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Extended Abstract

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

Małgorzata A Broda, Teobald Kupk and Aneta Buczek, University of Opole, Poland

E-mail: broda@uni.opole.pl

Conformational propensities of N-t-butoxycarbonyl-glycine-(E/Z)-dehydrophenylalanine N′-methylamides (Boc-Gly-(E/Z)-ΔPhe-NHMe) in chloroform were investigated by NMR and IR techniques. The low-temperature crystal structure of the E isomer was determined by single crystal X-ray diffraction and the experimental data were elaborated by theoretical calculations using DFT (B3LYP, M06-2X) and MP2 approaches. The β-turn tendencies for both isomers were determined in the gas phase and in the presence of solvent. The obtained results reveal that the configuration of ΔPhe residue significantly affects the conformations of the studied dehydropeptides. The tendency to adopt β-turn conformations is significantly lower for the E isomer (Boc-Gly-(E)-ΔPhe-NHMe), both in gas phase and in chloroform solution. 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 could produce derivatives showing more desired pharmacological properties, for example, resistance to enzymatic degradation, receptor selectivity, enhanced potency, or bioavailability. For example, it is possible to introduce a dehydroamino acid residue and forcing a specific conformation of the chain fragment.

α,β-Dehydroamino acids are non-coded amino acid in which the Cα = Cβ bond freezes the χ1 torsion angle and sets the β-substituents in Z or E position. Both isomers of the dehydroresidues occur in nature and they often exhibit different biological properties. α,β-Dehydropeptides are more stable and resistant toward proteolytic degradation and thus could be used to design synthetic analogs of biologically active peptides. According to the literature on α,β-dehydropeptides, the (Z)-dehydrophenylalanine is the most often studied residues. It is known that (Z)-ΔPhe residue stabilizes β-turns in short peptides and 310 helix in longer ones. The conformational profile of the isomer E is much less recognized. According to literature data, (E)-ΔPhe adopts in its crystal structure the β (ϕ, ψ ~ −42°, 124°) conformation or the helical αL (ϕ, ψ ~51°, 49°) one. In non-polar solvents, the extended conformer C5 (ϕ, ψ ~ − 179°, 162°) can be also found [21]. Spectroscopic and theoretical investigations of dehydropeptides analogs with E or Z isomers of dehydroamino acid residues in peptide chain suggest their different conformational preference in solution has different conformational preferences in solution.

Our DFT study on Ac-Gly-(E/Z)-ΔPhe-NHMe pointed out that (E)-ΔPhe has strong tendency to adopt the extended conformation while the Z isomer of Ac-Gly-ΔPhe-NHMe has the disposition to occur in the gas phase as type II and in solvents as type I β-turn conformation. However, the dihedral angles ϕ1, ψ1, and ϕ2, ψ2 are uncommon in standard amino acids.

The aim of the current study is to support the above theoretical results by experimental data. We were interested in determination of the impact of dehydrophenylalanine configuration on the formation of β-turn by the peptide backbone. Thus, we report on the single crystal X-ray study of E isomer of N- and C-protected dipeptide Boc-Gly-ΔPhe-NHMe. In addition, we conducted spectroscopic (FTIR and NMR) conformational research for both E and Z isomers and detailed theoretical analysis. The molecular structure of Boc-Gly-(E)-ΔPhe-NHMe. The majority of dimensions of the studied compound are, in principal, in agreement with related compounds. There are, however, some differences, due to different intra- and intermolecular interactions. The torsion ϕ1, ψ1, ϕ2, ψ2 angles for Boc-Gly-(E)-ΔPhe-NHMe are 100.33(12)°, 173.32(9)° (Gly), − 23.38(15)° and − 73.51(12)° (E-ΔPhe). The opposite –ϕ and –ψ angles were also found for the corresponding symmetry-related molecules. Apart from ϕ2, torsion C3-N2-C2-C21 (158.70(10)°), N2-C2-C21-C1P (173.53(11)°), and C2-C21-C1P-C2P (179.21(11)°) show that phenyl ring, C2 = C21 double bond, and N-terminal amide are basically coplanar indicating possible extended π-electron conjugation, whereas the C-terminal amide group is in perpendicular position resulting from a steric hindrance imposed by the phenyl ring at E position.

For Z analogue Boc-Gly-(Z)-ΔPhe-NHMe [52], the torsion ϕ1, ψ1, ϕ2, ψ2 angles are 57.2(6)°, − 141.2(4)° (Gly), − 71.5(6)°, and − 7.2(6)° (Z-ΔPhe), respectively. The values of torsion ϕ2, ψ2 indicate that C-terminal amide bond is coplanar with double bond and phenyl ring, and due to steric crowding imposed by the phenyl ring at the position Z, the N-terminal amide group is perpendicular to this molecular fragment. As a result, the perpendicular position of the N-terminal amide group enables formation of intermolecular N–H···O hydrogen bonds. As can be seen, position of the phenyl ring in space, Z or E, changes the conformation of the ΔPhe residue and influences the intermolecular pattern of hydrogen bonds interactions. It also has a profound effect on the torsion angles of neighboring Gly residue, and in consequence, on the whole molecular conformation.

Bottom Note: *This work is partly presented at 5th International Conference on Physical and Theoretical Chemistry*