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Conformational preferences, experimental and theoretical vibrational spectra of cyclo(Gly–Val) dipeptide

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ABSTRACT

The theoretical conformational analysis of cyclic dipeptide, cyclo(glycine–valine), which has anticancer activity, has been performed by molecular mechanics method, in order to examine the energetically optimal conformational states. The relative positions of the side chain residues of the stable conformations of dipeptide were obtained. The obtained geometry of the most stable conformation of the cyclo(Gly–Val) was optimized using DFT method at B3LYP/6-31++G(d,p) level of theory. Afterwards dimeric forms of the dipeptide were formed and energetically preferred conformations of dimers were investigated using the same method and the same level of theory. The experimental IR and micro-Raman spectra of solid cyclo(Gly–Val) were reported for the first time. The vibrational normal modes and associated wavenumbers, IR intensities and Raman activities of the monomeric and dimeric forms of the dipeptide were calculated using DFT method at B3LYP/6-31++G(d,p) level of theory and the results were compared with the experimental data. 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

Due to their simplicity and stability cyclic dipeptides provide excellent models for theoretical studies as well as the development of pharmaceutical compounds.

Glycine is known to have a protective role against alcohol induced liver damage. Bioglycin significantly improved retrieval from episodic memory in both the young and the middle-aged groups, but it did not affect focused or divided attention [1].

Valine is an essential amino acid and also a branched-chain amino acid (such as isoleucine and leucine) found in high concentration in the muscles. It has a stimulating effect and is needed for muscle metabolism, repair and growth of tissue and maintaining the nitrogen balance in the body. Because valine is a branched-chain amino acid, it can be used as an energy source in the muscles. Cyclo(Gly–Val) is more active in terms of its ability to inhibit colon and cervical carcinoma cell lines [2].

The aims of this study are to give a complete description of the molecular geometry and molecular vibrations of monomeric and dimeric forms of cyclo(Gly–Val), in the framework of conformational analysis and DFT methods, and to investigate the hydrogen bonding interactions and the coordination effects. In this study, conformational analysis, theoretical vibrational spectra of cyclo (Gly–Val) dipeptide in its monomeric and dimeric forms, experimental IR and Raman spectra of solid cyclo(Gly–Val) were reported for the first time.

2. Experimental and computational details

The solid cyclo(Gly–Val) dipeptide was reagent grade (Sigma) and used as received. The FT-IR spectrum of KBr disc of the cyclic 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 spectrometer (1800 lines/mm or 1200 lines/mm grating and high sensitivity cooled CCD). Sample was excited with a 532 nm diode laser. A 20 × microscope objective (Olympus) was used to focus the laser and collect Raman scattering on the sample. The spectrometer was calibrated with the silicon phonon mode at 520 cm^{-1}. The exposure time was taken as 2 s and 100 spectra were accumulated. Spectral resolution was 3.9 cm^{-1}.

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Table 1
The torsional ring angles of cyclo(Gly–Val) in degrees.

Cyclo(Gly–Val)	ω1(N1–C22)	ω2(C6–N8)	φ1(N8–C10)	φ2(N1–C3)	ψ1(C10–C22)	ψ2(C3–C6)
DFT-B3LYP/6-31G(d,p)	−5.06	−3.01	18.29	20.56	−13.83	−15.95
DFT-B3LYP/6-31++G(d,p)	−8.06	−6.57	20.06	21.77	−12.20	−13.88

Table 2
Structural parameters for monomeric and dimeric forms of cyclo(Gly–Val) obtained by DFT/B3LYP (6-31G(d,p)), in comparison with the results of single crystal studies of 2,5-diketopiperazine [10] and cycle-(L-histidyl-L-aspartyl) trihydrate [12], and computed values of cyclo(histidyl–histidyl) dipeptide [13].

