Journal of Magnetic Resonance 215 (2012) 23–26

Contents lists available at SciVerse ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

Selective double quantum resolved correlation experiment for the complete separation of entire proton NMR spectra of enantiomers

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ARTICLE INFO

Article history:
Received 19 September 2011
Revised 5 December 2011
Available online 21 December 2011

Keywords:
Selective excitation
Multiple quantum coherences
COSY
Chiral discrimination

ABSTRACT

The present study reports a two dimensional NMR experiment which separates single quantum spectra of enantiomers from that of a racemic mixture. This is a blend of selective double quantum refocusing, for resolving couplings and chemical shift interactions along two dimensions followed by correlation of the selectively excited protons to the entire coupled spin network. The concept is solely based on the presence of distinct intra methyl dipolar couplings of different enantiomers when dissolved in chiral orienting media. The analysis of single enantiomer spectrum obtained from respective F_2 cross sections yield all the spectral information.

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1. Introduction

Enantiomers are distinguishable by NMR only if diastereomeric interactions are introduced. In isotropic solutions chiral solvating agents, chiral derivatizing agents and lanthanide shift reagents form diastereomeric complexes through covalent or non-covalent interactions with the enantiomers and alter the chemical shifts of the enantiomers allowing us to utilize this as the parameter for differentiation [1]. On the other hand in chiral anisotropic solvents, differential ordering of the molecules provide access to many additional NMR parameters, viz. chemical shift anisotropies, dipolar couplings and quadrupolar couplings (for nuclei with spin quantum number greater than half) [1–3]. The ^{2}H NMR, at natural abundance utilizing quadrupolar couplings, is one of the popular methods for discrimination of enantiomers [4,5]. Presence of protons in most of the chiral molecules and relatively small errors associated in the quantification of enantiomeric excess renders ^{1}H NMR experiments as a favorable choice. But numerous ^{1}H–^{1}H couplings result in significant loss of resolution in the spectra along with the overlap of transitions from different enantiomers. Several multi-dimensional, single and multiple quantum (MQ), resolved and correlation experiments have been developed in this direction [2]. Although many of the existing methods are able to extract most of the spectral parameters corresponding to the chiral molecules, they failed to separate the entire spectra of each enantiomer from their mixture. Hence there is a need to develop NMR experiments to analyze such complex spectra.

Generally in oriented systems all the protons are coupled to each other and hence it is possible to excite the coherence of the order of number of spins present in the system. These MQ coherences evolve under the sum of the individual ^{1}H chemical shift anisotropies (CSA). Even though protons have small value of CSA in weakly aligning media, usually not observable in single quantum spectra, at higher quantum coherences they add up resulting in improved visibility. Due to the differential ordering the CSAs of two enantiomers are different. Therefore a non-selective excitation of homonuclear highest quantum coherence yields a singlet for each enantiomer in the MQ (F_2) dimension. The F_2 cross sections, at each of such peaks pertain to single quantum single enantiomer spectra [6]. But such an experiment has inherent drawback that magnetic field inhomogeneity also gets scaled up linearly with the coherence order and hence contribute to significant line broadening along the MQ dimension. This results in poor resolution along the MQ dimension and the enantiopure spectrum obtained from the cross sections contains transitions of less intensity from the other enantiomer [6]. Also if two protons have CSA tensors in opposite directions the total CSA will be reduced or even nullified. One dimensional transition selective COSY is another experiment in which a transition corresponding to any one of the enantiomers is selectively excited and the coherence is transferred to other coupled states through a hard $\pi/2$ pulse [7]. Since there are no dipolar couplings between the enantiomers, the complete spectrum corresponding to the selectively excited enantiomer can be obtained. The limitations of the experiment are at least one isolated transition corresponding to each enantiomer must be present and the

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doi:10.1016/j.jmr.2011.12.008

selective excitation of single transition without perturbing those of other enantiomers is technically demanding. Selective excitation and refocusing (SERF) [8] and its variants are the other most explored class of experiments for the discrimination of oriented chiral molecules through ^{1}H NMR [2,3,9,10]. Recently a new technique entitled G-SERF has been reported [11,12], where the concept of spatial frequency encoding is employed. Though G-SERF is able to give most of the couplings corresponding to each enantiomer from a racemic mixture, the experiment requires optimization of the parameters, prior knowledge of dipolar couplings and it will not show separated full spectra of different enantiomers.

