



## Structural and IR and Raman spectral analysis of cyclo(His-Phe) dipeptide

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### ABSTRACT

A study was carried-out to measure and calculate infrared (4000–400 cm<sup>-1</sup>) and Raman (3500–50 cm<sup>-1</sup>) spectra of cyclo(His-Phe) dipeptide, which has anticancer activity. Conformational preferences of cyclo(His-Phe) dipeptide are investigated using theoretical conformational analysis followed by DFT calculations. The calculations of cyclo(His-Phe) dipeptide, as a function of side chain torsion angles, enable us to determine its energetically preferred conformations. The DFT calculations predict that the boat conformation is energetically more stable than the planar conformation. The dimeric forms of cyclo(His-Phe) dipeptide are constructed by bringing together two identical cyclo(His-Phe) monomers in possible configurations and three energetically favorable dimeric structures are obtained. The vibrational normal modes and associated wavenumbers, IR and Raman intensities of the global conformers of monomeric and dimeric units of cyclo(His-Phe) are calculated by DFT method at either both B3LYP/6-31G(d,p) and B3LYP/6-31++G(d,p) levels of theory (for monomer) or only at B3LYP/6-31G(d,p) level of theory (for dimeric unit). The total energy distributions (TED) of the vibrational modes are calculated by using the scaled quantum mechanical force field (SQM FF) method. Complete vibrational assignments of the observed spectra were performed by the aid of computed vibrational data. The *cis* amide II band is observed at 1481 cm<sup>-1</sup> in the Raman spectrum of solid cyclo(His-Phe), which is in agreement with previously reported Raman results for solid cyclic dipeptides, where the DKP ring adopts a boat conformation. The combination of the experimental and calculated spectra provide an insight into the structural and vibrational spectroscopic properties of cyclo(His-Phe) dipeptide. The energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of cyclo(His-Phe) are calculated by DFT method at B3LYP/6-31G(d,p) level of theory. HOMO is localized on histidine amino acid whereas LUMO is localized mostly on phenylalanine ring. The computed HOMO–LUMO energy gap corresponds to 6.3596 eV (146.65 kcal/mol).

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### 1. Introduction

In recent years considerable interest has been focused on the cyclic dipeptides, because of their remarkable bioactivity [1–3]. Diketopiperazines (DKPs) are found to be ideal lead compounds for the rational design of an agent capable of preventing metastasis, inhibiting tumor growth, and as potential chemotherapeutic, antiarrhythmic and antihypertensive agents, as well as potential antibacterial and antifungal agents [4]. Cyclic peptides occur both naturally and synthetically and can have important biological functions. They have been found in various foods. The bitter flavor of many foods has been attributed partially to DKPs. DKPs are used as antibiotics, toxins, ion-transport regulators, protein binding inhibitors and enzyme inhibitors [1,2]. Many of DKPs are therefore

considered as important metabolic intermediates rather than as protein artifacts [4]. Cyclo(His-Phe) has significant biological activity in the treatment of cancer, infectious and cardiovascular-related diseases [4]. It possesses significant anti-tumor activity, causing greatest reduction of cell viability in cervical carcinoma cells [4]. It also has remarkably prolonged the sleeping time in mice [5].

Cyclic dipeptides provide excellent models for theoretical studies as well as the development of new pharmaceutical compounds due to their simplicity and limited conformational freedom. In recent years there has been a growing awareness to understand the specific function of each peptide and their structure. It is known that the biological functions of the peptides in living systems are related with their three-dimensional structures. Thus, conformational properties of the biologically active peptides are very important to investigate their functional structure. On the other hand electronic and vibrational properties of the molecules are related with the conformational structure. A number of X-ray crystallographic studies have been reported for DKPs and cyclic

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dipeptides [6–12], however no reports on X-ray crystallographic study has yet been reported for cyclo(His-Phe). In our previous study we have investigated conformational properties and vibrational spectra of cyclo(Gly-Val) dipeptide [13]. As continuation of our studies on cyclic dipeptides, herein, we report the results of an experimental spectroscopic study on cyclo(His-Phe) in conjunction with density functional theory (DFT) modeling. The objectives of this study are to give a complete description of the molecular geometry and molecular vibrations of monomeric and dimeric units of cyclo(His-Phe) in the framework of conformational analysis and the density functional method, and to investigate the hydrogen bonding interactions and the coordination effects on the investigated molecule. The experimental IR and Raman spectra of cyclo(His-Phe) are also reported for the first time.

## 2. Methods and calculations

### 2.1. Experimental

The solid cyclo(His-Phe) dipeptide was reagent grade (Sigma) and used as received. The IR spectrum of the KBr disc of cyclo(His-Phe) was recorded on a Jasco 300E FT-IR spectrometer (2 cm<sup>-1</sup> resolution) between 400 and 4000 cm<sup>-1</sup> spectral region. The Raman spectrum of the sample was taken with a Jasco NRS-3100 micro-Raman spectrometer (1800 lines/mm grating and high sensitivity cooled CCD). The spectrometer was calibrated with the silicon phonon mode at 520 cm<sup>-1</sup>. Either 532 nm or 785 nm lines of the diode lasers was used for excitation. The exposure time was taken as 2 s and 100 spectra were accumulated. Spectral resolution was 3.9 cm<sup>-1</sup>. 1 mM aqueous suspension was prepared. The IR spectrum of the aqueous suspension was recorded between ZnSe plates.

