

Summary of the doctoral dissertation entitled „**The role of hydrogen bonding in determining stability of biologically active compounds: molecular modelling and experimental studies**”

This doctoral dissertation consists of five thematically related research articles (**P1–P5**) and investigates the role of hydrogen bonding in determining the stability of selected biologically active compounds, such as uracil and cannabidiol (CBD), and their complexes with water molecules. The study employed an approach combining various computational methods including quantum-chemical calculations (DFT, MP2, and CCSD(T)) with Molecular Dynamics (MD) simulations, which enabled the determination of key hydrogen bond parameters, identification of the most stable conformations and water complexes, and estimation of hydrogen bond energy. Experimental studies using Fourier-Transform Infrared (FT-IR) and Nuclear Magnetic Resonance (NMR) spectroscopy complemented the computational results.

Studies on uracil–water complexes (**P1**) revealed that, in addition to the well-known five arrangements with single or double hydrogen bonds, two less stable complexes exist, bonded by a single hydrogen bond, representing shallow energy minima. These complexes are not visible in FT-IR spectra but significantly expand the understanding of nucleobase–water interactions.

In the next study (**P2**), it was shown that hydrogen bond strength in uracil and *N*-methylacetamide (NMA) complexes with water depends on the inclusion of dispersion corrections and solvent polarity, highlighting the importance of precise modeling of hydrogen-bond interactions.

A methodological study (**P3**) demonstrated that accurate NMR parameter calculations for 2-thiouracil and third-period hydrides require appropriate basis sets and vibrational corrections. These methods were subsequently applied to bioactive compounds, improving the reliability of spectroscopic predictions.

FT-IR and NMR studies on weak hydrogen bonds in CBD (**P4**) showed that one hydroxyl group is free while the other participates in intramolecular hydrogen bonding, affecting characteristic vibrational bands and proton chemical shifts. These observations agree with theoretical data showing that the dominant conformer is stabilized by an intramolecular O–H··· π hydrogen bond. It underlines the role of intramolecular hydrogen bonding in shaping the spectroscopic properties of bioactive compounds.

Quantum-chemical DFT calculations (**P5**) revealed that the diequatorial CBD conformer is the most stable, stabilized by an O–H $\cdots\pi$ intramolecular hydrogen bond. MD simulations confirmed the presence of this stable conformer and further showed that in aqueous environments, only one hydroxyl group is partially solvated while the other is stabilized by intramolecular hydrogen bonding. This limited availability promotes CBD aggregation and explains its low solubility, despite the presence of polar groups.

The dissertation concludes that hydrogen bonds are decisive not only for molecular stability but also for solubility and aggregation behavior. The balance between intramolecular and intermolecular interactions determines molecular bioavailability, providing important guidance for the design of pharmaceutical drugs and other bioactive compounds, where hydrogen bonds play a key role in shaping biological properties.