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Detailed NOESY/T-ROESY analysis as an effective method for eliminating spin diffusion from 2D NOE spectra of small flexible molecules

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ABSTRACT

An intriguing property of the multistep magnetization transfer, so-called spin diffusion, is that it can affect the results of NMR-based analysis of conformer distribution of small molecules in solution. Therefore, the contribution of spin diffusion should be subtracted in order to obtain accurate data on molecular conformations and their distributions. Several methods have been developed for this purpose, but many of them have a lack of versatility. These methods were critically analysed, and two approaches to eliminate spin diffusion were tested during the study of felodipine as the drug molecule of small size. QUIET-NOESY was found to be a powerful technique to solve this problem. The second method, combined analysis of two sets of spectra, NOESY and T-ROESY, was tested and proved to be the most correct way of obtaining exact internuclear distances in a flexible molecule in solution.

1. Introduction

Nuclear Overhauser effect spectroscopy has become a powerful tool for determining conformations of both large [1,2] and small [3,4] molecules. NOE intensities, however, depend not only on distances between nuclei, but also on numerous factors, including fast and slow molecular motion, ability of free rotation of functional groups, etc. (various aspects of NOESY are described, for instance, in Ref. [5]). Obtaining internuclear distances as accurately as possible turns thus into a complicated problem requiring computer simulations of molecular flexibility and thorough analysis of experimental values of NOEs. One of the main sources of errors, spin diffusion, is considered; different approaches to eliminate its effect are tested in a study of a small drug molecule, felodipine.

Generally, observable properties of molecules undergoing fast conformational exchange can be represented as averaged values of corresponding parameters of individual conformers. In the case of NMR, this applies for chemical shifts and cross-relaxation rates. It is possible to reveal the amount of different conformers in solution, if sufficient experimental data on chemical shifts and/or NOE intensities have been obtained and the properties of individual conformers are known (e. g., from quantum chemistry calculations). The accuracy of estimates of the fractions depends on the dispersion of properties of the conformers (the more the dispersion, the easier to distinguish between them) and on the accuracy of the measurements. While the difference between individual structures is determined by the investigated object itself, a researcher can make effort to improve the measurement accuracy.

NOESY allows determination of atom–atom distances up to 5 Å, and thus gives direct information about spatial structure of a molecule. However, the distance range accessible to this method (from 2 to 5 Å) is relatively small, and typical distance error of 0.1–0.2 Å affords obtaining reliable results only in the case of macromolecules, when a large set of internuclear distances is measured and analysed simultaneously.

Low-molecular-weight compounds require a thorough measurement and analysis of NMR data. Spin diffusion is a phenomenon which can impede distance measurements. This effect occurs when the spin magnetization is transferred through intermediate nuclei, and becomes prominent at long mixing times. The indirect

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