Kazan Federal University
Zavoisky Physical-Technical Institute
Institute of Perspective Research
Tatarstan Academy of Sciences
Russian Foundation for Basic Research
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ACTUAL PROBLEMS OF MAGNETIC RESONANCE AND ITS APPLICATION

XIX International Youth Scientific School

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KAZAN

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Kazan
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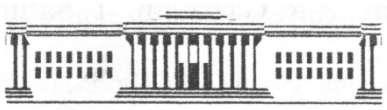

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Conformational NMR analysis of small flexible molecules by 2D NOESY

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In recent decades two-dimensional NMR spectroscopy has been showed to be a useful technique for the spatial structure determination of small flexible molecules [1,2]. Knowing the conformational state of small drug molecules, is important to considering the phenomenon of polymorphism [3,4]. Information on the conformation distribution in saturated solutions can facilitate our understanding of the mechanisms of nucleation of a given crystalline form of the studied compound. NMR spectroscopy has become the leading method in the field. There are several spectroscopic ways to obtain information on the preferred conformation of small molecules. The first way is the analysis of NMR lineshapes or measuring integral intensities from two different conformers of a small molecule at a low temperature.[5-7]. The ain restriction of this approach is the fact that conformational preferences may be different at various temperatures. This approach is useful only for conformers with a significant difference in their energies. The second way is to analyze the ^{1}H-^{1}H scalar coupling constants ($^{2}J_{HH}$ and $^{3}J_{HH}$) to obtain the configuration of pairs of geminal and vicinal protons.[8]. The value of this constant provides detailed information on the orientation and dihedral angle between the two hydrogen atoms. However, it deals with one-dimensional ^{1}H NMR spectra which usually do not allow to observing observe NH and OH groups. The third way is based on the residual dipolar coupling (RDC) effect. It is observed if the molecules in solution exhibit a partial alignment in anisotropic media. The resulting RDC values are used in determination of proton dipole-dipole interaction. This approach is less sensitive to small population changes.[4]. The best way of structure determination of small molecules is the nuclear Overhauser effect spectroscopy (NOESY) analysis. It was shown by Craig Butts [1-3] and others that the NOESY technique yields reasonably accurate interproton distances (with the relative inaccuracy of several per cent) for small organic molecules, as exemplified on strychnine – the model compound for NMR studies. Note that this method is readily applied only for rigid molecules, and special precautions should be made when studying compounds with fast conformational exchange. Intramolecular mobility should be taken into account and effective (mean) internuclear distances should be correctly found. Moreover, the influence of spin diffusion (relayed magnetization transfer) should be considered for in studies of small flexible molecules because it can distort the results noticeably. These techniques were critically analysed, and two methods were tested during the study of felodipine as the drug molecule of small size. 2D QUIET-NOESY was found to be a powerful technique to the conformational preference determination. The second way, combined analysis of two sets data of spectra, NOESY and T-ROESY, was tested and proved to be the most correct way of obtaining conformational preference for the flexible molecule in solution.

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