	Cyclo(Gly–Val)		Refs.				Cyclo(Gly–Val)		Refs.			Cyclo(Gly–Val)		Ref.				Ref.
Atoms	Mono	Dimer	[10]	[12]	[13]	Atoms	Mono	Dimer	[10]	[12]	Atoms	Mono	Dimer	[12]	Atoms	Mono	Dimer	[12]
R(1,2)	1.0131	1.0317			1.015	R(14,16)	1.0947	1.0948			A(3,6,7)	120.27	120.49	118.2	A(14,12,18)	111.41	111.34	
R(1,3)	1.4565	1.4565	1.410	1.458	1.464	R(14,17)	1.0961	1.0959			A(3,6,8)	116.52	116.54	119.9	A(12,14,15)	111.81	111.89	
R(1,22)	1.3597	1.3414	1.330	1.336	1.355	R(18,19)	1.0969	1.0969			A(7,6,8)	123.21	122.97	122.0	A(12,14,16)	110.25	110.26	
R(3,4)	1.0933	1.0936				R(18,20)	1.0948	1.0948			A(6,8,9)	114.10	114.18		A(12,14,17)	111.39	111.26	
R(3,5)	1.0988	1.0981				R(18,21)	1.0963	1.0963			A(6,8,10)	127.72	127.63	126.9	A(15,14,16)	107.31	107.42	
R(3,6)	1.5221	1.5201	1.470	1.496	1.541	R(22,23)	1.2279	1.2445	1.250	1.226	A(9,8,10)	117.86	117.95		A(15,14,17)	108.45	108.33	
R(6,7)	1.2272	1.2273	1.250	1.245	1.222	R(2,24)		1.8406			A(8,10,11)	107.59	107.82		A(16,14,17)	107.44	107.50	
R(6,8)	1.3583	1.3593	1.330	1.320	1.355	R(23,28)		1.8402			A(8,10,12)	113.54	113.40		A(12,18,19)	111.85	111.80	
R(8,9)	1.0131	1.013				A(5,3,6)	107.31	107.44			A(8,10,22)	112.73	112.46	113.8	A(12,18,20)	110.33	110.31	
R(8,10)	1.464	1.462	1.410	1.460	1.465	A(2,1,3)	118.41	117.63			A(11,10,12)	107.30	107.21		A(12,18,21)	111.62	111.68	
R(10,11)	1.0965	1.0968				A(2,1,22)	114.45	116.14			A(11,10,22)	104.53	104.67		A(19,18,20)	106.95	106.93	
R(10,12)	1.5566	1.558				A(3,1,22)	126.56	126.09		127.3	A(12,10,22)	110.55	110.71		A(19,18,21)	108.30	108.31	
R(10,22)	1.5296	1.5264	1.470	1.504	1.541	A(1,3,4)	109.78	109.44			A(10,12,13)	104.57	104.68		A(20,18,21)	107.58	107.60	
R(12,13)	1.0965	1.0964				A(1,3,5)	111.52	110.89			A(10,12,14)	112.65	112.59		A(1,22,10)	117.47	118.83	118.7
R(12,14)	1.535	1.5352				A(1,3,6)	113.95	114.81		113.4	A(10,12,18)	111.06	110.96		A(1,22,23)	122.55	122.89	122.3
R(12,18)	1.536	1.536				A(4,3,5)	107.31	106.94			A(13,12,14)	108.58	108.71		A(10,22,23)	119.98	118.27	119.0
R(14,15)	1.0954	1.0953				A(4,3,6)	106.65	106.96			A(13,12,18)	108.22	108.24					

Table 3
Calculated energy for the most stable conformation of planar and boat conformers of cyclo(Gly–Val).

Cyclo(Gly–Val)	DFT-B3LYP/6-31G(d,p)	DFT-B3LYP/6-31++G(d,p)
Boat conformer	−533.972 a.u.	−533.997 a.u.
Planar conformer	−533.924 a.u.	−533.948 a.u.

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. [3]. The low energy conformations of dipeptide have been determined by using the Ramachandran maps [4,5].

Density functional theory (DFT) studies were performed with Gaussian03 computational package [6]. The geometrical parameters and the vibrational frequencies of cyclo(Gly–Val) and its dimer have been calculated by using DFT method with Becke3Lyp functional [7] and 6-31G(d,p) and 6-31++G(d,p) basis sets. The differences between the calculated and the experimental values for the same mode are often attributed to the neglect of anharmonicity and incomplete inclusion of electronic correlation effects. In order to correct overestimation between unscaled wavenumbers and observed frequencies dual scaling factors were used. All the wavenumbers under 1800 cm^{-1} were scaled with the scale factor either 0.967 or 0.977 for B3LYP/6-31G(d,p) and B3LYP/6-31++G(d,p) levels of theory, respectively, whereas the wavenumbers over 1800 cm^{-1} were scaled with the scale factor 0.955 for both B3LYP/6-31G(d,p) and B3LYP/6-31++G(d,p) levels of theory [8].

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 [9].

