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^{13}C solid-state NMR chromatography by magic angle spinning ^{1}H T_1 relaxation ordered spectroscopy

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ABSTRACT

An efficient method to separate the ^{13}C NMR spectra of solid mixtures is introduced. The ^{1}H longitudinal (T_1) relaxation time is used to separate the overlapping ^{13}C chemical shift spectra of solid mixtures via an inverse Laplace transform (ILT) of the relaxation dimension. The resulting 2D spectrum of the mixture contains separate ^{13}C spectra for each component of the mixture that are identical to ^{13}C spectra of the isolated materials. The separation is based on the equalization of ^{1}H T_1 values in a single domain by rapid ^{1}H spin diffusion and on the ^{1}H T_1 value differences between different domains. The introduction of a general ILT scheme enables efficient and reduced data acquisition time. The method is demonstrated on a mixture of two disaccharides and on a commercial drug containing several compounds.

1. Introduction

Most magnetic resonance methods have been developed for pure substances and require sample purification prior to data collection. The spectra of mixtures, which are common in many applications, often contain overlapping resonances from the individual components, complicating the results. The traditional procedure to analyze a mixture is to isolate each component followed by collecting the magnetic resonance spectra of each component. Liquid-chromatography combined with solution NMR is widely used for the analysis of mixtures in solution [1]. Pseudo-chromatographic methods are an alternative approach to mixture characterization; the spectra of the mixture are separated into those of each component by a spectroscopic property without physically isolating the individual components. The solution NMR spectra of mixtures have been separated by the differences in the translational diffusion coefficients of each molecule using diffusion ordered spectroscopy (DOSY) methods [2,3]. The solid-state NMR spectra of quadrupolar nuclei and ESR spectra have been separated by differences in the longitudinal relaxation time (T_1) [4,5]. The strong T_1 relaxation dependence of quadrupolar nuclei and electron spins on the local environment forms the basis of the separation; however, these methods simply separate the spectra for each spin site but not for each component of the mixture. ^{13}C cross-polarization magic angle spinning (CPMAS) NMR spectra have been dispersed into two-dimensions (2D) by the ^{1}H longitudinal relaxation time in the rotating frame ($T_{1\rho}$); the resulting 2D spectra are used as a spectral fingerprint of the solid mixtures [6]. This method fails to clearly separate each component due to slow spin diffusion in the rotating frame and short $T_{1\rho}$ relaxation. $T_{1\rho}$ relaxation values would not be unique to each component in the mixture. Proton longitudinal relaxation time (T_1) has also been used to separate components of a polymorph mixture [7]. Rapid intra domain spin diffusion caused by strong ^{1}H–^{1}H homonuclear dipolar coupling in solid samples that are static or spinning at moderate speeds equalizes the ^{1}H T_1 relaxation in a domain. The ^{1}H T_1 relaxation behavior is dominated by fast-relaxing sites in the domain due to the rapid spin diffusion. The unique ^{1}H T_1 relaxation time for each domain in a solid sample is similar to the unique translational diffusion coefficient for each compound in a solution sample [8]. The previous method [7] was based on ^{1}H inversion recovery to sample ^{1}H relaxation space with a difference data acquisition scheme. The individual components were separated with the direct exponential curve resolution algorithm (DECRA) [9,10], which requires equally spaced data sampling in the relaxation dimension. Together these result in time consuming experiments with specific constraints on data collection in the relaxation dimension and the requirement of reference spectra for difference acquisition.

In this paper, we introduce a flexible, time efficient pseudo-chromatographic method based on a simplified data collection scheme to resolve ^{13}C CPMAS spectra in solid mixtures. The introduction of saturation recovery experiments and general inverse Laplace transform (ILT) data analysis allows logarithmically spaced sampling with reduced relaxation delay, leading to reduced exper-

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imental time. We use the spectra with longest recovery time instead of the reference spectra to obtain the difference spectra, which eliminates the additional experiment time to collect reference spectra. We call this procedure relaxation ordered spectroscopy (ROSY).

