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Conformational analysis and vibrational spectroscopic investigation of L-proline–tyrosine (L-Pro–Tyr) dipeptide

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ABSTRACT

In this study the conformational properties of the drug based dipeptide L-proline–L-tyrosine (Pro–Tyr) in its monomeric and dimeric forms, have been investigated by molecular mechanic and ab initio calculations. The energy calculations on Pro–Tyr dipeptide as a function of side chains torsion angles, enable us to determine their energetically preferred conformations. One-hundred and eight possible conformations of Pro–Tyr dipeptide have been investigated by conformational analysis and the low energy conformations of dipeptide have been determined by using the Ramachandran maps. Afterwards, the geometrical parameters of obtained stable conformations were used as starting parameters for quantum chemical calculations. The molecular structure of Pro–Tyr dipeptide, in the ground electronic state (in vacuum) was optimized by density functional theory method with B3LYP functional and using 6-31G(d,p) and 6-31++G(d,p) basis sets. The dimeric forms of the dipeptide were also formed and energetically preferred conformations of dimers were investigated using the same method and the same level of theory by using 6-31G(d,p) basic set. The fundamental vibrational wavenumbers, IR intensities and Raman activities of the global conformation of monomeric and dimeric forms of the dipeptide were calculated and compared with the experimental vibrational spectra of solid Pro–Tyr dipeptide. The total energy distributions (TED) of the vibrational modes were calculated by using Scaled Quantum Mechanical (SQM) analysis. Vibrational assignment was performed on the basis of calculated total energy distribution (TED) of the modes.

1. Introduction

Tyrosine is a non-essential amino acid which is found in almost all proteins in the body. It helps to regulate mood, stimulates the nervous system and support the formation of neurotransmitters including dopamine, norepinephrine and epinephrine. Tyrosine is involved in the synthesis of melanin which protects against the harmful effects of ultraviolet light [1] and, also been used for treatment of allergies, headaches and Parkinson's disease. Tyrosine is needed for normal functioning of the thyroid, pituitary, and adrenal glands. On the other hand proline is an amino acid which is needed for the production of collagen and cartilage, which are important for the formation of bone. It keeps muscles and joints flexible and helps reduce sagging and wrinkling. Pro–Tyr–NH_2 dipeptide is the simplest peptide analogs of sulpiride [2], which has antipsychotic properties. Despite of biological importance, to the best of our knowledge, no conformational analysis, or ab initio, DFT calculations have been reported yet for Pro–Tyr dipeptide, although there are a number of studies on tyrosine [3–5] and proline [6–13] amino acids. Proline mono peptide has particular rigid structure [6–13]; it has an imino group is fixed within a pyrrolidine ring, which makes proline conformationally less flexible, in comparison with most other amino acids. The conformational behavior of proline in the Pro–Tyr dipeptide, therefore, is thought to be interesting. Besides, the determination of conformational possibilities of L-Pro–Tyr dipeptide may be useful as a base for synthesis of its more effective structural analogs. In this study, conformational analysis, theoretical and experimental vibrational spectra of Pro–Tyr dipeptide in its monomeric and dimeric forms are reported for the first time.

2. Experimental and computational details

The Pro–Tyr dipeptide was purchased from GL-biochem Ltd., and used as received. The FT-IR spectrum of KBr disk of the dipeptide was recorded on a Jasco 300E FT-IR spectrometer in the range 400–4000 cm^{-1} with a resolution of 2 cm^{-1} based on averaging 200 sample and 30 background scans. The Raman spectrum of the sample was taken with a Jasco NRS-3100 micro Raman

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spectrometer (1800 lines/mm or 1200 lines/mm grating and high sensitivity cooled CCD). Sample was excited with a 531.96 nm diode laser. The Raman system was calibrated with a silicon semiconductor using the Raman peak at 520 cm^{-1}. A 20× microscope objective (Olympus) was used to focus the laser and collect Raman scattering on the sample. Spectral resolution was 3.9 cm^{-1} and 100 spectra were accumulated.

The conformational analysis was carried out by sequential method with combining all low energy conformations of constitutive residues and by using a program proposed by Godjaev et al. [14]. The low energy conformations of dipeptide have been determined by using the Ramachandran maps [15,16]. All the ab initio calculations are performed by using Gaussian 03 program [17] package. Due to success in calculating the electronic structure and energy, the calculations were carried out by using the hybrid density functional theory (DFT/B3LYP) method. For monomeric calculations both 6-31G(d,p) and 6-31++G(d,p) basic sets and for dimeric calculations only 6-31G(d,p) basis set were used. We could not use 6-31++G(d,p) basic set for the dimeric form due to inadequate capacity of our computer.

The total energy distribution (TED) of the vibrational modes of the molecules was calculated with the Scaled Quantum Mechanics (SQM) method by using the Parallel Quantum Mechanics Solutions (PQS) program [18].

3. Results and discussion

The Pro–Tyr dipeptide ($C_{14}H_{18}N_2O_4$) consists of 38 atoms, accordingly has 108 vibrational modes. The molecular model of the Pro–Tyr dipeptide is given in Fig. 1a.