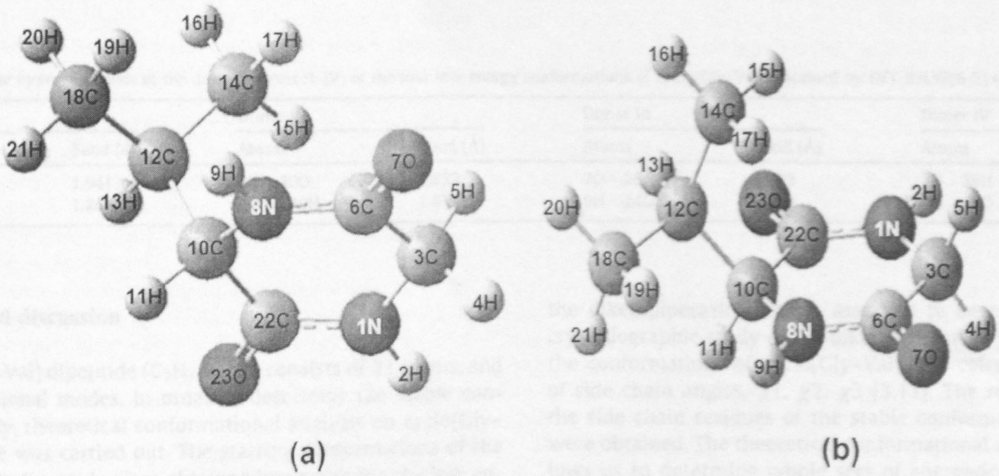

Fig. 1. The global conformations of boat (a) and planar (b) forms of monomeric cyclo(Gly–Val) dipeptide. Atom numbering used in Table 1 and 2 is indicated.

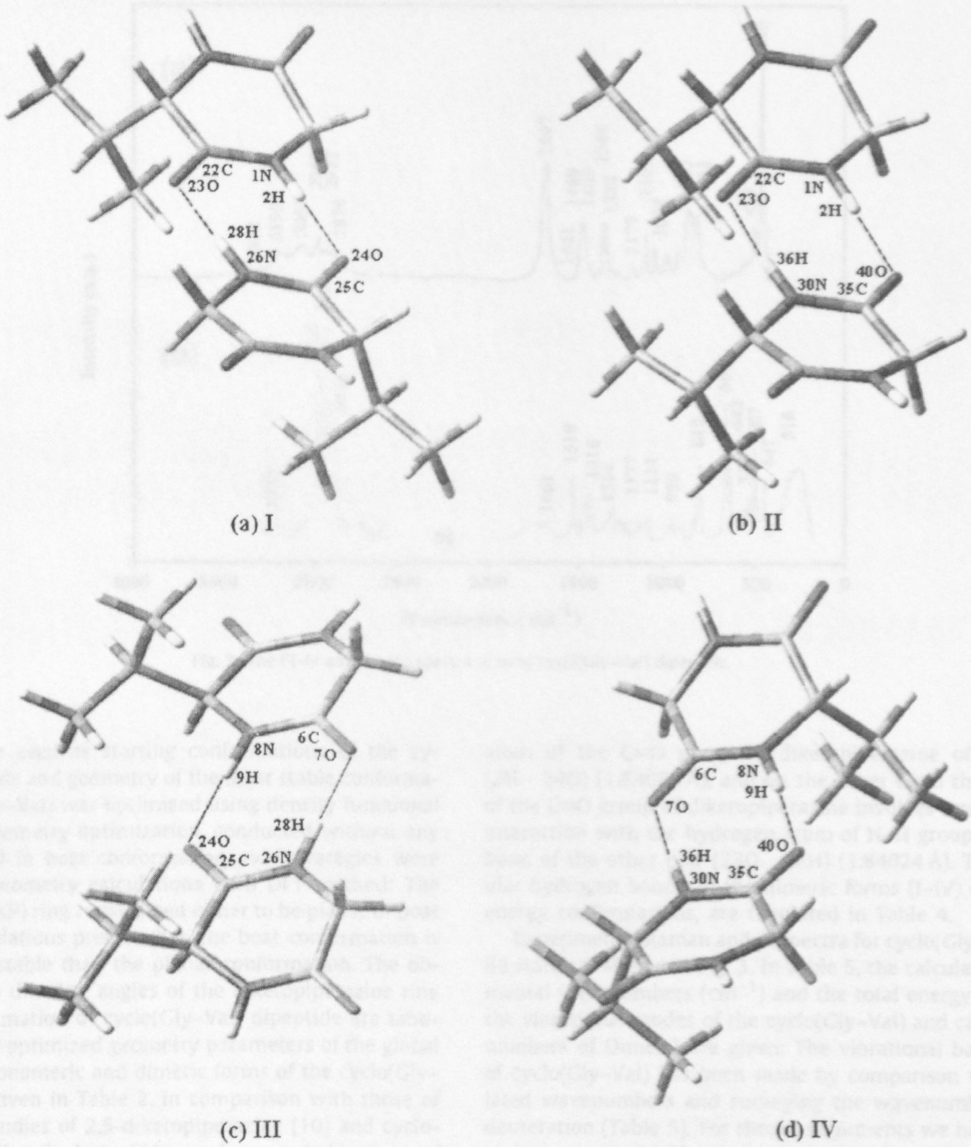

Fig. 2. The geometrical structures of four low energy conformers (I–IV) of dimeric forms of the cyclo(Gly–Val) dipeptide, predicted by DFT calculations. The energies obtained by DFT/B3LYP/6-31++G(d,p) level of theory are $E = -670183.4669998$ kcal/mol (I) (a), $E = -670183.2041890$ kcal/mol (II) (b), $E = -670183.2010703$ kcal/mol (III) (c), $E = -670183.0384215$ kcal/mol (IV) (d).