2. ROSY procedure

The ROSY experiment is a standard ^{1}H NMR T_1 relaxation measurement monitored via a ^{13}C CPMAS spectrum (Fig. 1). A set of ^{13}C CPMAS spectra is recorded after ^{1}H saturation followed by recovery time τ with ^{1}H to ^{13}C magnetization transfer of the recovered ^{1}H magnetization via CP [11]. The successive scan starts after the relaxation delay time τ_{rd}. The ^{13}C spectra of the mixture components can be separated by ^{1}H T_1 relaxation time for each domain. The separation achieved by the ILT procedure allows for an arbitrary set of recovery times τ. Logarithmically spaced recovery times τ achieve enhanced efficiency; this enables us expand τ range with fine τ pitch at shorter τ's, avoiding substantial increases in experiment time. The ROSY spectra $I(\nu, T_1)$ are displayed in a 2D manner with the ^{1}H T_1 dimension in addition to the standard ^{13}C dimension, where ν is a ^{13}C frequency.

The time domain NMR signal $S(t, \tau)$ obtained by the experiments described above can be written as

$$S(t,\tau) = \int\int d\nu dT_1 I(\nu, T_1)\exp(i\nu t)G(T_1,\tau), \quad (1)$$

where t is ^{13}C acquisition time and $G(T_1, \tau)$ is the relaxation kernel; $G(T_1,\tau) = 1 - \exp(-\tau/T_1)$ for saturation recovery. Applying an ILT to the exponential decay function $\exp(-\tau/T_1)$ results in distinct peaks at specific T_1 values. The exponential decay is obtained by the difference spectra; the ROSY spectra, $I(\nu, T_1)$, are obtained by Fourier transform of $S(t,\infty) - S(t,\tau)$ in the t-domain followed by ILT in the τ-domain, where $S(t,\infty)$ is the NMR signal at the thermal equilibrium. In order to save experiment time to observe reference spectra $S(t,\infty)$, we approximate $S(t,\infty)$ as $S(t,\tau_{max})$ in the following ROSY procedure, where τ_{max} is the maximum value of τ.

ILT is an ill-posed transformation, thus many possible solutions exist for a given decaying signal. Several methods exist for solving the ILT among them, non-negative nonlinear least squares (NNLS) fitting, such as a modification of the standard Levenberg–Marquardt [12] algorithm to exclude solutions corresponding to negative T_1 values. The major drawback to NNLS is the number of decaying components at each value ν of $I(\nu, T_1)$ needs to be provided. Incorrect estimations of the number of components will lead to extra peaks along the relaxation axis and distorted line shape in the frequency axis. Another option for solving the ILT is SPLMOD [13,14] a NNLS solver with an integrated method for estimating the number of components at each frequency. Since both standard NNLS and SPLMOD assume an explicit model of a sum of exponential decays they are most appropriate when the number of components in the mixture is small, typically less than 10. For cases where there are a large number or a distribution of components, the CONTIN [15–17] method may be more appropriate. CONTIN differs from NNLS methods in that it does not assume a model of a sum of exponential decays, estimating the contribution of a set of possible relaxation rates to the observed data. CONTIN is similar to Maximum Entropy Methods in distinguishing between possible solutions based on an objective criterion: given two likely solutions to an ILT problem CONTIN will choose the smoothest solution whereas Maximum Entropy will choose that with the largest measured entropy. A drawback to all three ILT estimation methods mentioned so far is they operate on each frequency channel of the ROSY spectrum independently, which causes difficulty in regions where peaks from two different components overlap since the correct estimate of the number of components changes in those regions. Direct curve exponential curve resolution algorithm (DECRA) [9,10] is a method that uses the entire ROSY spectrum at once in estimating the relaxation parameters. The advantage of DECRA is that using the entire spectrum allows line shape to be preserved, even in overlapping regions, however like NNLS methods DECRA requires an estimate of the number of components to be made, as well as another parameter corresponding to a shift of the data in the relaxation dimension to which the accuracy of the ILT estimate is sensitive. Unlike the NNLS methods and CONTIN, DECRA requires that the data be sampled at equally spaced points in the relaxation dimension which has implications for the total experiment time required as will be discussed in the following.

