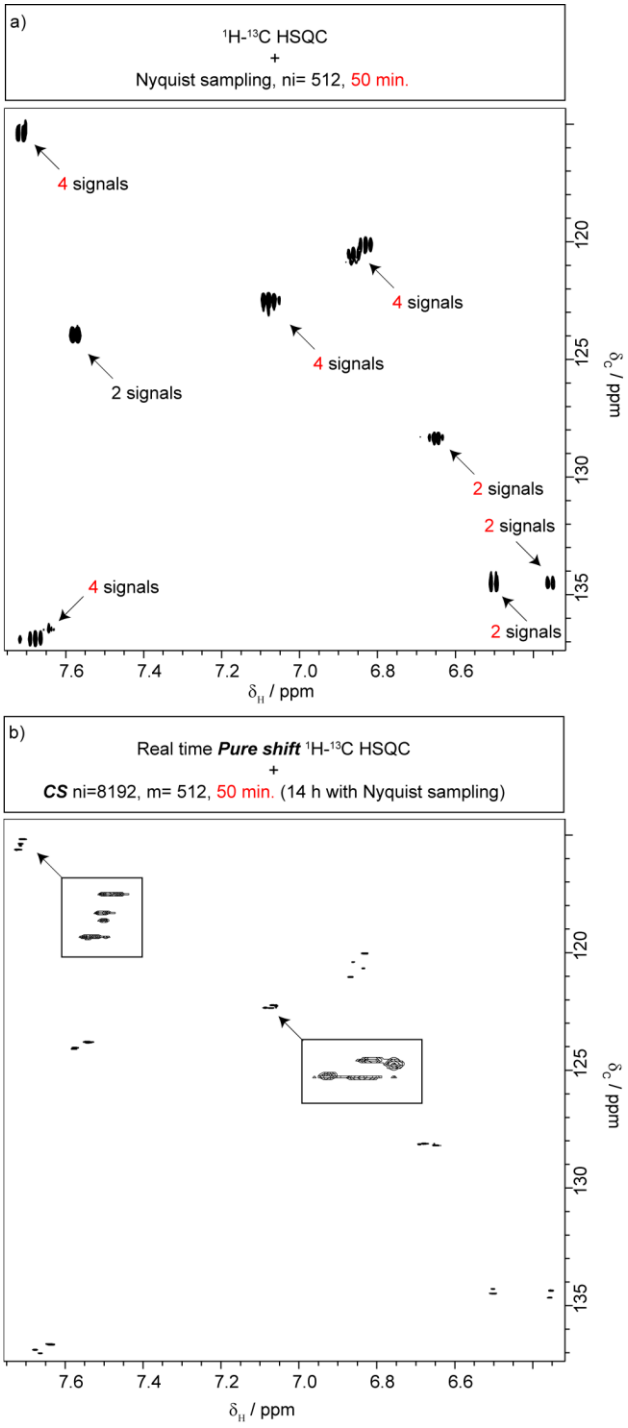

Figure 3. ^{1}H-^{13}C HSQC spectra of the sample used in Figure 2. There is no indication that most of the apparent peaks are actually an unresolved superposition of real peaks. It can be seen that this is the case when resolution is improved by combining *CS* (ni=8196, m=512) with *pure shift* techniques (b). Note that b) is a true *pure shift* experiment, whereas a) is only a *pure shift* experiment in the carbon dimension. Both experiments took 50 min to acquire.

increment (Figures 2a and 3a). Nothing in these spectra indicates that two isomers might be present.

Using only *CS* to increase the digital resolution of the TOCSY produces a beautiful spectrum (Figure 2b), but it does not

