Universität Basel

Research Project

Carbohydrate mimics for therapeutic applications: exploring their conformational preference in the gas and micro-hydrated phases.

Third-party funded project

Project title Carbohydrate mimics for therapeutic applications: exploring their conformational preference in the gas and micro-hydrated phases.
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Carbohydrate mimics for therapeutic applications: exploring their conformational preference in the gas and micro-hydrated phases. Martin Smieško, Oliver Schwardt, Pierre Çarçabal Carbohydrates, along with nucleic acids and proteins, are ubiquitous structural biopolymers in living organisms. Small carbohydrates – particularly oligosaccharides – are directly linked to metabolism and biosynthesis while polysaccharides serve as the energy reserve for living cells. In the human body, carbohydrates play an important role in immune response, infection and inflammation, tumor metastasis, angiogenesis, cell growth, proliferation as well as cell-to-cell communication. They are also involved in the post-translational modification of proteins (Varki 2009). As strongly polar molecules, carbohydrates are capable of displacing water molecules from the molecular surface of receptors, and even mimicking water's hydrogen bonding properties, thus acting like preorganized water oligomers. Complex structure, high flexibility of glycosidic linkages, high proportion of polar groups, weak binding affinity and polyvalency, and, last but not least, complicated synthesis: all these elements made carbohydrates historically considered as non- or hardly "drugable" molecules. However, recent developments provide evidence, that carbohydrate mimics have a huge potential in many therapeutic areas (Ernst 2009), taking advantage of their extraordinary properties of molecular recognition. In medicinal chemistry, knowledge of the bioactive conformation and stability of a compound of interest is the key prerequisite for successful lead optimization. Even if it is nowadays possible to identify global and local minima for moderately sized carbohydrates, information about the stability and biological relevance of particular conformations is far from being exhaustive. Carbohydrates, rich in hydrogen bond donors and acceptors have an option to stabilize their conformation by creating a network of intramolecular hydrogen bonds, however, most of those donors and acceptors are water exposed, therefore experiencing a strong competition from the surrounding water molecules. As a consequence, water plays a central role in the binding process of a carbohydrate and its target biomolecular receptor. The energetic balance between the desolvation of the carbohydrate and/or the receptor directly affects the free energy of carbohydrate-receptor complex formation and thus co-determines whether such a molecular association will take place efficiently enough to guarantee some biologically relevant response. Moreover, due to specific interactions water molecules may 'sculpt' the carbohydrates to restrain their conformational lansdcape or promote specific conformations, 'tailor made' to optimize the activity of the biomolecule. The methods and research tasks included within this project proposal aim at exploring the solvation effects on the carbohydrate 3D structure at the atomic level. Gas phase laser spectroscopy in combination with ab initio quantum chemical calculations

can provide unique information about the 3D structure of completely or partially desolvated molecular species, which if compared to bound (X-ray crystallography) or solvent-phase conformation (NMR, MD simulations) could significantly improve our insight into the forces driving preferred carbohydrate conformations, along with nature and extent of their stabilization and decode essential as well as modifiable structural features of carbohydrates.

Keywords chemical synthesis, carbohydrate, solvation effects, spectroscopy, quantum chemical calculations, conformation
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