In the present study we have improved the earlier DQ-SERF sequence, where the discrimination was achieved only in the methyl region [10]. The significance of the present method is that it yields separate spectrum based on the different values of methyl dipolar couplings for each enantiomer, independent of the remaining couplings. This is a unique report of the kind where complete separation of ^{1}H spectra of enantiomers is achieved using only one dipolar coupling in the experiment.

2. Experimental details

The experiment is demonstrated on chiral (*R*/*S*)-propylene carbonate (see Fig. 1a). The sample was aligned in the chiral liquid–crystalline phase of PBLG/$CDCl_3$ [13]. The composition of the sample was 55 mg of racemic mixture in 100 mg of PBLG and 660 mg of $CDCl_3$. The shaped pulses used in the pulse sequence (see Fig. 1b) were 60 ms long 90° EBurp and 180° REBurp [14]. The spectra were recorded on 500 MHz (Bruker, DRX) NMR spectrometer using TXI-probe with *z*-gradient. The temperature was maintained at 298 K.

3. Results and discussion

The DQ-SERF sequence consists of selective excitation of double quantum coherences of methyl protons followed by an evolution period (t_1) at the center of which a selective π pulse is applied to retain the evolution under active couplings only. When a molecule possessing a methyl group is dissolved in the orienting medium, the methyl selective DQ-SERF experiment yields a doublet in F_1 dimension due to intra methyl dipolar couplings. Due to differential ordering these couplings are different for different enantiomers resulting in different doublets for each of them. Simultaneous excitation of DQ coherences is possible due to the negligible difference in CSA of protons in different enantiomers in low ordered media. In this work we have used a non-selective mixing after the t_1 period which transfers the magnetization of previously excited methyl protons to the entire coupled network of protons in that molecule. The result is analogous to mixing in the TOCSY sequence in solution state NMR. The product operator description of the evolution of magnetization during the pulse sequence is described here

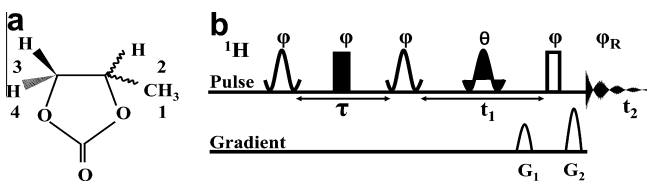

Fig. 1. (a) The chemical structure and the numbering of protons in (*R*/*S*)-propylene carbonate. (b) The pulse sequence for DQ-SERF-COSY. The shaped pulses used were Burp2 and EBurp2. Open and filled hard/selective pulses represent $\pi/2$ and π rotations respectively. The pulse phases were $\Phi = x, x$; $\theta = x, -x$ and the receiver phase was $\Phi_R = x, x$. Double coherence selection is achieved by setting the gradient ratio G_1:G_2 to 1:2. Duration of the shaped pulses was 62 ms and the delay τ was 12.5 ms.

[7,15]. In spite of weak ordering, in general, all the protons are dipolar coupled among them permitting the replacement of the isotropic mixing sequence by a hard $\pi/2$ pulse.

An explanation of the pulse sequence (Fig. 1b) and the resulting spectrum (Fig. 2) using product operators is given below [15].

The magnetization at thermal equilibrium for a homonuclear I_3S spin system is given by

$$M_{eq} = I_{1z} + I_{2z} + I_{3z} + S_z$$

After selective excitation of $\boldsymbol{I}_3$ spins

$$M_{+} = -I_{1y} - I_{2y} - I_{3y} + S_z$$

These $\boldsymbol{I}$ spin coherences evolve under all the couplings T_{II} and T_{IS} during $\tau - \pi - \tau$ and results in following anti-phase terms. Note that the π pulse is on both $\boldsymbol{I}$ and $\boldsymbol{S}$ spins.