Table 4
The intermolecular hydrogen bonds of the dimeric forms (I–IV) of the four low energy conformations of cyclo(Gly–Val), obtained by DFT-B3LYP/6-31++G(d,p).

Dimer I		Dimer II		Dimer III		Dimer IV	
Atoms	Bond (Å)	Atoms	Bond (Å)	Atoms	Bond (Å)	Atoms	Bond (Å)
2H···24O	1.841	2H···40O	1.832	7O···28H	1.832	7O···36H	1.860
23O···28H	1.840	23O···36H	1.874	9H···24O	1.873	9H···40O	1.861

3. Results and discussion

Cyclo(Gly–Val) dipeptide ($C_7H_{12}N_2O_2$) consists of 23 atoms, and has 63 vibrational modes. In order to determine the stable conformers, firstly, theoretical conformational analysis on cyclo(Gly–Val) dipeptide was carried out. The starting conformations of the cyclo(Gly–Val) dipeptide were obtained by combining the low energy structures of constitutive residues. At this part of the study the diketopiperazine ring is assumed to be planar according to crystallographic study of 2,5-diketopiperazine [10]. The energy of the conformations of cyclo(Gly–Val) was calculated as functions of side chain angles, $\chi 1$, $\chi 2$, $\chi 3$ [3,11]. The relative positions of the side chain residues of the stable conformations of dipeptide were obtained. The theoretical conformational analysis method allows us to determine whole sets of energetically preferred conformers of peptide molecule. After then the obtained stable

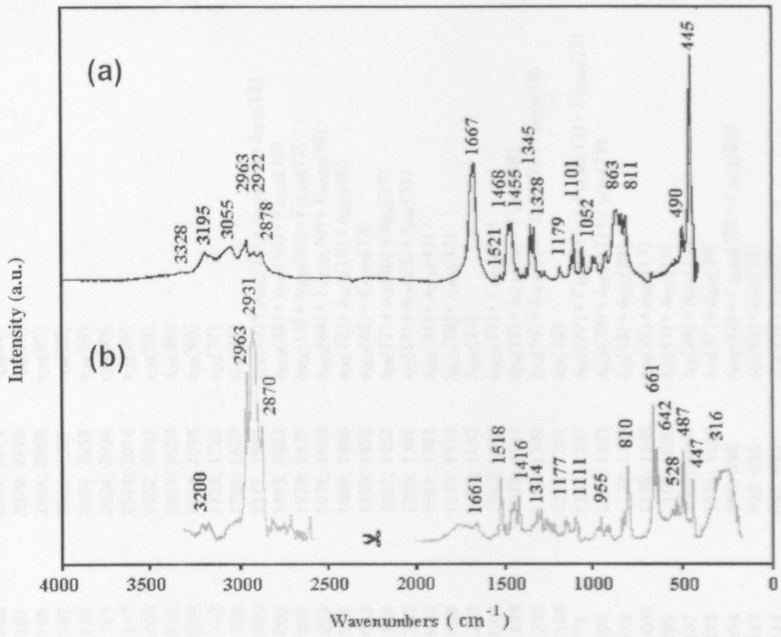

Fig. 3. The FT-IR and Raman spectra of solid cyclo(Gly–Val) dipeptide.

conformations were used as starting conformations of the cyclo(Gly–Val) dipeptide and geometry of the most stable conformation of the cyclo(Gly–Val) was optimized using density functional theory. Since the geometry optimization, conducted without any constraints, resulted in boat conformation, two strategies were employed for the geometry calculations with DFT method: The diketopiperazine (DKP) ring constrained either to be planar or boat form. The DFT calculations predict that, the boat conformation is energetically more stable than the planar conformation. The obtained values of the dihedral angles of the diketopiperazine ring of the global conformation of cyclo(Gly–Val) dipeptide are tabulated in Table 1. The optimized geometry parameters of the global conformations of monomeric and dimeric forms of the cyclo(Gly–Val) dipeptide are given in Table 2, in comparison with those of the single crystal studies of 2,5-diketopiperazine [10] and cyclo-(L-histidyl-L-aspartyl) trihydrate [12], and computed values of cyclo(histidyl–histidyl) dipeptide [13]. In Table 3, the calculated energy value of the global conformation of monomeric form of cyclo(Gly–Val) dipeptide by DFT/B3LYP functional and 6-31G(d,p) and 6-31++G(d,p) basis sets are given. The DFT calculations predict that, the boat conformation is energetically more stable than the planar conformation. The energy of the planar conformer is higher by 30.75 kcal/mol (DFT/B3LYP6-31++G(d,p)) compared to that of boat conformer. 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 intermolecular forces such as hydrogen bonding which occurs in the solid state and in aqueous solution. Fig. 1 shows the global conformations of boat and planar forms of monomeric cyclo(Gly–Val) dipeptide.