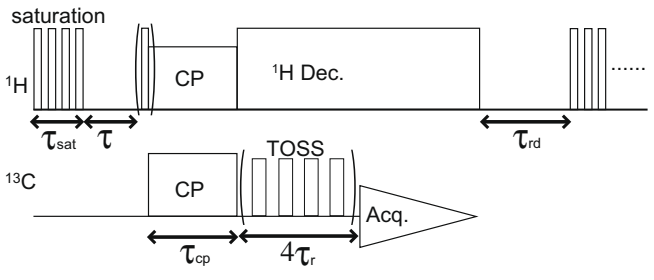

Fig. 1. Pulse scheme used for the ROSY experiments. Saturation pulses are applied to prior to recover period τ. The pulses in parentheses are optionally used for traditional ^{1}H spin-lock CP and TOSS.

The keys to reducing the experimental time are saturation recovery, logarithmic spacing of sample points, and efficient generation of an exponential decay curve to sample the ^{1}H relaxation times. In order to obtain an accurate estimate for T_1, τ_{rd} in an inversion recovery experiment should be larger than five times T_1, i.e. $\tau_{rd} = 5T_1$. τ_{rd} in the saturation recovery could in principle be zero; however; in practice τ_{rd} is limited by the rf duty cycle required to avoid probe damage at small τ values. The ROSY experiment combined with SPLMOD or CONTIN data processing allows for the use of logarithmically spaced recovery times. Logarithmically spaced τ values require less total experiment time than the equally spaced τ values required by the DECRA procedure [7]. This holds as long as the number and range of τ values is the same for both methods. The ROSY experiment does not require additional reference scans to obtain the difference spectrum, providing additional time savings. The total time saving can be as large as a factor of 20 for a 100 s ^{1}H T_1 collected with 18 points over a τ range of 0.1–400 s.

Logarithmically spaced sampling has an additional advantage from a practical point of view. Since the T_1 value is not known for most cases, it is difficult to properly determine the τ range in advance. For the sample with unknown T_1, it is better to start experiments from very short τ and to temporarily set the final τ sufficiently long, which covers a wide range of T_1. Observing the signal intensity, one can stop the experiment when the signal strength is saturated. This avoids spending time to acquire unnecessary long τ values.

3. Experimental

3.1. Materials

Sucrose was purchased from Wako Pure Chemical Industries Ltd., and cellobiose, 2-ethoxybenzamide (ethenzamide), and N-(4-hydroxyphenyl)acetamide (acetaminophen) were purchased from Tokyo Chemical Industry Ltd. All the samples were used without further purification. The test mixture of sucrose and cellobiose was prepared by finely milling together equal weights of the

disaccharides. The over-the-counter (OTC) drug, Norshin White, an analgesic and antipyretic drug, was purchased from Arax Co., Ltd., and was milled prior to sample packing.

3.2. NMR spectroscopy

The solid-state NMR experiments were performed at ^{1}H frequencies of 600.17 MHz using a JEOL JNM-ECA system equipped with a JEOL 3.2 mm CPMAS probe for ROSY and CPMAS experiments at a spinning frequency of 15 kHz and a JEOL 2.5 mm CPMAS probe for the fast MAS ^{1}H T_1 measurements. Experimental ^{13}C shifts were referenced to TMS at 0 ppm with sample substitution referencing to the adamantane methylene at 37.77 ppm [18]. All data were collected at ambient probe temperatures. The initial ^{1}H magnetization was saturated by a train of hundred $\pi/2$ pulses (2.05 μs) during the 0.1 s saturation period τ_{sat}. The ^{1}H magnetization was allowed to recover along z-axis during the relaxation period τ. Nuclear integrated CP (NICP) [19] with a contact time τ_{cp} of 6 ms, a constant ^{13}C rf-field strength of 87 kHz, and a ^{1}H frequency sweep of 100 kHz at a constant strength of 100 kHz was used for magnetization transfer from ^{1}H to ^{13}C. Note that NICP does not require a $\pi/2$ pulse prior to spin-lock; the ^{1}H frequency sweep adiabatically rotates the ^{1}H magnetization from z-axis to xy-plane and spin-locks the ^{1}H magnetization in the xy-plane. The $\pi/2$ pulse bracketed in Fig. 1 is required if conventional CP schemes are used to develop the ^{13}C magnetization. The OTC remedy data were collected with a cogwheel phase cycled TOSS scheme [20,21]. Four π pulses were applied at (0.811179, 1.769947, 2.188821, 3.230053) τ_r prior to ^{13}C observation which starts at $4\tau_r$ [22], where τ_r was the rotor period. SW_f-TPPM ^{1}H decoupling [23] with an rf-field strength of 125 kHz was applied during the TOSS rotor periods and ^{13}C data acquisition. All the ROSY spectra were processed by SPLMOD, which is appropriate for separating discrete T_1 values.