Spectral manipulations, such as baseline corrections and band fitting procedures, were performed using the GRAMS/AI 7.02 (Thermo Electron Corporation) software package. Band fitting was done using either Gaussian function (for Raman spectrum) or Gaussian+Lorentzian mixed function (for IR), and fitting was undertaken until reproducible and converged results were obtained with squared correlations better than  $r^2 \sim 0.9998$ . The second derivative profile gives valuable information about the position of the bands and band widths. Thus for the band fitting procedure (to locate the position of the peaks), the second derivative of the IR (absorption) or Raman spectrum was used as a guide. The second derivatives of the spectra were obtained by using Savitzky-Golay function (two polynomial degrees, 19 points).

### 2.2. Computational details

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 were determined by using the Ramachandran maps [15,16].

DFT studies were performed with Gaussian03 computational package [17] in which Becke3LYP function [18] was used. For all studied compounds, geometry optimizations were conducted without any constraints. The geometrical parameters and the vibrational frequencies of cyclo(His-Phe) were calculated by using both 6-31G(d,p) and 6-31++G(d,p) basis sets for monomeric form. The 6-31++G(d,p) basis set for the dimeric form could not be used, due to unavailability of the powerful computer system. Thus, only calculated vibrational results with 6-31G(d,p) basis set of monomeric and dimeric units were compared.

The differences between the calculated and the experimental values for the same mode are often attributed to the lack of anharmonic and incomplete electronic correlation. In order

to correct overestimation of the computed wavenumbers, dual scaling factors were used. Computed harmonic wavenumbers under 1800 cm<sup>-1</sup> were multiplied by either 0.967 {for B3LYP/6-31G(d,p)} or 0.977 {for B3LYP/6-31++G(d,p)} and wavenumbers over 1800 cm<sup>-1</sup> were multiplied by 0.955 {for both B3LYP/6-31G(d,p), B3LYP/6-31++G(d,p)} [19]. 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 [20].

The theoretical Raman intensity ( $I_i$ ), which corresponds to the measured Raman spectrum is calculated according to the formula [21,22]:

$$I_i = \frac{f(\nu_0 - \nu_i)^4 S_i}{\nu_i B_i},$$

where  $B_i = 1 - \exp(-h\nu_i/kT)$ ,  $S_i$  is the Raman scattering activity of the normal mode  $Q_i$  calculated by DFT methods,  $\nu_0$  is the exciting frequency (in cm<sup>-1</sup> units),  $\nu_i$  is the vibrational wavenumber of the  $i$ th normal mode,  $h$ ;  $c$  and  $k$  are fundamental constants, and  $f$  is a suitably chosen common normalization factor for all peak intensities. In this work, we assumed the excitation frequency,  $\nu_0 = 18798.4$  cm<sup>-1</sup>, which corresponds to the wavelength of 532 nm of a diode laser.  $B_i$  is a temperature factor which accounts for the intensity contribution of excited vibrational states. For  $T = 300$  K, we assume  $B_i$  equal to 1 [21].

The rms errors of wavenumbers were obtained in this study using the following expression:

$$\text{rms} = \sqrt{\frac{1}{n-1} \sum_i^n (\nu_i^{\text{calculated}} - \nu_i^{\text{experimental}})^2}$$

The simulated IR and Raman spectra were plotted using a Lorentzian band shape with a half-width at half-height (HWHH) of 7 cm<sup>-1</sup>.

## 3. Results and discussion

### 3.1. Conformational analysis and geometrical optimization

In order to determine the stable conformers of cyclo(His-Phe) dipeptide, theoretical conformational analysis was carried out. The three dimensional structures of the cyclo(His-Phe) have been investigated based on the low-energy conformations of mono peptides, histidine and phenylalanine. The geometry optimization and vibrational frequency calculations were performed by DFT method on the most stable conformation of cyclo(His-Phe) obtained by conformational analysis. The geometry optimization by DFT method, conducted without any constraints, resulted in boat conformation. After then the geometry calculations with DFT method were performed by constraining the diketopiperazine (DKP) ring either to be planar or boat form. The atom numbering scheme for cyclo(His-Phe) in boat and planar forms are shown in Fig. 1. The DFT calculations predict that the boat conformation is energetically more stable than the planar conformation. The three dihedral angles,  $\omega$ ,  $\varphi$  and  $\psi$ , which are related to the geometry of the peptide bond, can be determined by analyzing the corresponding dihedral angles  $C^\alpha-N-C'-C^\alpha$ ,  $C'-N-C^\alpha-C'$  and  $N-C'-C^\alpha-N$ . The computed values of these dihedral angles are tabulated in Table 1. The energy of the boat conformer is found to be lower by 42.67 kcal/mol (DFT/B3LYP6-31++G(d,p)) compared to that of planar conformer. In Table 2, the calculated energies and energy differences obtained by DFT/B3LYP6-31G(d,p) and DFT/B3LYP6-31++G(d,p) levels of theory are given. It is important to note that the calculated structure is based on a single molecule in the gas phase, and does not take into account intermolecu-

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