In the first part of this study, the theoretical conformational analysis on Pro–Tyr dipeptide was carried out in order to determine its energetically preferred conformers. The stable conformations of the Pro–Tyr dipeptide were calculated by examination of all possible combinations of the local minima of the two amino acid residues. The starting structural approximations for this dipeptide were chosen with regard to the limitations associated with the Pro residue. The global conformation of Pro–Tyr dipeptide has been determined by using Ramachandran maps [15,16]. These maps have four regions (B, R, L and P) and the backbone rotations are characterized with φ and Ψ angles which values are restricted between +180° and −180°; B(φ = −180–0°, Ψ = 0–180°), R(φ, Ψ = −180–0°), L(φ, Ψ = 0–180°) and P(φ = 0–180°, Ψ = −180–0°). On the other hand, rotations of the side chains are determined with χ angles [19]. The possible extended or folded backbone conformations are named shape. The dipeptide shape is divided into two forms; folded (f) and extended (e). RR, RB, BP, LL, LP, LR, PB and BL forms produce (f) shape and BB, BR, RL, LB, LR, RP, PL and PP forms produce (e) shape of the dipeptides. In Fig. 1a, the backbone and the side chains angles of Pro–Tyr dipeptide, together with the atom numbering, used in DFT calculations, were given.

For Pro–Tyr dipeptide, the values of dihedral angles were taken from the B and R areas for proline and the B, R and L areas for the tyrosine. The values of dihedral angles of the side chains $\chi^1$and χ^2 were taken to be 60°, 180°, −60° and 90°, −90° respectively (see Fig. 1). The angle χ^3 of Tyr was taken as equal to 180°.

We examined 108 conformers for mono-L-Pro–Tyr dipeptide. The global conformation of the mono L-Pro–Tyr dipeptide is characterized by the folded backbone shape in the RR conformational range, with −7.14 kcal/mol energy. The conformational energy of mono-L-Pro–Tyr molecule (E_{tot} = −7.14 kcal/mol) was found as the sum of the van der Waals (E_{vdW} = −5.74 kcal/mol), electrostatic (E_{el} = −1.57 kcal/mol), torsional (E_{tor} = 0.17 kcal/mol) energies. The optimized values of the dihedral angles of backbone and side chains of the Pro–Tyr dipeptide are found to be; Ψ_1 = −52.37, ω = 179.40, φ = −139.83, χ_{21} = −57.13, χ_{22} = 101.32, χ_{23} = 179.82, Ψ_2 = −60.00.

In the second part of this study, the geometry optimization of the obtained global conformation was performed by DFT/B3LYP method by using both 6-31G(d,p) and 6-31++G(d,p) basis sets, and after then the vibrational wavenumbers were calculated. The same calculations were repeated for the dimeric form of the dipeptide, but, only by using 6-31G(d,p) basis set.

The molecular structure of the neutral monomeric and dimeric forms of L-Pro–Tyr with the atom numbering and the optimized dihedral angles are shown in Fig. 1. Calculated bond distances, interbond angles and torsion angles of monomeric (for both 6-31G(d,p) and 6-31++(G(d,p) basic sets) and dimeric forms (6-31G(d,p)) of Pro–Tyr dipeptide are tabulated in Table 1. We could not use 6-31++G(d,p) basis set for the dimeric form of Pro–Tyr dipeptide due to inadequate capacity of our computer. However, as seen in Table 1, considerable changes were not obtained using 6-31++G(d,p) basic set instead of 6-31G(d,p), in the monomeric form of Pro–Tyr dipeptide. As a result, we compared calculation results with 6-31G(d,p) basis set of monomeric form to those of dimeric form.

Two possible intra H-bonding interactions between H(17) and O(36) (2.60 Å), N(2) and H(17)(2.13 Å) were predicted for the global conformation of monomeric L-Pro–Tyr dipeptide.

L-Pro–Tyr dipeptide has applicable geometry to constitute a dimeric form due to its carboxyl groups. The dimeric forms of the

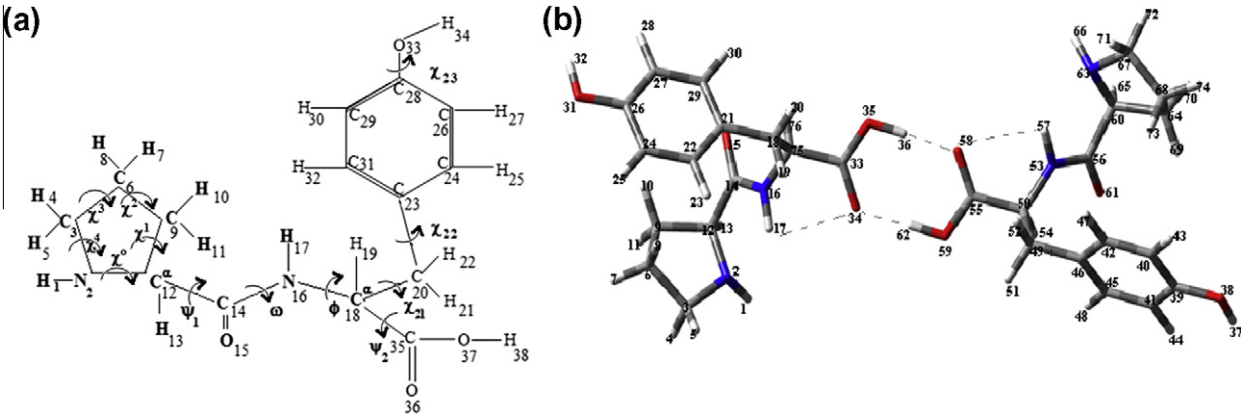

Fig. 1. The molecular model of neutral L-Pro–Tyr dipeptide (a). Atom numbering and dihedral angles were shown. The global conformation of dimeric form of Pro–Tyr dipeptide (b). Predicted H-bonding interactions are shown as broken lines.