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In situ study of reaction kinetics using compressed sensing NMR

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We demonstrate the application of Compressed Sensing-NMR to decrease the data acquisition time of 2D COSY NMR from >5 h to ~1.5 h such that the kinetics of a reaction are followed, along with identification of intermediate and product species.

The evaluation of kinetic models, rate of reaction and product distribution in chemical processes is of widespread importance in catalyst selection, process optimization and reactor design. Ideally, these studies should be carried out non-invasively, with a good temporal resolution and with high accuracy in terms of species identification and composition measurement. NMR spectroscopy is well-established as a method for characterising multi-component systems. In many systems and most certainly in catalysis, it is invaluable to be able to monitor a reaction process *in situ* and, whenever possible, at reaction conditions. Under such acquisition conditions, the linewidths will be significantly broader than those typically encountered in liquid-state NMR, and therefore the ability to use 2D NMR becomes of increasing importance. In addition, we require time-resolved composition measurement for subsequent kinetic analysis. However, the use of conventional 2D NMR spectroscopy is too slow for such studies.

Various techniques are available to encode dynamic information using multidimensional NMR, including spectral line shape analysis,[1] short repetition excitations,[2] ultra-fast NMR,[3] and non-uniform sampling (NUS).[4] Such techniques have been applied to study dynamic processes in chemistry[3,5] and biochemistry.[2,6] However, except for NUS, each of these approaches has limitations in their application to spatially heterogeneous systems. The challenge in employing NUS is that the resulting data sets are not well-suited to conventional Fourier transform reconstruction. Instead, various algorithms have been developed, including forward maximum entropy, multi-dimensional decomposition, maximum likelihood, SIFT (Spectroscopy by Integration of Frequency and Time domain information) and compressed sensing (CS), some of which have been proven to give the quantitative spectra required for the study of reaction kinetics.[7–11]

CS provides a mathematical framework that quantifies how accurately a signal can be recovered when fewer data are acquired than traditional Nyquist sampling theory requires.[10] It has previously been used with undersampled, multi-dimensional NMR spectroscopy.[11,12] We demonstrate the principle of CS-NMR for tracking chemical reactions by using 2D ^{1}H–^{1}H COSY spectra to study a Meerwein–Ponndorf–Verley (MPV) reaction. The MPV reaction is a well-known method for reducing aldehydes and ketones to their corresponding alcohols in the presence of a sacrificial alcohol.[13] For this reaction, the ^{1}H 1D NMR spectra took ~5 min to acquire, with the ^{1}H–^{1}H COSY acquisitions taking ~5 h if a conventional implementation is used; the lengthy acquisition times being required if the spectral intensities are to be quantitative which is essential if the data are to be used in kinetic studies. We demonstrate how a compressed sensing data acquisition strategy can be integrated with a 2D NUS NMR acquisition – in this case a ^{1}H–^{1}H COSY experiment – to reduce data acquisition times from >5 h to ~1.5 h, thereby providing sufficient temporal resolution that the changing chemical composition and the kinetics of reaction can be followed. In this reaction, due to the uncertainty regarding the exact reaction products, it is particularly useful to be able to identify all species from the NMR data without having to resort to gas chromatography (GC) analysis. Moreover, the *in situ* NMR study identifies intermediates formed during reaction which cannot be observed using GC analysis. We confirm the accuracy of the data obtained using this CS-NMR approach by showing that the data extracted from the CS-NMR analysis are consistent with the 1D NMR and GC analysis, and that they enable a kinetic analysis of the MPV reaction to the same accuracy as these other techniques. Finally, we complete the identification of all species present by following the temporal evolution of cross-peaks in the 2D CS-NMR spectra; this assignment is not possible using the 1D NMR data.

The MPV reaction was selected as a system which provides sufficient complexity in the reaction that 2D NMR spectroscopy

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is required to identify the species present and in which that assignment is aided by being able to track the temporal evolution of spectral resonances. MPV reactions show a variety of side reactions including the formation of aldol condensation species, which may subsequently form unsaturated carbonyl compounds upon dehydration. If these routes are followed, at least two intermediate species might be expected.[14] Such condensation reactions may occur between the same carbonyl species (*i.e.*, self aldol condensation) but also between two different carbonyl species (*i.e.*, cross aldol condensation). The MPV reaction studied in this work was the reduction of the carbonyl group of propionaldehyde to form 1-propanol in an excess of 2-propanol and a catalyst, aluminium isopropoxide. The propionaldehyde is reduced to 1-propanol, whilst the 2-propanol is oxidised to acetone. It follows that a variety of further products can be formed. For example, the self aldol condensation of the acetone product may lead to the formation of diacetone alcohol, which may dehydrate to mesityl oxide; self aldol condensation of propionaldehyde may lead to the formation 3-hydroxy-2-methylpentanal, and the unsaturated dehydration product 2-methylpentenal.[15] Cross aldol condensation between propionaldehyde and acetone may also occur. Another possibility might be the Tishchenko reaction which yields isopropyl propionate.[14]

