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BOOK OF ABSTRACTS

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The conformational manifolds of drug-like molecules as studied in combination of experimental and computational techniques

M. Kiselev[1], I. Khodov[2], M. Nikiforov[2] , R. Oparin[2] , A. Frolov[2] , A. Agapov[2,3] and A. Idrissi [3]

[1] *Institute of solution chemistry of the RAS, Akademicheskaya st.1, 153045, Ivanovo, Russia, mgk@isc-ras.ru*
[2] *Institute of solution chemistry of the RAS, Akademicheskaya st.1, 153045, Ivanovo, Russia*

[3] *Laboratoire de Spectrochimie Infrarouge et Raman (UMR CNRS A8516), Université des Sciences et Technologies de Lille, 59655 Villeneuve d'Ascq Cedex, France*.

ABSTRACT

All drug-like molecules are conformationally flexible and theirs physico-chemical properties critically depend on population of conformations. These conformations may determine the polymorphic forms, which appear as result of nucleation of crystal from liquid solutions. Therefore the study of conformational manifolds of drug-like molecules is important for pharmaceutical chemistry. However, there are only few publications in the literature where this problem has been considered. The main reason is the residence time of conformations which is around of 10^{-12} – 10^{-7} sec and, therefore, experimental techniques (NMR, infra red spectroscopy) give a smeared picture that is difficult to resolve from the point of view the contribution of different conformations. The computational methods, in turns, either don't take into consideration solvent at molecular level (quantum chemical calculations) or use an effective potential, so the electronic structure is assumed to be constant for whole simulation. In order to overcome these problems, we apply several techniques for the study of conformational manifolds in this work. The results of the simulation of paracetamol - dimethylformamide mixture by molecular dynamics, quantum chemical calculations and metadynamics will be discussed in this presentation. The intermolecular interactions are described in the frame of a "force field" approximation. We compared three well known force fields in this work: OPLS-AA (optimized molecular potential for liquid simulations) [1], GGenFF(charmm general force field) [2], GAFF (general amber force field) [3]. The method of metadynamics has been used for effective sampling of conformational manifold. As for the experimental methods, 2-D NMR and infrared spectroscopy approaches were used for the study of the conformations. The NOESY(NMR) method estimating of internuclear distances for various pairs of protons in a molecule is based on the existence of a strong dependence of the cross-relaxation rate constant σ_{ij} on the distance r_{ij} between the interacting nuclear spins. The reason for combination of several computational and experimental techniques for the study of the conformations will be discussed in the presentation.

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REFERENCES

[1] 1. Jorgensen W.L., Maxwell D.S., Tirado-Rives J., *J. Am. Chem. Soc.* **1996**, 118 (45), 11225–11236
2. Vanommeslaeghe K. Et al., *J. Comput. Chem.* **2010**, 31(4), 671-90.
3. Wang J., Wolf R.M., Caldwell J.W., Kollman P.A., Case D.A. *J. Comput. Chem.* **2004**, 25(9), 1157-74.