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Structure and spectroscopy of E and Z isomers of Boc-Gly-ΔPhe-NHMe

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Biological activity of numerous small size molecules is directly related to their conformational properties. It is possible to control pharmaco-kinetic properties of naturally occurring peptides by introduction of nonstandard amino acid residues into their backbone chain which can result in analogues with improved pharmacological properties, such as resistance to enzymatic degradation, receptor selectivity, enhanced potency and bioavailability. For example, it is possible to introduce a dehydroamino acid residue and forcing a specific conformation of the chain fragment. Conformational properties of N-t-butoxycarbonyl-glycine-(E/Z)-dehydrophenylalanine N'-methylamides (Boc-Gly-(E/Z)- ΔPhe-NHMe) in chloroform were studied by NMR and IR spectroscopy. The low temperature crystal structure of the E isomer was determined by single crystal X-ray diffraction. The experimental findings were supported by extensive calculations at DFT (B3LYP, M06-2X) and MP2 levels of theory and the β-turn tendency for both isomers of the studied dipeptide were determined in vacuum and in solution. The obtained results reveal that the configuration of ΔPhe residue significantly affects the conformational properties of studied dehydropeptides. Theoretical conformational analysis reveals that the tendency to adopt β-turn conformations is much weaker for the E isomer (Boc-Gly-(E)-ΔPhe-NHMe), both in vacuum and in polar environment. We also showed a very good agreement between theoretical chemical shifts and calculated ones by using newly introduced relatively small and computationally inexpensive STO-3G_{mag} basis sets. The obtained results suggest a possibility of controlling dipeptide conformation by a simple chemical modification and thus allowing a future rational design of peptidomimetics.

Figure 6 The different conformations adopted by Boc-Gly-(Z)-ΔPhe-NHMe (a) and Boc-Gly-(Z)-ΔPhe-NHMe (b) isomers in their crystal structures. The dotted green lines represent intermolecular hydrogen bonds interactions (hydrogen atoms have been omitted for clarity).

Recent Publications

1. Bock J E, Gavenonis J and Kritzer JA (2013) Getting in shape: controlling peptide bioactivity and bioavailability using conformational constraints. ACS Chemical Biology. 8(3):488-499.
2. Crisma M et al. (2015) Handedness preference and switching of peptide helices. Part II: helices based on noncoded α-amino acids. Journal of Peptide Science. 21(3):148-177.
3. Siodłak D (2015) α,β-Dehydroamino acids in naturally occurring peptides. Amino Acids. 47:1-17.
4. Buczek A et al. (2014) Toward engineering efficient peptidomimetics: screening conformational landscape of two modified dehydroamino acids. Biopolymers. 101(1):28-40.
5. Buczek A, Wałęsa R and Broda MA (2012) β-turn tendency in N-methylated peptides with dehydrophenylalanine residue: DFT study. Biopolymers. 97(7):518-528.

Biography

Małgorzata A Broda is working as a Professor at Faculty of Chemistry, University of Opole, Poland. She has her expertise in molecular modeling and characterization of amino acid structure, electronic and spectroscopic properties. Her open minded approach to find energetic landscape of small, flexible biologically active molecules combines both theoretical prediction and experimental X-ray, NMR and IR studies. This results in wide interests about her research topic between other research groups and students. Her teaching of theoretical chemistry and spectroscopy at the University motivates several students to pursue the path of scientific carrier.

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