Intermolecular hydrogen bonds studied by NMR spectroscopy

Hydrogen bonds (H-bonds) play a crucial role in many chemical and biological processes. The H-bond is a bond between an electron-deficient hydrogen (donor) and a region of high electron density (acceptor). The donor/acceptor character of a functional group can be interchanged by two common processes: tautomerism and (de)protonation. We propose to exploit the H-bond donor/acceptor switching for the determination of free energy of binding between natural and modified nucleobases, for the design of molecules working as H-bonding sensors and promiscuous H-bonding partners. These H-bonding "chameleons" can work e.g. as universal nucleobases binding non-selectively with natural nucleobases, or as small molecules binding to multiple targets. The ultimate goal of the project is to understand better the H-bonding interaction of biomolecules and how they can be controlled by structural and environmental changes.

One example of the investigated phenomena is the protonation of nucleic-acid bases, which is an extremely important structure-controlling and regulation mechanism. It has been shown that although free nucleobases are neutral at physiological pH, intermolecular interactions can stabilise the (de)protonated forms (with the pK_A values shifted by several units). The protonated forms participate, for example, in the formation of triple-stranded DNA, in the catalytic function of RNA enzymes, in the stabilisation of RNA loops or in various pathological processes. Intermolecular H-bonding interactions increase the stability of the (de)prtonated structures with the hydrogen-bonding pattern that participates in the intermolecular binding. This is ilustrated in Figure 1, where we show schematically the expected dependence of NMR chemical shifts on pH of free nucleobases and of nucleobases in the presence of a suitable H-bonding partner. The experimentally observed change of the pK_A value will be used for the calculation of the free energy change associated with the intermolecular binding.

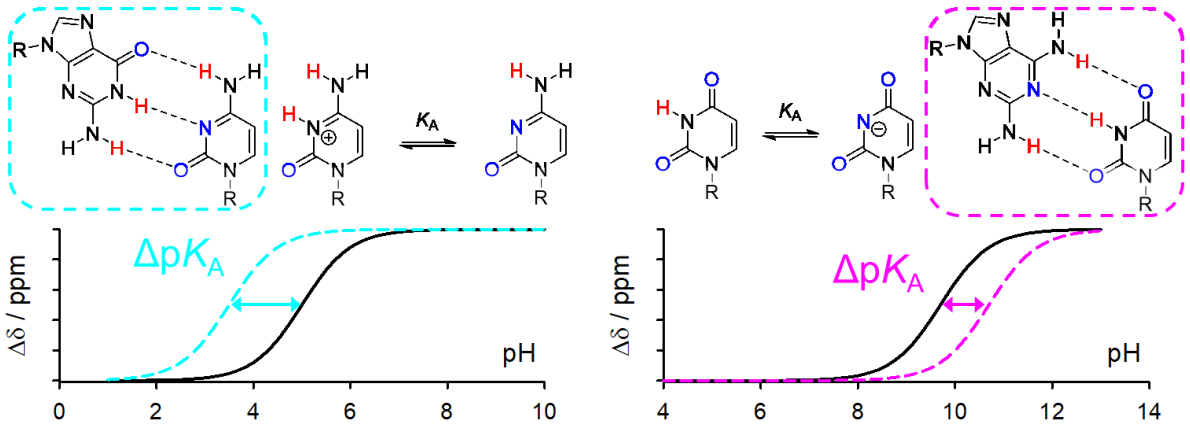

Figure 1. Left: The expected chemical-shift dependence on pH of a free cytosine derivative (black line) and of cytosine in the presence of a guanine derivative (blue dashed line). Right: The expected chemical-shift dependence on pH of a free uracil derivative (black line) and of uracil in the presence of a 2,6-diaminopurine derivative (pink dashed line).

The aim of the PhD project is to bring new information about intermolecular H-bonding of biologically important molecules and about structural adaptations induced by a binding partner capable of H-bonding. A methodology based on NMR experiments for the determination of free energy changes upon hydrogen bond formation will be developed. The student will investigate, for example, H-bonding interactions between modified bases of nucleic acids. The model compounds will be synthesised in collaborating IOCB labs. The experimental data will be supported with DFT calculations of complexation energies and NMR parameters.