1D CPMAS spectra of OTC remedy, acetaminophen, and ethenzamide were collected using the NICP, SW_f-TPPM, and TOSS conditions described above.

4. Results and discussion

The experimental spectra of two disaccharides, sucrose and cellobiose, are presented in Fig. 2 as a physical mixture and as the individual pure compounds. The ^{13}C CPMAS spectrum of the mixture contains overlapped signals from each disaccharide and is difficult to assign. The experimental data was collected with logarithmically spaced sampling with 15 points from $\tau = 0.5$ s to 180 s. The resulting ROSY spectrum clearly shows two distinct peaks in the ^{1}H T_1 dimension. Slices of the ROSY spectrum along the ^{13}C dimension agree well with the ^{13}C CPMAS spectra of pure sucrose and pure cellobiose (Fig. 2(c)); all the peaks can be correctly assigned to each component. The ROSY procedure is successful even though the ^{1}H T_1 values differ by less than 10%, 58 s for sucrose and 53 s for cellobiose. The experimental time for the ROSY spectrum is about 19 h with τ_{rd} of 1 s. The equivalent inversion recovery experiment with linear sampling for DECRA would take about 203 h over the same τ range for 128 scans and τ_{rd} of 290 s, five times the T_1 of 58 s for the sucrose. This saves a factor of 11 in time or a factor of 19 in time when the reference scans in the originally proposed scheme are included. We found that additional reduction of experimental time is achieved by omitting the data point with the largest τ value, i.e. $\tau = 180$ s. The same 1D slices are obtained, though the T_1 value is incorrect (not shown). This reduces the experimental time at the cost of inaccurate T_1 values in the T_1 axis of the ROSY spectrum.

Fig. 3 shows a ROSY spectrum of the OTC drug. Each tablet of the drug contains, 190 mg ethenzamide, 150 mg acetaminophen, 60 mg caffeine, and 160 mg of excipients, primarily starch. The spinning sidebands were suppressed with cogwheel phase cycled total sideband suppression (TOSS) [20,21]. The ROSY spectrum clearly shows three peaks in the ^{1}H T_1 dimension. These peaks correspond to ethenzamide, acetaminophen, and the excipient matrix. The broad peak at the 2.2 s ^{1}H T_1 can be assigned to the excipient matrix. The peak width for SPLMOD in the relaxation dimension does not represent a distribution of the relaxation time but a measure of uncertainty. CONTIN is appropriate for analyzing the T_1 distribution. The ROSY slices agree well with the ^{13}C CPMAS spectra of pure ethenzamide and acetaminophen with no missing resonances. The overlapped peaks near 120 ppm and 133 ppm are separated into two ^{1}H T_1 values for these two compounds. The caffeine signal is not observed in the ROSY spectrum due to low signal intensity and broad lineshape as shown in the CPMAS spectrum (Fig. 3(a)) at 30 ppm. The experimental time for the experiment is 52 h. This contrasts with over 500 h for the equivalent inversion recovery/DECRA based experiment, assuming a