The geometrical structures of four low energy conformers (I–IV) of dimeric forms of the cyclo(Gly–Val) dipeptide, predicted by DFT calculations are given in Fig. 2. The energies of these four low energy dimers (I–IV), obtained by DFT/B3LYP/6-31++G(d,p) level of theory, are $E = -670183.4669998$ kcal/mol (I), $E = -670183.2041890$ kcal/mol (II), $E = -670183.2010703$ kcal/mol (III), $E = -670183.0384215$ kcal/mol (IV). In the Dimer I structure, one of the hydrogen atom of N–H group of the peptide bond involves hydrogen bonding interaction with the oxygen atom of the C=O group of diketopiperazine of the first pair (2H···24O) (1.84060 Å), and on the other hand the oxygen atom of the C=O group of diketopiperazine involves hydrogen bonding interaction with the hydrogen atom of N–H group of the peptide bond of the other pair (23O···28H) (1.84024 Å). The intermolecular hydrogen bonds, of the dimeric forms (I–IV) of the four low energy conformations, are tabulated in Table 4.

Experimental Raman and IR spectra for cyclo(Gly–Val) in the solid state are shown in Fig. 3. In Table 5, the calculated and experimental wavenumbers (cm^{-1}) and the total energy distribution of the vibrational modes of the cyclo(Gly–Val) and calculated wavenumbers of Dimer I are given. The vibrational band assignment of cyclo(Gly–Val) has been made by comparison with the calculated wavenumbers and surveying the wavenumber shifts upon deuteration (Table 5). For these assignments we have utilized the assignments available in the literature for different polyatomic molecules and amino acids with similar groups ([13–14] and references therein). The calculated IR spectra, using 6-31G(d,p) and 6-31++G(d,p) basis sets, are given in Fig. 4, in comparison with the experimental IR spectra of solid cyclo(Gly–Val) dipeptide.

The two N–H stretching modes for cyclo(Gly–Val) are relatively weak in the IR and Raman spectra and are assigned at 3328 cm^{-1} (IR) and 3195 cm^{-1} (IR), 3200 cm^{-1} (R). From the theoretical calculations these modes are computed at 3438 cm^{-1} and 3437 cm^{-1} (6-31++(d,p)) for monomeric cyclo(Gly–Val) and, 3441 cm^{-1} and 3141–3098 cm^{-1} for dimeric cyclo(Gly–Val). Experimental results for solid cyclo(Gly–Val) are found to be more close to those of calculated dimeric form than those of calculated monomeric dipeptide. For the deuterated derivative, υ(ND) vibrations are computed at 2517 and 2516 cm^{-1} for monomeric dipeptide. The theoretical isotopic ratio are 0.74 and 0.73 for the ν(D)/ν(H) value, respectively. The comparison of this isotopic ratio with cited in literature are in excellent agreement.

In this work $\upsilon_{C=O}$ stretching vibrations calculated at 1723 cm^{-1} and 1720 cm^{-1} for monomeric and 1723–1723 cm^{-1} and 1702–1677 cm^{-1} for dimeric forms of cyclo(Gly–Val) dipeptide. Rippon et al. [15] assigned the 1643 (R) cm^{-1} and 1645 (IR) cm^{-1} bands to these vibrations for L-proline. In this study, these bands

Table 5
Calculated and experimental wavenumbers (cm^{-1}) and the total energy distribution of the vibrational modes of the cyclo(Gly–Val) and calculated wavenumbers of Dimer I.

