STUDY OF NSAIDS MOLECULAR DYNAMICS BY INELASTIC NEUTRON SCATTERING AND COMPLEMENTARY METHODS

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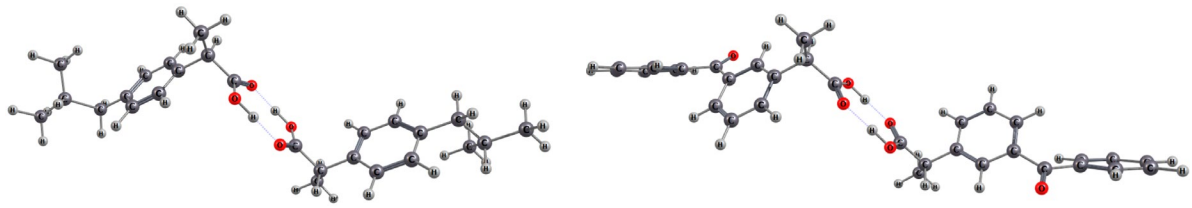
Ibuprofen and ketoprofen are well-known NSAIDs (propionic acid derivatives) that inhibit cyclooxygenase-II. They contain a chiral center and are used clinically as racemates, although only the S-enantiomers are biologically active (the R-forms are converted in vivo to S-enantiomers). Chemical structures of ibuprofen and ketoprofen include three key fragments: a hydrophilic carboxyl group, an aromatic ring, and a hydrophobic alkyl or keto-aryl substituent. Lability of these fragments will be one of the main factors ensuring dynamic complementarity in the formation of a complex with an enzyme. Combining experimental and computational methods for drug characterization is now common practice, but the choice of structural model critically affects result interpretation. Previous IR, Raman, and molecular modeling studies [1, 2] showed good correlation for most spectral parameters; however, data on carboxyl group vibrations remain inconsistent.

Here we report on the intra- and intermolecular dynamics of racemic ibuprofen and racemic ketoprofen using a combination of experimental methods: IR, Raman, and inelastic neutron scattering (INS) spectroscopy, complemented by DFT molecular modeling at the BP86/def2-TZVP level of theory. INS measurements were performed on the NERA spectrometer at the IBR-2 reactor (JINR, Dubna) over a temperature range of 5–200 K. The INS technique provides unique access to low-frequency vibrational modes, with spectra dominated by hydrogen atom motions and free from optical selection rules, thereby offering critical information that complements optical spectroscopy.



a b

Figure 1 – Equilibrium geometries of cyclic S-R dimers of ibuprofen (a) and ketoprofen (b), obtained at the BP86/def2-TZVP level of theory.

For computational modeling, cyclic dimers were used as a small-cluster representation of the ibuprofen and ketoprofen structures (Fig. 1), explicitly accounting for intermolecular hydrogen bonds. DFT calculations of vibrational frequencies based on these dimer models yielded good correlations with experimental data for both compounds. Key vibrational frequencies of the carboxyl group were identified, which can serve as reliable markers for investigating the molecular dynamics of these NSAIDs.

[1] K. Logacheva (2024). Vibrational spectroscopic features of ibuprofen and ketoprofen: IR and Raman spectroscopy combined with DFT calculations. Part. Nuclei Lett. 21, 839-842.
[2] P. Gergelezhiu (2025). Structure and Dynamics Investigation of Ibuprofen Dimers by DFT MethodPhys. Part. Nuclei Lett. 22, 1102-1105.