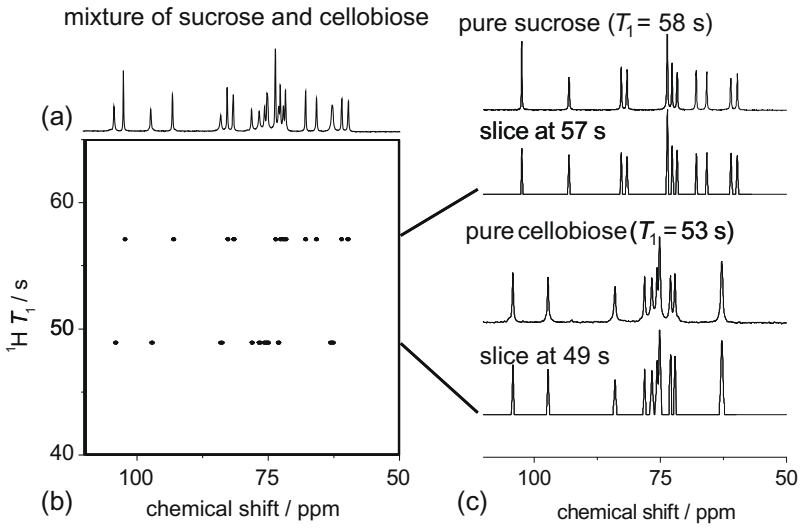

Fig. 2. ^{13}C spectra of mixture/pure material of sucrose and cellobiose at 15 kHz MAS. (a) ^{13}C CPMAS and (b) ROSY spectra of the mixture. (c) ^{13}C CPMAS spectra of the pure compounds and slices of the ROSY spectrum along the ^{13}C dimension. 15 spectra were recorded with τ = 0.5–180 s for the ROSY spectrum. The data were transformed by SPLMOD into the ROSY presentation.

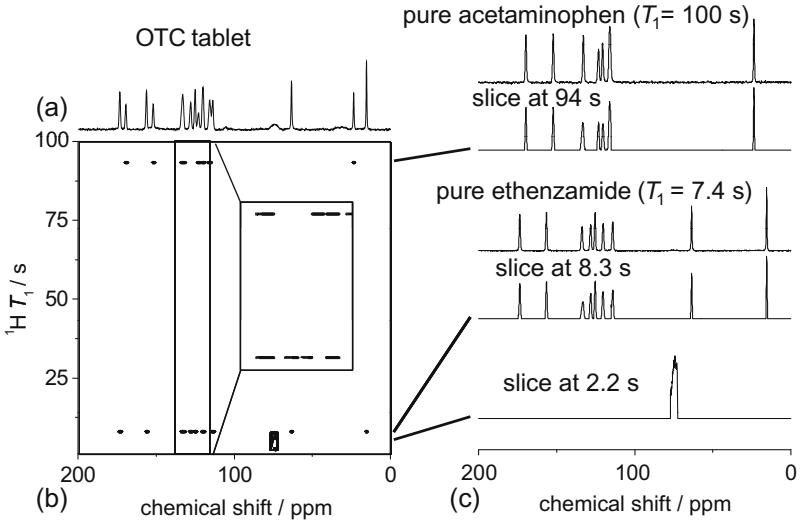

Fig. 3. ^{13}C spectra of an OTC drug and two pure materials, ethenzamide and acetaminophen, at 15 kHz MAS. (a) ^{13}C CPMAS and (b) ROSY spectra of the OTC drug. 18 spectra were recorded with τ = 0.1–400 s for the ROSY spectrum. An expansion from 117 to 138 ppm is superimposed on the ROSY spectrum. (c) ^{13}C CPMAS and ROSY slices.

100 s T_1 for the acetaminophen. Further reduction can be achieved by omitting the data points with $\tau > 100$ s at the cost of inaccurate T_1 values, thus reducing the experimental time to 13 h.

The assumption that all the ^{1}H nuclei have uniform T_1 relaxation does not hold at high MAS speeds. High frequency MAS partially decouples ^{1}H–^{1}H dipolar resulting in resolved ^{1}H peaks for each group. This slows the rate of ^{1}H–^{1}H spin diffusion between sites and increases the ^{1}H T_1 value, differentiating T_1 values for each ^{1}H site. The spinning frequency dependence of ^{1}H T_1 can be different for each sample. To confirm these phenomena ^{1}H T_1 relaxation times of L-alanine and ethenzamide were measured at spinning frequencies from 0 to 32 kHz (Fig. 4). Note, the data were not corrected for temperature changes caused by the increasing spinning speed. Although all the ^{13}C peaks of L-alanine have an identical ^{1}H T_1 value at 0 to 32 kHz, the aromatic peaks of ethenzamide have ^{1}H T_1 values more than twice than those of the ethoxy peaks due to ^{1}H–^{1}H decoupling at spinning frequency higher than 24 kHz. At spinning frequencies less than 20 kHz the ^{1}H T_1 values are uniform for all the ethenzamide signals. The difficulties caused by ^{1}H T_1 variations can be avoided by using moderate MAS frequencies to reduce ^{1}H–^{1}H decoupling, and robust CP schemes such as NICP with long contact times to utilize ^{1}H magnetization from a larger volume of ^{1}H spins.