$$M_{\text{anti phase}} = -8I_{1z}I_{2z}I_{3y}S_z - 8I_{1z}I_{2y}I_{3z}S_z - 8I_{1y}I_{2z}I_{3z}S_z$$

The selective $\pi/2$ pulse creates terms that are mixtures of DQ and zero quantum (ZQ) coherences.

$$M_{DQ} = -8I_{1y}I_{2y}I_{3z}S_z - 8I_{1y}I_{2z}I_{3y}S_z - 8I_{1z}I_{2y}I_{3y}S_z$$

These DQ coherences evolve during $t_1/2 - \pi - t_1/2$ only under T_{II} couplings. This is because the selective pulse is on methyl protons. But the last non-selective $\pi/2$ pulse correlates these DQ coherences to all coupled spin SQ coherences. All these SQ coherences detected during t_2 are modulated by the methyl proton DQ coherence evolution during t_1. This explanation can be extended to the present spin system of the kind A_3MPX also.

The methyl regions in the F_2 cross sections with the magnitude mode representation result in a triplet with the intensity pattern of 1:2:3 or 3:2:1 due to intra methyl couplings. Both the F_2 cross sections corresponding to each enantiomer in the DQ-SERF-COSY spectrum were thus added to normalize this intensity distribution. The region of the spectrum enclosed in the broken rectangle of Fig. 2a, corresponding to the proton H_3, is expanded in Fig. 2b as a representative in measuring the couplings. Similarly other regions can be expanded to get the remaining couplings. The various couplings thus obtained are reported in Table 1.

The cross sections at the doublets of both *R* and *S* enantiomers, in 2D DQ-SERF-COSY (see Fig. 2a), along F_2 dimension were extracted (see Fig. 3b and a). The appearance of intensity pattern in the methyl region, along F_2 dimension is discussed here.

Initially we consider one DQ coherence, coupled to the remaining $\boldsymbol{I}$ and $\boldsymbol{S}$ spins, present during t_1 and derive an explanation for the intensities. In terms of polarization operators such coherence can be represented as $I_1 - I_2 - I_{3\alpha}S_\alpha$ Action of the non-selective $\pi/2$ pulse on this term will be as follows.

$$I_1 - I_2 - I_{3\alpha}S_\alpha \xrightarrow{\frac{\pi}{2}} \left[\frac{1}{2}I_{1-} + \frac{1}{2}I_{1+} - \frac{1}{2}i(I_{1\alpha} - I_{1\beta})\right] * \left[\frac{1}{2}I_{2-} + \frac{1}{2}I_{2+} - \frac{1}{2}i(I_{2\alpha} - I_{2\beta})\right] * \left[\frac{1}{2}I_{3\alpha} + \frac{1}{2}I_{3\beta} - \frac{1}{2}i(I_{3+} - I_{3-})\right] * \left[\frac{1}{2}S_{2\alpha} + \frac{1}{2}S_{3\beta} - \frac{1}{2}i(S_{3+} - S_{3-})\right]$$

Multiplying and rearranging these terms we obtain 12 $\boldsymbol{I}$ spin terms.

$$\frac{1}{16i}[^{-}(I_1 - I_{2\alpha}I_{3\alpha}S_\alpha) + (I_1 - I_{2\alpha}I_{3\beta}S_\alpha) - (I_{1-}I_{2\beta}I_{3\alpha}S_\alpha) + (I_1 - I_{2\beta}I_{3\beta}S_\alpha) - (I_{1\alpha}I_{2-}I_{3\alpha}S_\alpha) + (I_{1\alpha}I_{2-}I_{3\alpha}S_\alpha) - (I_{1\beta}I_{2-}I_{3\beta}S_\alpha) + (I_{1\beta}I_2 - I_{3\beta}S_\alpha) + (I_{1\alpha}I_{2\alpha}I_{3-}S_\alpha) - (I_{1\alpha}I_{2\beta}I_{3-}S_\alpha) - (I_{1\beta}I_{2\alpha}I_{3-}S_\alpha) + (I_{1\beta}I_{2\beta}I_{3-}S_\alpha)$$

All $\boldsymbol{I}$ terms along each column have the same frequency, since I_1, I_2 and I_3 are equivalent spins. Due to the same reason, second and

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