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A Practical Strategy for the Accurate Measurement of Residual Dipolar Couplings in Strongly Aligned Small Molecules

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Abstract

Accurate measurement of residual dipolar couplings (RDCs) requires an appropriate degree of alignment in order to optimize data quality. An overly weak alignment yields very small anisotropic data that are susceptible to measurement errors, whereas an overly strong alignment introduces extensive anisotropic effects that severely degrade spectral quality. The ideal alignment amplitude also depends on the specific pulse sequence used for the coupling measurement. In this work, we introduce a practical strategy for the accurate measurement of one-bond ^{13}C - ^1H RDCs up to a range of ca. -300 to +300 Hz, corresponding to an alignment that is an order of magnitude stronger than typically employed for small molecule structural elucidation. This strong alignment was generated in the mesophase of the commercially available poly- γ -(benzyl-L-glutamate) polymer. The total coupling was measured by the simple and well-studied heteronuclear two-dimensional J -resolved experiment, which performs well in the presence of strong anisotropic effects. In order to unequivocally determine the sign of the total coupling and resolve ambiguities in assigning total couplings in the CH_2 group, coupling measurements were conducted at an isotropic condition plus two anisotropic conditions of different alignment amplitudes. Most RDCs could be readily extracted from these measurements whereas more complicated spectral effects resulting from strong homonuclear coupling could be interpreted either theoretically or by simulation. Importantly, measurement of these very large RDCs actually offers significantly improved data quality and utility for the structure determination of small organic molecules.

1. Introduction

The degree of alignment (or alignment amplitude) is an important practical factor to consider in the utilization of residual dipolar coupling (RDC) as a structural elucidation technique. Studies prior to the 1990s either employed very strong alignment in mesophases of nematic solvents [1-3] or very weak field-induced alignments from the intrinsic magnetic susceptibility anisotropy of paramagnetic [4] or even diamagnetic molecules [5]. Modern applications were developed with a particular emphasis on biomolecules and primarily utilized tunable alignment media, such as dilute lyotropic mesophases [6-12] or strained polymeric gels [13-16]. In these tunable media, the alignment amplitude can be modulated and optimized by adjusting specific conditions or concentrations of the medium. RDC measurement using tunable alignment methods based on mesophases [17-19] and polymeric gels [20-27] also found applications in structural elucidation of small organic molecules.

When HSQC-based experiments are used to measure the one-bond ^{13}C - ^1H RDCs, the ideal alignment should typically yield RDCs with a 10-30 Hz magnitude. Values within this range are large enough for accurate measurement, but still much smaller than the ^1H - ^{13}C scalar (J) couplings, facilitating both NMR measurement and spectral interpretation. In practice, obtaining the desired alignment amplitude is not always easy. Optimization often involves trial-and-error, as different molecules have varying propensities to align that are hard to predict *a priori*. A frequently encountered scenario is that a particular molecule becomes too strongly aligned under a “typical” condition, and consequently signal intensities associated with large RDCs are very poor in HSQC-based experiments. Furthermore, alignment media based on mesophase of certain polymers, such as the synthetic polymer poly- γ -(benzyl-L-glutamate) (PBLG), undergo isotropic-to-nematic (I-N) phase transition only at a relatively high concentration [28,29] and therefore can only

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