The ROSY based ^{1}H T_1 relaxation times for each mixture component are similar to those of the pure materials. This indicates spin diffusion is not occurring between different crystalline domains of the mixtures within 58 s for the disaccharides and 100 s for the OTC remedy. Assuming a ^{1}H spin diffusion rate of 10^{-15} m^2 s^{-1} [24], we can estimate the domain size to be at least 0.24 mm for the former and 0.32 mm for the latter.

It has been shown that the ^{1}H T_1 relaxation time is affected by temperature, MAS frequency, the static magnetic field strength, sample preparation procedure, and so on [25,26]. The ROSY method fails to separate spectra for domains accidentally having the same ^{1}H T_1 value, since the ROSY separation is based on ^{1}H T_1 difference. For such case, the spectra could be separated by changing sample temperature, MAS frequency, or the magnetic field strength; the ^{1}H T_1 dependence on these experimental parameters being different for each domain. Although T_1 value could be changed by sample preparation, such as grounding, ROSY works well as long as the ^{1}H T_1 value is uniform within the domain. This assumption holds as long as each domain is large enough to have a uniform T_1 value independent on the other domain. The T_1 values extracted from the ROSY experiments reflect the environment of each domain in the sample. This is one of the advantages of ROSY which can analyze the mixture without sample modification.

5. Conclusion

We have introduced an efficient and time-reducing method to separate ^{13}C CPMAS spectra of solid mixtures into those of each component based on ^{1}H T_1 relaxation values. The ROSY procedure enables one to obtain separated ^{13}C spectra of mixtures within the

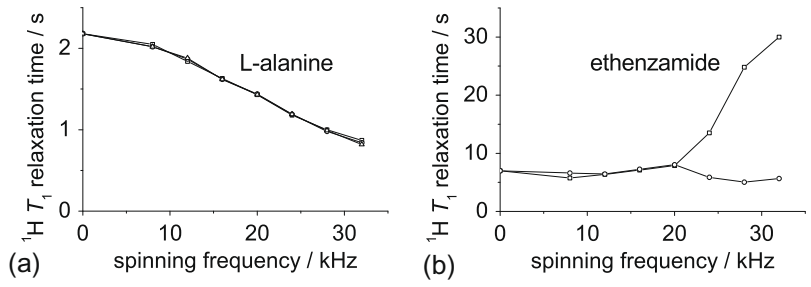

Fig. 4. Spinning frequency dependence of ^{1}H T_1 relaxation time for (a) L-alanine and (b) ethenzamide. The T_1 values are measured by ^{1}H saturation recovery experiment. The open square (□) is for (a) amino and (b) aromatic protons, the open circle (○) is for (a) methine and (b) ethoxy protons, and the open triangle (Δ) is for (a) methyl protons. At the static conditions, i.e. a spinning frequency of 0 Hz, all peaks merges each other and the value at peak top is presented for all protons.

experiment time comparable to standard ^{13}C CPMAS spectra. Since the ROSY separation is based only on T_1 differences for each domain, the method can be applied not only to mixtures of different compounds, but also crystalline polymorphs and amorphous/crystalline mixtures of single compounds. Although we have demonstrated the ROSY experiments on 1D ^{13}C spectra, the extension to two- or more-dimensional experiments is straightforward. The ROSY method can be applied to not only $^{1}H/^{13}C$ systems but also other systems in which the T_1 values are equalized by spin diffusion. It is also possible to apply the ROSY method to separate high resolution ^{1}H spectra by replacing CP and ^{13}C observation with high resolution ^{1}H observation using windowed homonuclear decoupling schemes. We believe the ROSY method can have a broad impact especially for scientific research, material science, industrial, and pharmaceutical sciences.

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