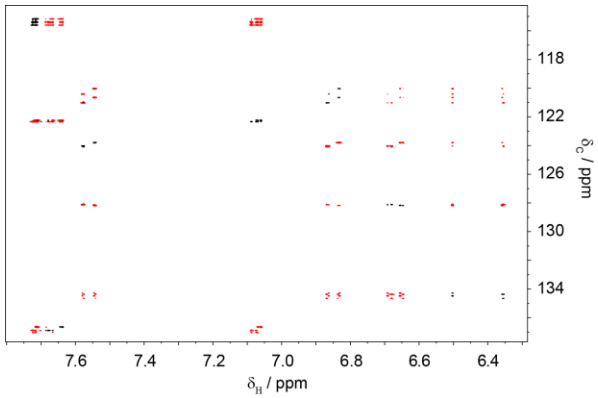

Figure 4. A *pure shift* ^{1}H-^{13}C HSQC-TOCSY produced combining the real-time *pure shift* ^{1}H-^{13}C HSQC of Figure 3b with the ^{1}H-^{1}H F1-PSYCHE-TOCSY of Figure 2b' using generalized indirect covariance. Both experiments were acquired and reconstructed following *CS* principles. Direct ^{1}H-^{13}C correlations have been coloured black. TOCSY peaks have been coloured red.

improve the situation; neither does covariance (Figure 2c). Replacing *CS* with a *pure shift* technique as a means of increasing resolution reveals nothing, as the digital resolution that can be produced in under one hour is insufficient to tell the difference between a singlet and a multiplet (Figure 2a'). Combining *CS* and *pure shift* techniques, however, harnesses the full potential of the spectrometer (Figure 2b') and reveals that all signals are duplicated, thus indicating the presence of two isomers. Now that signals have been resolved, the experiment can be used to extract coupling constants to further help structural analysis. Covariance can also be used to simplify the layout of the peaks, as in Figure 2c'. A similar situation arises in the case of the HSQC spectrum. The conventional high resolution HSQC does not reveal the existence of the isomers. What appear to be single peaks are actually composites of several peaks. The problem is solved using *CS* to produce a very high digital resolution in the carbon dimension, and using proton broad-band homo-decoupling to produce a true *pure shift* experiment. Note that although the F1-PSYCHE-TOCSY spectrum (Figure 2b') is not a true *pure shift* experiment, (only one of the dimensions features singlets), the HSQC of Figure 3b is. Fortunately, the F1-PSYCHE-TOCSY spectrum (Figure 2b') can be turned into a true *pure shift* spectrum in both dimensions using covariance methods (Figure 2c'). Covariance can also be exploited to produce *pure shift* experiments that are impractical to acquire.[61,62] For example a *pure shift* HSQC-TOCSY can be produced by combining the F1-PSYCHE TOCSY of Figure 2b' with the real-time *pure shift* HSQC of Figure 3b using generalized indirect covariance (Figure 4).[62] However, the use of covariance has a price; it produces extra peaks (labelled r in Figure 2).[69] Here running *pure shift* experiments with high digital resolution in both dimensions helps; another reason to use *CS* and *pure shift* techniques jointly. Another problem of covariance processing is that noise is not randomly distributed in the covariance spectrum. This has the risk of producing false peaks where noise produced by two signals coincides. The problem can be a real nuisance in spectra with a non-uniform signal intensity distribution, for example, in spectra of mixtures of products of different concentrations, or in spectra of samples containing single components where COSY, HMBC, or NOESY experiments are

acquired. The problem could be solved by developing true *pure shift* experiments in which all dimensions are fully decoupled, combining several homo-decoupling methods. However, these would be quite time consuming, most of them being three dimensional experiments. The use of *CS* techniques should make these practical.

Conclusions

Combining *pure shift* and *CS* techniques allows NMR practitioners to harness the full potential resolving power of the NMR spectrometer in an unprecedented and practical manner. The combination is synergistic in the sense that *pure shift* techniques allow *CS* to overcome the limitations imposed by the existence of multiplets. Conversely, *CS* techniques allow multidimensional *pure shift* experiments to be carried out in a practical manner at an appropriate digital resolution. However, challenges remain regarding the sensitivity of the hardware and of the pulse sequences used, as well as regarding the limited implementation of reconstructing algorithms.

