Kazan Federal University
Zavoiskii Physical-Technical Institute
Russian Academy of Sciences
Bruker Ltd (Moscow)
"Dynasty" Foundation
Russian Foundation for Basic Reserch

ACTUAL PROBLEMS OF MAGNETIC RESONANCE AND ITS APPLICATION

XVI International Youth Scientific School

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KAZAN

Program
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Preferred conformation of ibuprofen in chloroform by 2D NOESY

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Determination of spatial structure and conformational state of biologically active molecules attracts an increasing interest today [1–3]. Polymorphism of drug compounds is known to affect their biological activity, and thus it plays an important role in the production of pharmaceuticals. In turn, properties of a polymorph depend on the structure of the molecules and their ability to exist in different conformations in a solvent from which recrystallization is conducted. For this reason, seeking for new polymorphic forms of drugs is closely related to investigations of conformational state of biologically active molecules in saturated solvents.

In this work, we determined the preferred conformation among known structures A–H (fig. 1) and parameters of conformational equilibrium of ibuprofen in chloroform by two independent methods: nuclear Overhauser effect spectroscopy (NOESY) and comparison of ^{13}C NMR data with quantum chemical calculations [1–3]. Observed 13C NMR chemical shifts were in qualitative agreement with conformers G and H dominating in solution. The

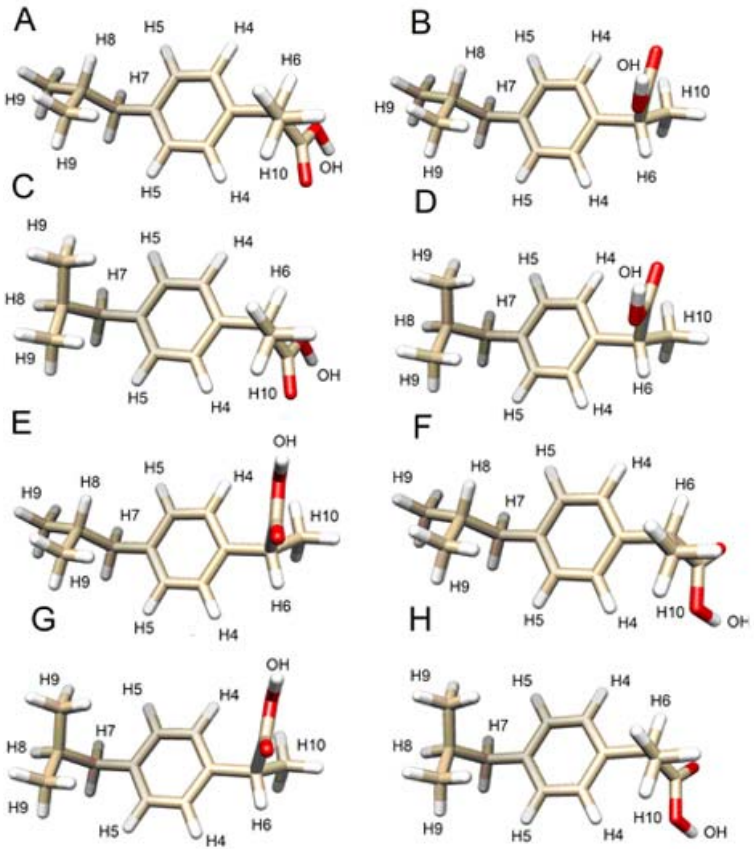

Fig.1. Main possible conformation of (*R*)-ibuprofen, according to the quantum chemical calculations [4].

choice of solvent was justified by high solubility of ibuprofen in $CHCl_3$ and practical significance of this solvent in the recrystallization process. Information on the distribution of conformers at maximal solution saturation may be used in studying processes of crystal nucleation from the solvent. Results of our experiments were also analyzed in the light of literature data, obtained by other methods.

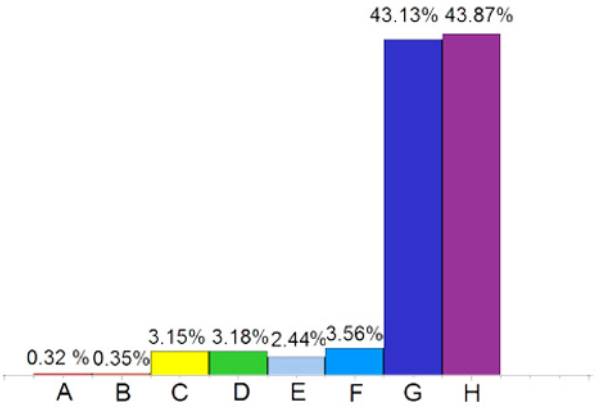

Fig.2. Distribution of ibuprofen conformers in the saturated solution by 2D NOESY analysis.

We proposed an approach to establish conformational state (preferred conformers) of small molecules in solutions, close to saturation, using the ibuprofen–chloroform system as an example. It was revealed by two independent methods that conformers G and H dominate in the saturated solution (fig. 2).

More accurate quantitative data on the distribution of conformers were obtained with the aid of the advanced analysis approach (ridge-regression analysis). An inversion-like change in the distribution was found upon transition from an unsaturated solution to the saturated one (fig. 3). Comparison of results of NOESY and X-ray data was used to demonstrate the importance of knowledge of preferred conformers in solutions: two different polymorph modifications are close to the structures which turn to dominate under different conditions in solution. On the present stage, however, we cannot determine relations between

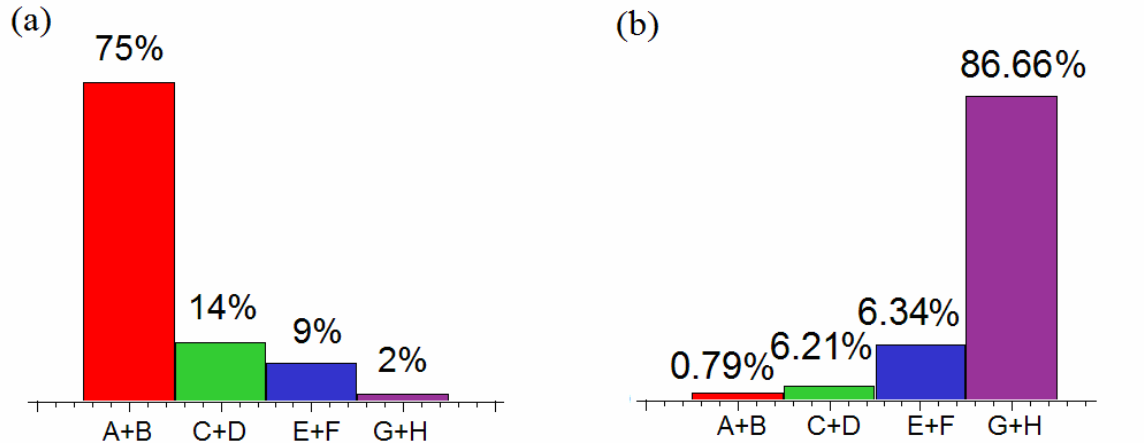

Fig.3. Distribution of ibuprofen conformers obtained from (a) quantum chemical calculations [4] and (b) analysis of 2D NOESY spectra in saturated $CDCl_3$ solution.

conformational state in solution and molecular structure in a given crystalline polymorph, since more detailed analysis of screening and X-ray data [5] for a crystal grown from chloroform are needed. (Literature data used here refer to a crystal grown from another solvent.) We hope that our general approach may help to shed light on fundamental laws regulating nucleation of crystalline polymorphs of other compounds.

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