The reactant mixture was prepared by adding 0.5 g of a solution of 3.4 mol% aluminium isopropoxide in cyclohexane to 0.29 g of propionaldehyde and 1.5 g of 2-propanol. The mole fractions of this mixture were 0.140 (propionaldehyde): 0.701 (2-propanol): 0.005 (aluminium isopropoxide): 0.154 (cyclohexane). The mixture was sampled by NMR and GC over 25 h, by which time the reaction had reached its equilibrium conversion. GC measurements were made every 40 min using a GC analyser (Agilent Technologies 7890A) equipped with a HP-INNOWAX capillary column. NMR experiments were performed using a Bruker DMX 300 NMR spectrometer operating at a ^{1}H frequency of 300.13 MHz equipped with a DIFF30 probe. 1D NMR spectra were acquired using a single 90° pulse. 16 averages were acquired with a recycle delay of 20 s, giving a total acquisition time of 5 min. For the acquisition of 2D magnitude mode COSY spectra, a COSY-45 pulse sequence was employed with a 16 step phase cycle. Fully-sampled 2D spectra were acquired with 256 points in the indirect dimension and processed by Fourier transformation. Under-sampled CS-NMR spectra were obtained by acquiring 77 points (30% sampling) using an exponentially-weighted sampling pattern in the indirect dimension and reconstructing with CS. A recycle time of 4 s (1.3 × average T_1 observed for the system; the T_1 of species present differ by <10%) was used as a compromise between the experiment duration and quantification. With this recycle time, the NMR spectra were quantitative to within 5% for all compositions measured. The experimental time for each fully- and 30%-sampled 2D spectrum was 5 h 12 min and 1 h 34 min, respectively. CS reconstruction was performed with a fast iterative soft thresholding algorithm (FISTA)[16] with parameters $t(0) = 1$, $\lambda = 10^{-6}$ where 1 corresponds to the maximum intensity in the fully sampled spectrum; the step size is taken as 1.

Fig. 1 shows a comparison of a 100%-sampled conventional and 30%-sampled CS-NMR ^{1}H–^{1}H COSY acquisition. The data

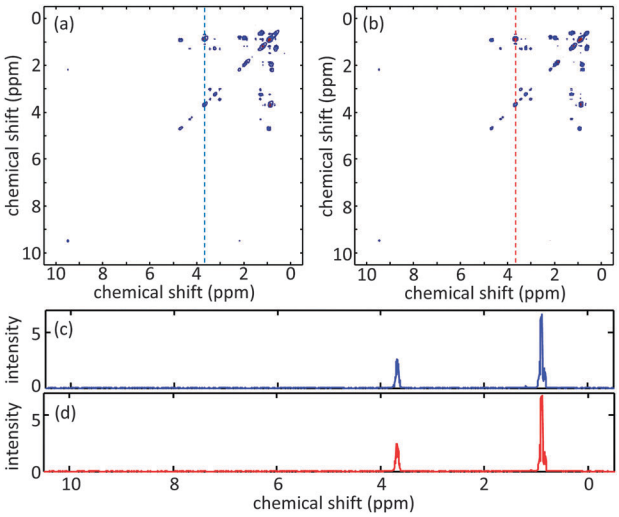

Fig. 1 2D ^{1}H–^{1}H COSY NMR spectra acquired from (a) full sampling and (b) 30% sampling with CS reconstruction, on a non-reacting sample consisting of propionaldehyde, 2-propanol, cyclohexane, 1-propanol, acetone and isopropyl propionate at mole fractions of 0.109, 0.544, 0.130, 0.109, 0.054, and 0.054, respectively. All chemical shifts are referenced to the ^{1}H resonance of tetramethylsilane (TMS). (c) and (d) are 1D spectra extracted at 3.68 ppm through the 2D spectra in (a) and (b) respectively, as indicated by the dashed lines.

are recorded for a (non-reacting) mixture of reactants and products found in this MPV reaction. All peaks are recovered in the 2D CS-NMR and there are no obvious distortions in peak position or shape. The error in the peak position is less than the spectral resolution of the fully sampled data set. CS-NMR is able to recover the intensity accurately across the full dynamic range, with the RMS error for most peaks <5%, which is comparable to the error introduced by experimental uncertainty. The intensity is recovered with greater accuracy as the peak intensity increases, as has been shown previously.[9] The uncertainty in peak intensity is only noticeably increased in the lowest intensity range, where the RMS error in peak intensity is 12% including both uncertainty arising from CS-NMR and noise in the experimental measurements. These results confirm that CS-NMR is able to reduce the acquisition time of 2D NMR, without reducing the spectral resolution or quantitative nature of the data obtained.

