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Journal of Molecular Structure: THEOCHEM 812 (2007) 25–37

THEO CHEM

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Molecular properties of a representative glycine-rich sequence of elastin – BocVGGVGOEt: A combined FTIR experimental and quantum chemical investigation

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Received 25 November 2006; received in revised form 8 February 2007; accepted 9 February 2007
Available online 20 February 2007

Abstract

The intriguing relationship between molecular geometry and the vibrational frequencies of the protected BocValGlyGlyValGlyOEt peptide has been studied by density functional calculations and FTIR spectroscopy. B3LYP/6-31G* data show several folded structures stabilised by labile intramolecular hydrogen bonds, lying very close in energy. The great fluxionality of the peptide chain has been ascribed to the low steric encumbrance of the substituents in the C_α of glycine residues. In any case, the most stable conformations involve large pseudocycles (C13 or C14), H-bonded with the carbonyl of terminal groups (urethane or ester). FTIR spectra of the NH and ND isotopomers of the BocValGlyGlyValGlyOEt peptide recorded in the solid state and in solution of chloroform, trifluoroethanol (TFE), or dimethyl-sulfoxide (DMSO) have been interpreted using B3LYP data as well as FTIR data of closely related molecules. The frequency and intensity of normal modes associated with *v*C=O and *v*N–H stretching are modulated by hydrogen bonding thus providing a direct correspondence with the given structures. FTIR data in the solid state support a single folded structure stabilised by intramolecular hydrogen bonding and by electrostatic interactions with surrounding peptides. Experimental data in $CHCl_3$ and TFE solutions also support intramolecular hydrogen bonding. However, the concomitant presence of various folded structures in rapid equilibrium hampers a good separation of bands. Conversely, the substantial hydrogen bonding between >N–H groups of the peptide and DMSO solvent molecules seems to favour an extended structure.

Keywords: Peptide conformation; Hydrogen bond; DFT; Vibrational frequencies; FTIR

1. Introduction

Considerable scientific interest in polypeptides is currently fuelled by the desire to rationalise the conformation and function of the parent proteins. Peptides show rich variegate structural features (extended, α-helices, 3_{10}-helices, β-turns, etc.) depending on the nature of their amino acid components. Almost all spectroscopies have been largely applied to gain information about chain conformations, both in solution and solid state, and thus a considerable body of empirical structure-spectroscopic parameters correlation has been established [1–7]. Nevertheless, an exhaustive understanding of the relationship between the structure and spectroscopic properties is far from being accomplished. In this regard, electronic structure studies can be of great relevance to the structural biochemistry community in providing complementary and independent information on stability, geometry, and several spectroscopic parameters.

Polypeptide sequences of the type "YGlyGlyZGly" (Y, Z = Val, Leu, or Ala) frequently repeat themselves in elastin, the protein that provides elasticity in vertebrates [8]. These peptides exhibit conformations that are strongly dependent on the physical state and on the nature of the solvent in which they are dissolved [9–11]. Indeed, various kinds of β-turns, half turns, polyprolines II, and extended

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doi:10.1016/j.theochem.2007.02.019

structures have been proposed. The large variety of possible structures prompted us to investigate molecular properties of the representative BocValGlyGlyValGlyOEt peptide by a combined theoretical quantum chemical and experimental FTIR approach. Particular attention has been devoted to subtle details of hydrogen bond networks, which often determine conformation preference [12]. To this purpose, the geometry of a large number of conformers has been determined at the DFT-B3LYP level and computed vibrational frequencies have been compared with various experimental spectra recorded in the solid state and in different kind of solvents. This work builds upon ab initio calculations of the electronic structure of BocValGlyGlyValGlyOEt peptide combined with X-ray photoelectron spectroscopic (XPS) measurements (Fig. 1) [13,14].

2. Methods

2.1. Synthesis and FT-IR spectra

The synthesis of the protected peptide BocVGGVGOEt was described elsewhere [13]. The peptide was dissolved in deuterated water/DMSO solution, lyophilised and then dried in order to prepare the N-D isotopomer (BocVGGVGOEt-d_5).

IR spectra were recorded on a Jasco FT/IR 460 spectrophotometer, using a resolution of 2 cm^{-1} and 200 scans. The spectra were taken at room temperature in the solid phase (KBr pellet) and in $CHCl_3$, TFE and DMSO solutions (deuterated solvents were used for BocVGGVGOEt-d_5) using a cell with either CaF_2 or NaCl windows. The sample concentration was varied from 0.1% to 0.02% and no aggregation effects were observed. Because of the very low solubility in chloroform the spectra were recorded in a saturated solution using a 1 mm pathlength cell.

2.2. Computational details

Computations were performed at the density functional level employing the hybrid B3LYP functional and the 6-31G* basis set for all atoms. According to recent studies on various peptides, the B3LYP/6-31G* electronic structure approach is sufficient for taking into account structural, energetic and vibrational frequencies [15,16].

The geometries of all the structures involved were fully optimised using gradient techniques. The nature of the most stable stationary points was determined by evaluations of a hessian matrix and of the associated harmonic vibrational frequencies. The vibrational frequencies computed at the B3LYP/6-31G* level allows an exhaustive rationalisation of experimental FTIR spectra. All the calculations were performed using the Gaussian-03 program [17].

3. Results and discussion

3.1. Geometrical structure of BocVGGVGOEt

The BocVGGVGOEt molecule can adopt several conformations, depending on the formation of intramolecular hydrogen bonds between various >NH protons and carbonyl oxygens belonging to two distinct amino acid residues of the polypeptide backbone [12]. In the simplest case, the molecular chain assumes a linear disposition (extended, Z) with all torsion bond angles (ϕ_i, ψ_i, and ω_i) near to 180°. Alternatively, the BocVGGVGOEt molecule can adopt different types of helices (R_α, L_α, δ, 3_{10}, etc.) and several types of β-turns depending on the ϕ_i and ψ_i torsion angles. These conformers are all potential candidates as ground state of the BocVGGVGOEt molecule. However, a full characterisation of all minima on the Born–Oppenheimer surface is beyond the scope of the present investigation. Therefore, we limited our analysis to chemically significant cases:

(i) the right- and left-handed α-helices (R_α and L_α);
(ii) the types I and II β-turn conformations having V^1–G^2 at the corners;
(iii) the types I and II β-turn conformations having G^2–G^3 at the corners;
(iv) the β-turn types I and II conformations having G^3–V^4 at the corners.

Types I and II β-turn conformations defined on the portion V^4–G^5 cannot produce hydrogen bond enclosure

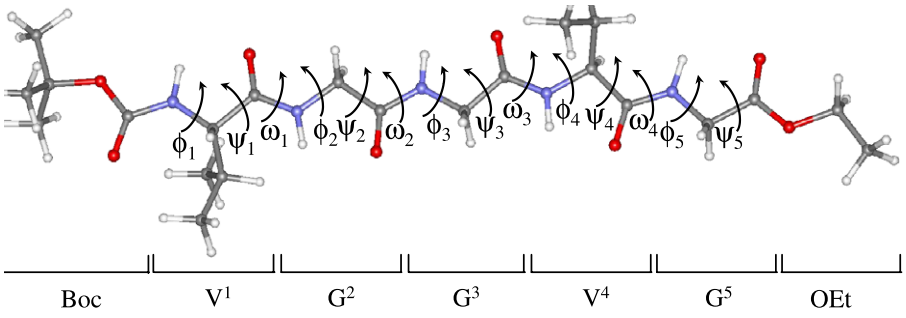

Fig. 1. Molecular structure of the extended, Z conformer of BocVGGVGOEt peptide and definition of dihedral angles.