Assignment	Cyclo(Gly–Val)		Gly[a]		Gly [16]		Val [a]		Val [17]	Monomer				TED%	
	IR	Raman	IR	Raman	IR	Raman	IR	Raman	Raman	DFT/B3LYP		deuterated	dimer		
										6-31G(d,p)	6-31++G(d,p)	6-31++G(d,p)	6-31++G(d,p)	cyclo(Gly–Val)	6-31++G(d,p)
	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{cal}[s]	ν_{cal}[s]	ν_{cal}[s]	ν_{cal}[s] ν_{cal}[s]		
ν_{HN}	3328 vw				3414					3300	3438	2517	3441; 3441	ν_{HN}(100)	
ν_{HN}	3195 w	3200 w	3169							3295	3437	2516	3141; 3098	ν_{HN}(100)	
ν_{CH}	3055 w						2992		2999	2978	2971	2199	2971; 2971	ν_{CH}(99)	
ν_{CH}	2984 w	2984 w							2982	2974	2969	2197	2970; 2970	ν_{CH}(99)	
ν_{CH}	2963 w	2963 s		3047	3084	3050				2959	2968	2195	2966; 2966	ν_{CH}(99)	
ν_{CH}							2977	2966	2971	2973	2967	2197	2967; 2967	ν_{CH}(99)	
ν_{CH}							2954	2944	2950	2964	2957	2189	2958; 2958	ν_{CH}(99)	
ν_{CH}	2922 w	2931 s							2929	2912	2924	2153	2924; 2924	ν_{CH}(99)	
ν_{CH}		2914 s					2906		2910	2897	2918	2147	2914; 2914	ν_{CH}(99)	
ν_{CH}										2906	2901	2085	2902; 2902	ν_{CH}(99)	
ν_{CH}	2878 w	2870 m			2920	2930				2885	2894	2110	2903; 2903	ν_{CH}(99)	
ν_{CH}							2881	2875		2900	2894	2079	2894; 2894	ν_{CH}(99)	
ν_{CO}	1667 s	1661 vw			1703	1667				1705	1723	1712	1723; 1723	ν_{CO}(77)	
ν_{CO}	1658 m	1657 vw								1699	1720	1706	1702; 1677	ν_{CO}(76)	
δ_{CN}	1521 vw	1518 m	1559	1568						1495	1490	1409	1517; 1513	ν_{CN}(18) + δ_{HNC}(12) + δ_{HCN}(12) + δ_{HCH}(12)	
δ_{HCH}							1472	1465	1454	1478	1483	1065	1483; 1483	δ_{HCH}(48) + δ_{HCC}(10) + Γ_{CCCH}(16)	
δ_{HCH}							1457	1451	1448	1473	1479	1061	1479; 1479	δ_{HCC}(13) + δ_{HCH}(50) + Γ_{CCCH}(12)	
δ_{HCH}	1468 m	1467 w					1425	1426	1428	1464	1470	1058	1471; 1469	δ_{HCH}(48) + Γ_{CCCH}(19) + Γ_{HCCH}(10)	
δ_{NH}							1507	1506	1509	1456	1453	1074	1480; 1466	δ_{CN}(12) + δ_{HCH}(14) + δ_{HNC}(18)	
δ_{HCH}	1455 m	1449 w	1457	1455			1396	1396	1399	1453	1459	1053	1459; 1458	δ_{HCH}(49) + Γ_{CCCH}(13)	
δ_{NH}	1420 vw	1416 w	1444	1440						1445	1441	1149	1452; 1452	δ_{CN}(17) + δ_{CO}(10) + δ_{HNC}(27)	
δ_{NH}			1412	1411	1410	1410				1403	1396	1393	1395; 1395	δ_{CC}(13) + δ_{CN}(23) + δ_{HNC}(33)	
δ_{HCH}	1391 vw						1351	1349		1390	1396	1092	1381; 1381	δ_{HCC}(38) + δ_{HCH}(43)	
δ_{HCH}	1368 vw						1342	1341		1370	1377	1048	1373; 1373	δ_{HCC}(38) + δ_{HCH}(43)	
δ_{NH}	1345 m	1348 vw								1361	1362	1252	1439; 1432	δ_{HNC}(24)	
δ_{CH}	1328 m						1319		1322	1340	1342	1004	1343; 1343	δ_{HCC}(23) + Γ_{HCCH}(14)	
Γ_{CH}	1317 vw	1314 vw					1270	1270	1271	1318	1322	1179	1328; 1327	δ_{CN}(12) + δ_{HCC}(18) + Γ_{HCCH}(28)	
w_{CH_2}	1293 vw	1291 vw								1291	1293	1219	1303; 1302	δ_{CN}(16) + δ_{HCN}(10) + δ_{HCC}(12) + Γ_{HCCH}(10)	
δ_{CN}	1264 vw	1265 vw	1227				1190	1189		1277	1277	1195	1282; 1281	δ_{CN}(16)	
δ_{CH}		1251 vw					1178	1178		1256	1263	771	1267; 1267	δ_{HCC}(27) + Γ_{HCNC}(11) + Γ_{HCNH}(12) + Γ_{CCCH}(15)	
δ_{CH}		1231 vw								1214	1223	907	1223; 1223	δ_{HCN}(39) + δ_{HCC}(27) + Γ_{NCCH}(15)	
δ_{CH}	1179 vw	1177 vw	1132		1142		1124			1166	1172	979	1172; 1171	δ_{CC}(18) + δ_{HCC}(39)	
δ_{CN}	1114 w	1111 vw	1111		1111		1139	1144		1132	1138	1047	1148; 1148	δ_{CN}(25) + δ_{HCC}(13)	
δ_{CC}	1101 m									1092	1097	905	1100; 1099	δ_{CC}(43) + δ_{HCC}(11)	
δ_{CN}	1052 w						1065	1065	1068	1077	1080	827	1091; 1091	δ_{CN}(24) + δ_{HCC}(13)	
δ_{CN}	992 w		1033	1037	1034	1033	1034	1034	1036	1019	1022	878	1031; 1030	δ_{CN}(37) + δ_{HCC}(10)	
r_{CH2}	974 w	975 vw								987	991	864	988; 988	δ_{HCC}(12) + Γ_{HCNH}(12) + Γ_{OCCH}(22)	
δ_{CC}		955 vw					948	947	950	950	956	817	958; 958	δ_{CC}(33) + δ_{HCC}(16)	
δ_{CC}	927 w								945	940	944	724	943; 943	δ_{CC}(35) + δ_{HCC}(35)	
δ_{CH}	917 w	918 vw	892	895	893					909	915	675	916; 915	δ_{HCC}(62)	
δ_{CC}	863 m						902	901	903	894	897	860	900; 899	δ_{CC}(36) + δ_{HCC}(11)	
δ_{CC}	835 m	833 vw					823	823		811	815	706	818; 817	δ_{CC}(58)	
δ_{CC}	811 m	810 m					775	775		783	786	698	793; 791	δ_{CC}(25) + δ_{NCC}(17)	
δ_{CN}							753	752		782	783	759	787; 786	δ_{CN}(25) + δ_{CC}(16)	
δ_{CC}							716	714		717	663	617	882; 845	δ_{CC}(24) + Γ_{OCNH}(24)	
Γ_{NH}	662 vw	661 m	607	605	607	602	664	663		708	643	578	647; 645	Γ_{HNCC}(16) + Γ_{HNCO}(29)	
δ_{ring}		642 m								626	614	539	642; 638	δ_{CC}(15) + δ_{OCC}(11) + δ_{OCN}(19) + Γ_{HNCO}(10)	
Γ_{NH}		552 vw								617	564	404	616; 616	Γ_{HCNH}(12) + Γ_{CCNH}(31) + Γ_{OCNH}(14)	