Experimental section

The zTOCSY of Figures 2a, b and c were produced using a 600 MHz Varian spectrometer equipped with an Agilent OneNMR Probe able to deliver a maximum pulsed field gradient of 62 G cm^{-1}. Two scans per increment were collected, each comprising 8192 complex data points and a spectral width of 6 kHz. The repetition time was 1.7 s, of which 0.7 s comprised the acquisition time. Zero-quantum artefacts were attenuated as previously described.[70] A 60 ms DIPSI2 mixing composite pulse was used.[71] The number of dummy scans was 128. The t1 interval was sampled acquiring 512 increments randomly selected out of 4096 possibilities, the latter being the number of increments that need to be acquired using Nyquist sampling to produce a digital resolution of 1.5 Hz/point. The presence of large gaps in the sample schedule was minimized using a Poisson distribution with cosine weighting, as previously reported.[10,11] Spectra were reconstructed using both *IST* and *clean*, but only the latter is show in Figure 2. The *pure shift* versions of Figures 2a', 2b' and 2c' were produced using the same conditions but replacing the zTOCSY pulse sequence with a F1-PSYCHE-zTOCSY one.[58] The PSYCHE pulse was created using a 10° WURST180 double sweep of 30 ms. A pulsed field gradient (0.8 G cm^{-1}) was applied for the duration of the WURST pulse. In the case of Figures 2c and 2c', covariance was used after reconstructing the spectrum. The total experimental time was 67 min. To simulate what the resolution would have been had just one hour been used to acquire the experiments with conventional Nyquist sampling, only the first 512 increments out of the reconstructed 4096 ones were used.

Figure 3 was produced using the same spectrometer as in Figure 2. Both HSQC's were acquired using two scans per increment, each comprising of 4200 complex data points and 8196 increments, of which only 512 were acquired. These were selected out of the 8196 possible ones following the same procedure used to produce Figure 2. One hundred and twenty eight dummy scans were used. The spectral width of the proton dimension spanned 6 kHz. The spectral width of the carbon dimension spanned 36 kHz. The repetition time was 1.35 s, of which 0.35 s comprised the acquisition time. The experiment took 50 min to acquire. The real-time *pure shift* version of Figure 3b was produced using the same conditions, but replacing the HSQC pulse sequence with a real-time *pure shift* one, as described in ref. [53]. Twenty five ms long blocks of data were collected, apart from the first and the last blocks took half of the time each. Spectra were reconstructed using both *IST* and *clean*, but only the latter is show in Figure 3. To simulate what the resolution would have been had just 50 min been used to acquire the regular HSQC spectrum using conventional Nyquist sampling, only the first 512 increments out of the reconstructed 8192 increments were used to process the data.

The experimental process is exemplified graphically in the Supplementary Information section. The raw data used in this paper can be found here: doi:10.15128/r14q77fr33z .

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REFERENCES

[1] E. J. Candès, M. B. Wakin, *IEEE Signal Process. Mag.* **2008**, *25*, 21.
[2] K. Zangger, *Prog. Nucl. Magn. Reson. Spectrosc.* **2015**, *86–87*, 1.
[3] L. Castañar, T. Parella, *Magn. Reson. Chem.* **2015**, *53*, 399.
[4] M. Unser, *Proc. IEEE* **2000**, *88*, 569.
[5] E. J. Candès, J. Romberg, T. Tao, *Inf. Theory IEEE Trans. On* **2006**, *52*, 489.
[6] E. Candès, J. Romberg, *Inverse Probl.* **2007**, *23*, 969.
[7] D. L. Donoho, *IEEE Trans. Inf. Theory* **2006**, *52*, 1289.
[8] M. Mobli, J. C. Hoch, *Prog. Nucl. Magn. Reson. Spectrosc.* **2014**, *83*, 21.
[9] E. J. Candès, T. Tao, *IEEE Trans. Inf. Theory* **2006**, *52*, 5406.
[10] S. G. Hyberts, K. Takeuchi, G. Wagner, *J. Am. Chem. Soc.* **2010**, *132*, 2145.
[11] S. G. Hyberts, A. G. Milbradt, A. B. Wagner, H. Arthanari, G. Wagner, *J. Biomol. NMR* **2012**, *52*, 315.
[12] K. Kazimierczuk, O. Lafon, P. Lesot, *The Analyst* **2014**, *139*, 2702.
[13] D. Rovnyak, M. Sarcone, Z. Jiang, *Magn. Reson. Chem.* **2011**, *49*, 483.
[14] A. Shchukina, P. Kasprzak, R. Dass, M. Nowakowski, K. Kazimierczuk, *J. Biomol. NMR* **2017**, *68*, 79.
[15] S. Qaisar, R. M. Bilal, W. Iqbal, M. Naureen, S. Lee, *J. Commun. Netw.* **2013**, *15*, 443.
[16] Y. C. Eldar, G. Kutyniok, Eds. , *Compressed Sensing: Theory and Applications*, Cambridge University Press, Cambridge ; New York, **2012**.
[17] S. Foucart, H. Rauhut, *A Mathematical Introduction to Compressive Sensing*, Springer New York, New York, NY, **2013**.
[18] E. J. Candès, B. Recht, *Found. Comput. Math.* **2009**, *9*, 717.
[19] S. S. Chen, D. L. Donoho, M. A. Saunders, *SIAM Rev.* **2001**, *43*, 129.