We now apply this CS-NMR method to the MPV reaction. Fig. 2 shows the 1D spectra acquired at the start and end of the reaction (~25 h). Peaks for which direct assignment is not possible are at 5.65, 4.65, 4.28 and 1.97 ppm. Assignment of all peaks is challenging because additional peaks will be present but overlapping with other peaks in the 1D spectrum. Further assignment is made using the 2D ^{1}H–^{1}H COSY CS-NMR spectrum shown in Fig. 3(a); these data were acquired shortly after the start of reaction. The cross-peaks at ppm values (5.65, 4.28) and (4.28, 1.3) identify hemiacetal which exists as an intermediate species[17] and which would therefore not be seen by GC analysis. In the 1D spectrum we would expect to see hemiacetal resonances at 5.65, 4.28, 3.68, 1.30, 0.88 and 0.64 ppm. Only the resonances at 4.65 and 1.97 ppm in the 1D spectrum are now yet to be assigned and from Fig. 3(b) these are seen to show

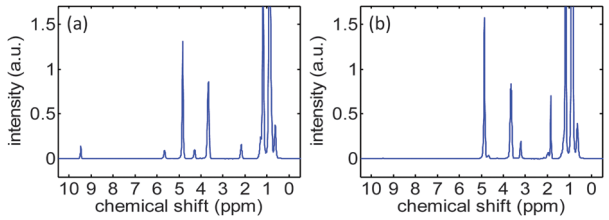

Fig. 2 1D NMR spectra recorded (a) 4.5 min after contacting the reagents and (b) at the end of the MPV reaction. The spectra clearly show the almost complete consumption of propionaldehyde (0.83 ppm, 2.15 ppm and 9.45 ppm) and the formation of the main reduction product 1-propanol (0.64 ppm, 1.3 ppm, 3.2 ppm and 4.8 ppm) along with acetone (1.89 ppm) which is produced as a result of the oxidation of 2-propanol (0.88 ppm, 3.68 ppm and 4.8 ppm). The peak at 1.2 ppm is assigned to the solvent, cyclohexane.

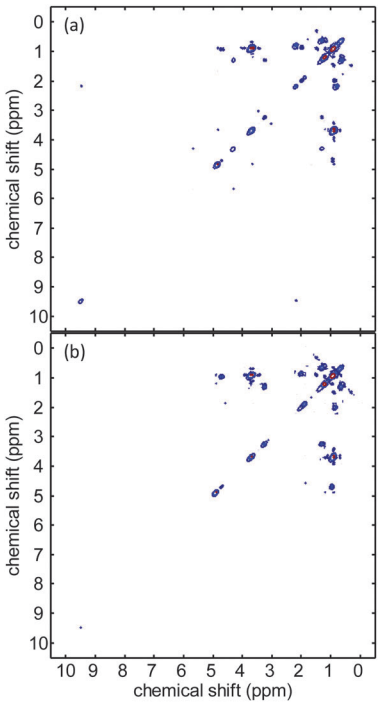

Fig. 3 CS reconstructed 2D NMR spectra from 30%-sampled data acquired (a) during the first 1 h 34 min and (b) at end of the MPV reaction.

correlations at (4.65, 0.88) and (1.97, 0.83). Having demonstrated the quantitative nature of the 2D CS-NMR experiment, we now show that the CS-NMR data are acquired at a sufficient rate and accuracy to follow the kinetics of the MPV reaction *in situ* and hence assign the remaining peaks at 4.65 and 1.97 ppm.

To do this we compare the evolution of propionaldehyde concentration as a function of time, as determined by GC, 1D NMR, 2D CS-NMR on the basis of a diagonal peak at (9.45, 9.45) ppm, and 2D CS-NMR on the basis of the cross peak at (2.15, 0.83) ppm. GC, 1D NMR and 2D CS-NMR data are recorded at time intervals of 40 min, 1 h 40 min and 1 h 40 min, respectively. These data are shown in Fig. 4. The time associated with the 1D NMR and 2D CS-NMR measurements are the mid-points of their respective data acquisition times.

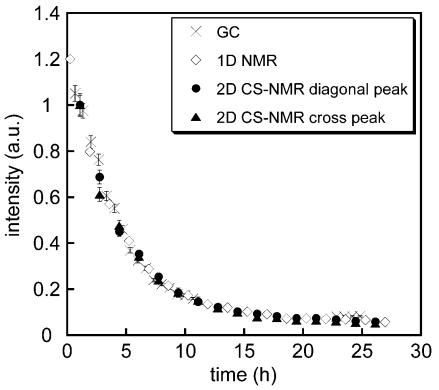

Fig. 4 The evolution of propionaldehyde obtained from GC, 1D NMR and 2D CS-NMR analysis.

