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The importance of suppressing spin diffusion effects in the accurate determination of the spatial structure of a flexible molecule by nuclear Overhauser effect spectroscopy

I.A. Khodov [a, b, *], S.V. Efimov [b], V.V. Klochkov [b], L.A.E. Batista de Carvalho [c], M.G. Kiselev [a]

[a] G.A. Krestov Institute of Solution Chemistry, Russian Academy of Sciences, Akademicheskaya St. 1, Ivanovo, 153045, Russia
[b] Institute of Physics, Kazan Federal University, Kremlevskaya St. 18, Kazan, 420008, Russia
[c] Molecular Physical Chemistry R&D Unit, University of Coimbra, Coimbra, 3004-535, Portugal

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ABSTRACT

Two-dimensional nuclear Overhauser effect spectroscopy is applied to the elucidation of conformation distribution of small molecules in solution. An essential influence of the nonlinear multistep magnetization transfer (spin diffusion) on the NMR-based analysis of conformers distribution for small druglike molecules in solution was revealed. Therefore, the spin diffusion should be eliminated from the obtained NMR data in order to obtain accurate results. Efficiency of QUIET-NOESY spectroscopy in solving the problem of accurate determination of inter-proton distances in a small molecule was shown in a study of ibuprofen. Although it requires much experimental time, this technique was found to be helpful to solve the spin diffusion problem.

1. Introduction

In recent years the nuclear Overhauser effect spectrosopy (NOESY) has been demonstrated to be a useful tool for the spatial structural determination of small organic molecules [1,2] and especially for high flexible systems [3,4]. Butts et al. showed that the technique yields the relative structural preference for small rigid molecules based on experimental interproton distances derived from an accurate quantitative NOESY analysis [5–7]. Recently, the quantitative NOESY-based technique has been extended to small flexible molecules, and the reliability of the approach for the analysis of systems with fast conformation exchange was shown [8–12]. Due to some experimental constraints of this quantitative NOESY-based technique, the identification of the configuration of highly flexible compounds is still a great challenge. These limitations include the absence of a correct accounting for the intramolecular group rotation and spin diffusion. We have recently demonstrated that an integrated approach combining the NOESY-based technique in parallel with correct averaging of internuclear distances within rotating groups obtained from quantum chemical calculations leads to better estimates of the conformer distribution [8,9]. However, consideration of the effect of spin diffusion on the accuracy of distance determinations is not properly developed.

In fact, the spin diffusion effect was shown to increase when conditions approach the slow motion limit [13]. Small molecules in relatively viscous solvents may also be prone to this effect due to reduction of rotational flexibility [14].

Spin diffusion can be eliminated either by carrying out measurements with short mixing times (in the range from tens to hundreds milliseconds) [15] or by applying special pulse programs and approaches which are listed below.

- MINSY (Mixing Irradiation during a NoeSY) is a modified NOESY experiment which includes a pulse sequence within the mixing period for suppression of the solvent signal (usually water) [16,17].
- QUIET-BIRD-NOESY is also a modified NOESY sequence with a bilinear rotation decoupling (BIRD) composite element inserted in the middle of the mixing period [18]; the BIRD element is a typical part of heteronuclear correlation experiments.
- One more class of experimental methods which involve dividing the spin systems into blocks with the aid of decoupling: BD-

* Corresponding author. G.A. Krestov Institute of Solution Chemistry, Russian Academy of Sciences, Akademicheskaya St. 1, Ivanovo, 153045, Russia.
E-mail address: Ilya.Khodov@gmail.com (I.A. Khodov).

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