[20] W. Lu, N. Vaswani, IEEE, **2010**, pp. 3926–3929.
[21] T. Blumensath, M. E. Davies, *Appl. Comput. Harmon. Anal.* **2009**, *27*, 265.
[22] P. Indyk, M. Ruzic, IEEE, **2008**, pp. 199–207.
[23] R. Berinde, P. Indyk, M. Ruzic, IEEE, **2008**, pp. 198–205.
[24] R. Berinde, P. Indyk, IEEE, **2009**, pp. 36–43.
[25] D. Baron, S. Sarvotham, R. G. Baraniuk, *IEEE Trans. Signal Process.* **2010**, *58*, 269.
[26] J. A. Hogbom, *Astron.Astrophys.Suppl.Ser.* **1974**, *15*, 417.
[27] E. Kupče, R. Freeman, *J. Magn. Reson.* **2005**, *173*, 317.
[28] S. G. Mallat, Zhifeng Zhang, *IEEE Trans. Signal Process.* **1993**, *41*, 3397.
[29] J. A. Tropp, A. C. Gilbert, *IEEE Trans. Inf. Theory* **2007**, *53*, 4655.
[30] K. Kazimierczuk, P. Kasprzak, *Sensors* **2014**, *15*, 234.
[31] D. Needell, R. Vershynin, *Found. Comput. Math.* **2009**, *9*, 317.
[32] D. L. Donoho, Y. Tsaig, I. Drori, J.-L. Starck, *IEEE Trans. Inf. Theory* **2012**, *58*, 1094.
[33] D. Needell, J. A. Tropp, *Appl. Comput. Harmon. Anal.* **2009**, *26*, 301.
[34] W. Dai, O. Milenkovic, *IEEE Trans. Inf. Theory* **2009**, *55*, 2230.
[35] Má. A. T. Figueiredo, R. D. Nowak, S. J. Wright, *IEEE J. Sel. Top. Signal Process.* **2007**, *1*, 586.
[36] E. Liu, V. N. Temlyakov, *IEEE Trans. Inf. Theory* **2012**, *58*, 2040.
[37] W. Yin, S. Osher, D. Goldfarb, J. Darbon, *SIAM J. Imaging Sci.* **2008**, *1*, 143.
[38] R. Chartrand, *IEEE Signal Process. Lett.* **2007**, *14*, 707.
[39] K. Kazimierczuk, V. Y. Orekhov, *J. Magn. Reson.* **2012**, *223*, 1.
[40] X. Qu, M. Mayzel, J.-F. Cai, Z. Chen, V. Orekhov, *Angew. Chem. Int. Ed.* **2015**, *54*, 852.
[41] A. S. Stern, J. C. Hoch, *Magn. Reson. Chem.* **2015**, *53*, 908.
[42] K. Zangger, H. Sterk, *J. Magn. Reson.* **1997**, *124*, 486.
[43] J. A. Aguilar, S. Faulkner, M. Nilsson, G. A. Morris, *Angew. Chem. Int. Ed.* **2010**, *49*, 3901.
[44] M. Foroozandeh, R. W. Adams, N. J. Meharry, D. Jeannerat, M. Nilsson, G. A. Morris, *Angew. Chem. Int. Ed.* **2014**, *53*, 6990.
[45] A. Bax, A. . Mehlkopf, J. Smidt, *J. Magn. Reson. 1969* **1979**, *35*, 167.
[46] A. Bax, R. Freeman, *J. Magn. Reson. 1969* **1981**, *44*, 542.
[47] M. Rance, G. Wagner, O. . Sørensen, K. Wüthrich, R. . Ernst, *J. Magn. Reson. 1969* **1984**, *59*, 250.
[48] J. A. Aguilar, J. Cassani, M. Delbianco, R. W. Adams, M. Nilsson, G. A. Morris, *Chem. - Eur. J.* **2015**, *21*, 6623.