(*continued on next page*)

Table 5 (*continued*)

Assignment	Cyclo(Gly–Val)		Gly[a]		Gly [16]		Val [a]		Val [17]	Monomer				TED%	
	IR	Raman	IR	Raman	IR	Raman	IR	Raman	Raman	DFT/B3LYP		deuterated	dimer		
										6-31G(d,p)	6-31++G(d,p)	6-31++G(d,p)	6-31++G(d,p)	cyclo(Gly–Val)	6-31++G(d,p)
	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{exp}	ν_{cal}^{s}	ν_{cal}^{s}	ν_{cal}^{s}	ν_{cal}^{s} ν_{cal}^{s}		
Γ_{NH}		528 vw	502	495	504	497	542	540		542	516	373	520; 520	$\Gamma_{HCNH}(15) + \Gamma_{HNCC}(22)$	
Γ_{NH}	490 w	487 w								507	488	479	511; 504	$\delta_{OCN}(13) + \Gamma_{CCNH}(22)$	
δ_{cyclo}	445 s	447 w					472	470		474	467	450	477; 475	$\delta_{CCN}(15)$	
δ_{cyclo}	423 vw						427	427		432	436	430	449; 441	$\nu_{CN}(12) + \delta_{OCC}(23) + \delta_{NCC}(29) + \delta_{CNC}(13)$	
δ_{CCO}	415 w							393	396	409	404	394	414; 410	$\delta_{OCC}(31) + \delta_{OCN}(25)$	
δ_{CCC}	404 vw		361					373	375	383	383	324	388; 386	$\delta_{CCC}(33)$	
δ_{CCC}		316 w						295		294	295	265	305; 302	$\nu_{CC}(11) + \delta_{CCC}(36)$	
γ_{CH}		283 vw						277		266	263	235	260; 260	$\delta_{NCC}(13) + \Gamma_{HCCC}(60)$	
γ_{CH}			200							247	248	181	243; 243	$\Gamma_{HCCC}(63) + \Gamma_{HCCH}(17)$	
γ_{CH}			183					210	212	238	233	168	224; 224	$\Gamma_{HCCC}(71) + \Gamma_{HCCH}(25)$	
δ_{CCC}			167					161		174	167	151	183; 183	$\delta_{CCC}(36) + \Gamma_{HCCC}(13)$	
τ_{cyclo}			113					136	134	123	128	116	159; 150	$\Gamma_{HCNC}(23) + \Gamma_{CCNC}(31) + \Gamma_{OCNC}(16)$	
τ_{cyclo}								112		89	78	75	89; 76	$\Gamma_{CNCC}(14) + \Gamma_{CNCO}(16) + \Gamma_{CCCC}(10)$	
τ_{cyclo}										72	64	57	59; 54	$\Gamma_{CCCN}(20) + \Gamma_{CCCH}(20) + \Gamma_{CCCC}(19)$	
τ_{cyclo}										50	48	43	50; 40	$\Gamma_{CCNC}(25) + \Gamma_{NCCC}(19) + \Gamma_{OCCC}(14)$	

[a] This study.
[s] Scaled wavenumbers.