Excellent agreement between all 4 sets of data is observed. The agreement in propionaldehyde concentration determined from both the diagonal and cross peaks is also important since it confirms that the change in amount of a chemical species present, that can only be identified by cross-peak information, are of sufficient quality for kinetic analysis. Analysis of the data shown in Fig. 4 was performed using eqn (1). The (reversible) MPV reaction, when performed under conditions of a large excess of 2-propanol, can be considered a reversible pseudo-first-order reaction, and the concentration of propionaldehyde is therefore governed by,[18]

$$[A] = [A]_0 \frac{k_b + k_f e^{-(k_b+k_f)t}}{k_b + k_f}, \quad (1)$$

where $[A]_0$ and $[A]$ represent the concentration of propionaldehyde initially and at time t, respectively, and k_f and k_b are the rate constants for the forward and backward reaction.

Table 1 reports the values of k_f and k_b obtained by fitting eqn (1) to each of these data sets. As follows from the data shown in Fig. 4, all four measurements are in excellent agreement, with all parameters agreeing to within the experimental uncertainty. Further, the uncertainty in the fitting parameters is equivalent for all four measurements. This analysis confirms that both the data from the diagonal and cross-peaks in the CS-NMR data can be used for kinetic analysis of reactions occurring over this timescale and, therefore, that the cross-peak data are of sufficient quality that they can be used for identification of chemical species.

It is now possible to complete the assignment of the spectral resonances at 4.65 and 1.97 ppm in the 1D spectrum. Fig. 5 shows a comparison of the time evolution of these two peaks.

Table 1 Estimated kinetics parameters from GC, 1D and 2D CS-NMR. R is the square root of the coefficient of determination

			2D CS-NMR	
	GC	1D NMR	diagonal	cross-peak
k_f	0.236 ± 0.009	0.228 ± 0.003	0.232 ± 0.005	0.233 ± 0.009
k_b	0.014 ± 0.003	0.013 ± 0.001	0.012 ± 0.001	0.011 ± 0.002
R	0.9966	0.9997	0.9994	0.9978

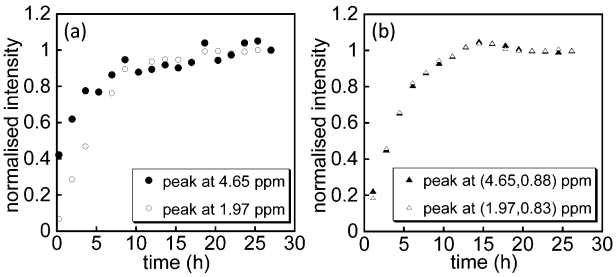

Fig. 5 The evolution of the two unknown peaks from (a) 1D NMR and (b) 2D CS-NMR. The signal intensities are normalised to the intensity of the final point for each peak.

Using the 1D NMR data (Fig. 5(a)) it is seen that intensity of the spectral peaks at 4.65 and 1.97 ppm increase at different rates. In contrast, the intensity of the cross-peaks (Fig. 5(b)) at (4.65, 0.88) and (1.97, 0.83) increase at exactly the same rate to within experimental error, providing strong evidence that the two resonances are associated with the same chemical species. Further support for this conclusion is that the GC data also show evidence of only one additional species to those already identified. On the basis of the 2D NMR, this final species is identified as isopropyl propionate, formed by a Tishchenko reaction[14] between propionaldehyde and acetone. The apparent lower quality of the data shown in Fig. 5(a), *i.e.*, the scattered nature of the data, is consistent with the two peaks at 4.65 and 1.97 ppm in the 1D NMR data containing intensity contributions from other species (which may be increasing or decreasing in amount as a function of time) in addition to the ester. This effect makes the 1D data of limited use in kinetics studies since reliable data may only be obtained for a limited number of chemical species.

In conclusion, a 2D CS-NMR technique has been developed to provide sufficient temporal resolution that reaction kinetics can be studied *in situ* without the loss of structural information or the quantitative nature of the measurement. This is demonstrated by comparison of the 2D CS-NMR data with that obtained using the standard 2D ^{1}H–^{1}H COSY NMR pulse sequence. The comparison of the 2D CS-NMR data with GC and 1D NMR data demonstrate that quantitative temporal data are also obtained. The method retains all the intrinsic advantages of NMR with regard to quantitation and the ability, by exploiting the *in situ* nature of the measurement, to monitor changes in intermediate species as well as reactant and products. The CS methodology demonstrated here is not specific to the ^{1}H–^{1}H COSY sequence used and can be achieved, in general, with any 2D-NMR pulse sequence.

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