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Chemical shift anisotropy edited complete unraveling of overlapped ^{1}H NMR spectra of enantiomers: Application to small chiral molecules

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Abstract

The differential values of NMR spectral parameters like chemical shift anisotropies, dipolar couplings and quadrupolar couplings of enantiomers in chiral liquid crystalline media are employed not only for their visualization but also for their quantification. Large differences in chemical shift anisotropies and the quadrupolar couplings between the enantiomers enable the use of ^{13}C and extensive ^{2}H NMR detection for such a purpose. In spite of high magnetic moment, high sensitivity and abundant presence of protons in all the chiral molecules, ^{1}H detection is not routinely employed due to severe overlap of unresolved transitions arising from short and long distance couplings. Furthermore, the doubling of the spectra from two enantiomers and their indistinguishable overlap due to negligible difference in chemical shift anisotropies hampers their discrimination. The present study demonstrates the use of proton chemical shift anisotropy as an exclusive parameter for such a discrimination. The method employs the non-selective excitation of homonuclear *N*th quantum coherence of *N* coupled protons. The simultaneous flipping of all the coupled spins results in a single transition in the multiple quantum dimension at the cumulative sum of their anisotropic chemical shifts for each enantiomer, with the measurable difference between them, resulting in their complete unraveling.

Keywords: Multiple quantum; Chemical shift anisotropy; Chiral discrimination

1. Introduction

NMR spectroscopic visualization of optical enantiomers is extensively practiced using the weakly aligned chiral lyotropic liquid crystalline media [1–3]. The difference in the orientational property of the enantiomers has been exploited for their visualization and to determine their excess. The elements of the Saupe order matrix of the enantiomers differ by a small magnitude and are of the order of 10^{-3} to 10^{-5} [4]. However, its effect on the anisotropic NMR spectral parameters like chemical shift anisotropies ($\Delta\sigma_i$), dipolar couplings (D_{ij}) and quadrupolar couplings (Q_i) are significant as far as the visualization of enantiomers is concerned. In the case of proton detection, the magnitudes of chemical shift anisotropies and their differential values between the enantiomers are not significant and many a time results in an indistinguishable overlap of the spectra. Thus the dipolar couplings among the protons are the obvious choice for their visualization. However, in chiral molecules with large number of interacting protons there is a significant loss of resolution due to several short and long distance dipolar couplings and the doubling of transitions from the two enantiomers. This severely hampers the complete unraveling of the spectra and their analyses. Nevertheless, the strengths of the dipolar couplings in chiral media are not large unlike in the strongly orienting thermotropic liquid crystals and in favorable cases permit the first order analyses of the spectra similar to that of liquid state spectra. But the challenging task of both unraveling of the spectra and achieving high resolution always persists. Hence the majority of NMR investiga-

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tions of enantiomeric differentiation have focused on ^{2}H NMR [5–11], taking advantage of the relatively large strengths of the quadrupole couplings compared to chemical shift anisotropies and dipolar couplings. The recent study also discusses the use of homo and heteronuclear two-dimensional methods to analyse a mixture of deuterated unlike and like stereo isomers [12]. There are also studies using ^{13}C [13,14] and ^{19}F [15,16]. In spite of severe overlap of the transitions, the proton detection is advantageous because of; (a) its high magnetic moment, (b) high natural abundance and (c) abundant presence in all the chiral organic molecules. Thus there are continuous efforts on methodological developments reported in the literature for discrimination of enantiomers, viz., selective refocusing (SERF) experiment [17] based on the selective excitation [18] used in liquid state studies to determine the scalar couplings, combined variable angle with selective refocusing [19], two-dimensional correlation [20], heteronuclear selective refocusing [21], *J*-resolved experiment with BIRD sequence [22]. Each of these methods has its own advantages.