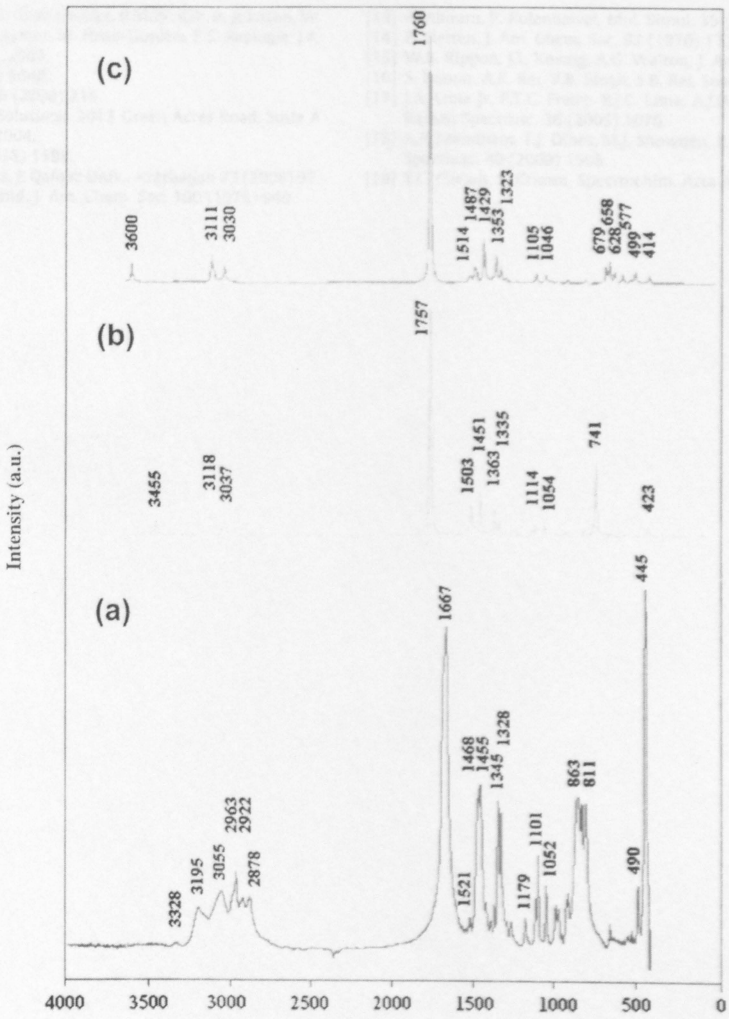

Fig. 4. Experimental IR spectrum of solid cyclo(Gly–Val) dipeptide (a) and the calculated IR spectra using 6-31G(d,p) (b) and 6-31++G(d,p) (c) basis sets.

observed at 1667 cm^{-1}(IR), 1661 cm^{-1} (R) and 1658 cm^{-1}(IR), 1657 cm^{-1}(R) in the vibrational spectra of solid cyclo(Gly–Val). A considerable amount of decrease in the vibrational wavenumber in comparison with the predicted values of monomeric form of cyclo(Gly–Val) have been obtained. This is because of the intermolecular hydrogen bonding between the oxygen atom of the C=O group of diketopiperazine and the hydrogen atom of N–H group of the peptide bond.

The C^{α}–H bending mode is assigned to the 1251 cm^{-1} Raman band in accord to [17], is calculated at 1263 cm^{-1} for monomeric cyclo(Gly–Val) dipeptide.

Amide II band is, mainly, an out-of-phase C–N stretch with a small contributions of the N–H and C–H in-plane bending vibration. The band observed 1521 cm^{-1} in IR spectrum and 1518 cm^{-1} in Raman spectrum of solid cyclo(Gly–Val) dipeptide is assigned to υ_{CN} stretching mode in agreement to vibrational spectra of diketopiperazine and cyclo(Gly–Gly) [18,19].

4. Conclusion

Purpose of this work is to investigate, the structural and vibrational characteristics of monomer and dimer structures of cyclo(Gly–Val) dipeptide. The determination of conformational details of biological macromolecules and conformational possibilities of cyclo(Gly–Val) dipeptide, is very important to understand their functions of a drug and may be useful as a base for synthesis of their more effective structural analogs. The DFT calculations predict that, the boat conformation is energetically more stable than the planar conformation.

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