[49] M. J. Thrippleton, R. A. E. Edden, J. Keeler, *J. Magn. Reson.* **2005**, *174*, 97.
[50] J. R. Garbow, D. P. Weitekamp, A. Pines, *Chem. Phys. Lett.* **1982**, *93*, 504.
[51] P. Sakhaii, B. Haase, W. Bermel, *J. Magn. Reson.* **2009**, *199*, 192.
[52] A. Lupulescu, G. L. Olsen, L. Frydman, *J. Magn. Reson.* **2012**, *218*, 141.
[53] L. Paudel, R. W. Adams, P. Király, J. A. Aguilar, M. Foroozandeh, M. J. Cliff, M. Nilsson, P. Sándor, J. P. Waltho, G. A. Morris, *Angew. Chem. Int. Ed.* **2013**, *52*, 11616.
[54] K. Mason, N. J. Rogers, E. A. Suturina, I. Kuprov, J. A. Aguilar, A. S. Batsanov, D. S. Yufit, D. Parker, *Inorg. Chem.* **2017**, *56*, 4028.
[55] A. Bax, *J. Magn. Reson. 1969* **1983**, *53*, 517.
[56] M. Perpick-Dumont, W. F. Reynolds, R. G. Enríquez, *Magn. Reson. Chem.* **1988**, *26*, 881.
[57] L. Kaltschnee, A. Kolmer, I. Timári, V. Schmidts, R. W. Adams, M. Nilsson, K. E. Kövér, G. A. Morris, C. M. Thiele, *Chem Commun* **2014**, *50*, 15702.
[58] M. Foroozandeh, R. W. Adams, M. Nilsson, G. A. Morris, *J. Am. Chem. Soc.* **2014**, *136*, 11867.
[59] G. A. Morris, J. A. Aguilar, R. Evans, S. Haiber, M. Nilsson, *J. Am. Chem. Soc.* **2010**, *132*, 12770.
[60] J. A. Aguilar, A. A. Colbourne, J. Cassani, M. Nilsson, G. A. Morris, *Angew. Chem. Int. Ed.* **2012**, *51*, 6460.
[61] R. Brüschweiler, F. Zhang, *J. Chem. Phys.* **2004**, *120*, 5253.
[62] M. Jaeger, R. L. E. G. Aspers, in *Annu. Rep. NMR Spectrosc.*, Elsevier, **2014**, pp. 271–349.
[63] L. Castañar, P. Nolis, A. Virgili, T. Parella, *Chem. - Eur. J.* **2013**, *19*, 17283.
[64] I. E. Ndukwe, A. Shchukina, K. Kazimierczuk, C. Cobas, C. P. Butts, *ChemPhysChem* **2016**, *17*, 2799.
[65] I. E. Ndukwe, A. Shchukina, K. Kazimierczuk, C. P. Butts, *Chem Commun* **2016**, *52*, 12769.
[66] I. E. Ndukwe, A. Shchukina, V. Zorin, C. Cobas, K. Kazimierczuk, C. P. Butts, *ChemPhysChem* **2017**, *18*, 2081.
[67] A. Fredi, P. Nolis, C. Cobas, T. Parella, *J. Magn. Reson.* **2016**, *270*, 161.
[68] A. Fredi, P. Nolis, C. Cobas, G. E. Martin, T. Parella, *J. Magn. Reson.* **2016**, *266*, 16.
[69] G. E. Martin, B. D. Hilton, K. A. Blinov, A. J. Williams, *Magn. Reson. Chem.* **2008**, *46*, 997.
[70] M. J. Thrippleton, J. Keeler, *Angew. Chem. Int. Ed.* **2003**, *42*, 3938.
[71] A. J. Shaka, C. J. Lee, A. Pines, *J. Magn. Reson. 1969* **1988**, *77*, 274.