In our recent study on heteronuclear spin systems, we have demonstrated the selective detection of single quantum (SQ) coherence based on the spin state of the heteronuclei using highest order of homonuclear multiple quantum (MQ) coherence [23]. The method simplified the analyses of the complex NMR spectra of strongly dipolar coupled spins and removed the redundancy in the number of observable SQ transitions as far as the determination of homonuclear couplings is concerned. We extended this methodology for the weakly aligned chiral molecules in the chiral liquid crystal media and developed the DQ-SERF (double quantum selective refocusing) experiment which does not utilize the spin state selection but provided unraveling of the overlapped peaks of the selectively excited methyl group proton resonances [24]. The advantages of the DQ-SERF experiment over SERF experiment have been extensively discussed. We have also pointed out that the SERF experiment does not require a biselective pulse and demonstrated that it can also be exploited for the determination of the long distance couplings in the direct dimension. All these methodologies exploit proton–proton dipolar couplings for enantiomeric discrimination.

The chemical shift anisotropy ($\Delta\sigma_i$) of proton is another spectral parameter which has not been utilized exclusively for chiral visualization. The magnitudes of $\Delta\sigma_i$ of protons are known to be very small and are within a few ppm, even in thermotropic liquid crystals where the orientational parameters are several orders of magnitude larger than in chiral liquid crystal. There are exceptional cases like CH_3F and C_2H_2 where the proton chemical shift anisotropies could be significant [25]. However, in general, it is imperative that the $\Delta\sigma_i$ of protons is negligibly smaller in chiral liquid crystals, indicating the reason for not utilizing this as a parameter for enantiomeric discrimination.

In our recent work on spin selective and non-selective excitation of multiple quantum, we have discussed the differences in the spin dynamics in both the situations, reported the theoretical understanding of the spin dynamics using product operator formalism. The study also demonstrated the applicability of spin selective excitation not only for spectral simplification but also for the determination of the relative signs and magnitudes of the scalar couplings [26]. This difference in the spin dynamics inspired us to extend the idea of non-selective excitation for complete unraveling of the optical enantiomers in the present study. The non-selective excitation of homonuclear highest quantum of all the coupled protons results in their simultaneous flipping, providing a singlet for each enantiomer at the sum of their anisotropic chemical shift values in the MQ dimension. In the higher quantum dimension the cumulative addition of anisotropic chemical shifts of each enantiomer provides a sizeable differential value of $\Delta\sigma_i$ between them enabling the complete unraveling. Since the basic requirement is the coupling among all the protons, we are aware of the fact that this methodology is applicable to small molecules. The selective detection of the particular order of the quantum is achieved by employing the gradients. The application and the limitation of the experimental methodology have been demonstrated on the chosen test molecules, each having a chiral centre, viz. (±)-2-chloropropanoic acid, (±)-3-butyn-2-ol, and the mixture of structural isomers of (±)-1-chloro-2-propanol and (±)-2-chloro-1-propanol aligned in the chiral liquid crystal poly(γ-benzyl-L-glutamate) (PBLG).

2. Experimental confirmation

The samples were purchased from Sigma and used without further purification. The racemic structures of these molecules are given in Fig. 1. The samples were prepared by the method described in the literature [11,22]. For the oriented (±)-2-chloropropanoic acid sample, 50 mg of the

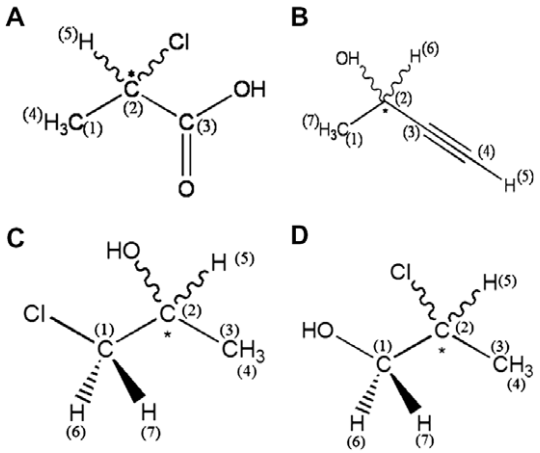

Fig. 1. (A–D) The racemic structures and the numbering of interacting spins in (*R*/*S*)-2-chloropropanoic acid, (*R*/*S*)-3-butyn-2-ol, (*R*/*S*)-1-chloro-2-propanol and (*R*/*S*)-2-chloro-1-propanol, respectively.