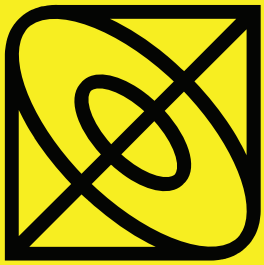

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# Abstract Book

# Spatial structure and conformational state of small flexible molecules by 2D NOESY

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Obtaining information about the structure of small molecules is quite an important task for the pharmaceutical sciences. A special problem is the study of small flexible molecules in liquid state. We can obtain information on both the spatial structure of molecules and the conformational distribution of small flexible molecules using nuclear Overhauser effect spectroscopy (NOESY) and internuclear distances. However, to solve this problem in the case of flexible molecules of drug compounds, some important precautions should be taken. First, correct averaging of interproton distances allowing for the type of intramolecular mobility should be made. Then, eliminating the influence of the spin diffusion effect on obtained NMR experimental data is important to obtain accurate results. In this report, we consider a number of small pharmaceutically active molecules. NMR approaches will be demonstrated which can be used for suppressing spin diffusion and averaging inter-proton distances.

NOE cross-relaxation rates are related to an efficient distance between interacting nuclei, which can be calculated from the distance characterizing individual conformers in different ways, depending on the rate of the conformer exchange [1]. Slow processes such as benzene ring flipping can be interpreted in terms of $\langle r^{-6} \rangle$ averaging; in the case of fast motions, $\langle r^{-3} \rangle$ averaging is a good choice. The most comprehensive formula was introduced by Tropp [2] and can be applied for rotating methyl groups.

Not all nuclei pairs, however, are convenient for use in NOESY analysis. Conformer fractions calculated based on different pairs may be ambiguous if some of them are prone to spin diffusion – process of indirect magnetization transfer in a spin system. This factor may be noticeable even in experiments with small-molecular-weight compounds [1, 3, 4]. To diminish its influence, either advanced experimental techniques or interpretation protocols should be used.

Example of the first approach is a study of ibuprofen (in saturated solution in $CDCl_3$) by the QUIET-NOESY method [1], which revealed a discrepancy in conformation equilibrium calculated from standard NOESY approach which disappears when a section for eliminating spin diffusion is introduced in the pulse sequence. Another method, based on comparison of two sets of spectra, NOESY and T-ROESY, and independent estimate of local correlation times, was applied to felodipine (in diluted solution in DMSO) [3] to establish its conformer distribution.

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