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Conformational Study of a Series of Dipeptides with Glycine

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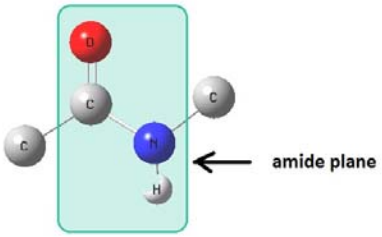
ABSTRACT

DFT calculations has been done by applying 6-31G* basis set on a series of dipeptides with *glycine* fixed at N-terminus position and the C-terminus position varied with eight different amino acids to get the optimized structures. Different geometrical parameters (bond angle, bond length, geometry around the α-carbon atom) are thoroughly investigated to study the effect of amino acid sequence on dipeptide. From dihedral angle data analysis it can be said that the combined effect of the sterric hindrance of – R group and hydrogen bonding is responsible for the deviation of amide plane from planarity. A potential energy scan is performed on *glycine* by rotating - COOH and – NH_2 groups separately, keeping the rest of the molecule fixed to get some idea about the conformational stability. The energy barrier to rotation is also calculated.

Keywords: *Glycine, Dipeptide, Peptide bond, DFT calculation, Potential energy scan*

1. Introduction

Peptides occur throughout the nature in a wide range of roles. They act as extracellular messengers: hormones, neurotransmitters and neuromodulators in plants, animals and thus influence vital function such as metabolism, immunedefence, respiration and reproduction. Indeed, they are essential to every biochemical process. This broad spectrum activity has attracted much attention to peptides from experimentalists as well as theoreticians point of view. A cornerstone of interdisciplinary research, which envelopes chemistry, physics and biology and includes both theoretical and experimental research program, has been the development of a fundamental framework for understanding the process of protein and peptide folding. Critical to the advancement of understanding of folding has been the development and application of molecular models. Three dimensional structures of peptide chains can be related to biological function of peptide and



protein on the molecular level. The better understanding of structure of peptides, protein molecules and their roles in various body functions is the subject of interest during last few decades and the process of generating three dimensional structure of protein from the primary structure is a topic of interest to reveal various interesting facts of protein folding. Understanding the details of protein folding still a huge working place for the scientific community and the complete knowledge at the atomic level is not likely in the near future.

A great deal of experimental and theoretical work had been done to understand the 3D structure of dipeptides. Earlier theoretical works on rigid geometries of the dipeptides and diamides were not sufficient as the technology was not advanced at that period. However in recent years the investigations have been made on the structure of dipeptides, short chain peptides and diamides. These studies have shown potential energy as only the function of torsion angle within the amino acid residues by way of the Ramachandran plot.

During the conformational study, even a simple molecule might be considered to exist in an infinite number of conformations if the positions of the atoms are defined with sufficient accuracy because bond lengths and bond angles vary at room temperature by ± 0.5Å and ± 5° respectively due to thermal vibration. For this reason, only the energetically most stable arrangement *i.e.* energy minima that are separated by distinct energy barriers are usually classified as individual conformation. Focus of this present study is to investigate the parameters involved in dipeptide structure as a part of protein structure. Planarity of the peptide bond is investigated with a series of dipeptides keeping N-terminus position fixed and varying the C-terminus with eight different amino acids and also the geometrical parameters like, dihedral angles of the amide planes, the geometry about α- carbon atom, the bond lengths, the bond angles of the amide plane have been examined. Due to its wide spread success in calculating the electronic structure for biomolecules we used DFT theory with B3LYP (6-31G*) hybrid functional to calculate the electronic structure and energy of the above mentioned eight different dipeptides. Potential energy scan (PES) study of *glycin*e amino acid is performed to know the internal energy barrier to rotation in *glycine* by rotating both - COOH and – NH_2 groups.

2. Computational Details

All the dipeptide structures studied in this article were optimized both at HF and DFT level individually. Becke's three parameter hybrid functional using Lee–Yang–Parr correlation function [B3LYP] is the density functional method applied for the calculation. The energy minimized structure of eight dipeptides at DFT – B3LYP / 6-31G* level is shown in Figure 1. Optimized energy values are obtained

with 6-31G* basis set in each case. All the computations have been done with Gaussian 03 program.

The generalized geometrical scheme with the atom numbering is given in Figure 2. Atom C17 represents the first atom of – R group. φ is the dihedral angle between atom C6 and C13 about N8–C10 bond. C4 and C10 are the α-carbon atoms. The optimized energies of the dipeptides are listed in Table 1. A plot of calculated energy *vs.* eight different dipeptides obtained by HF / 6-31G* and DFT – B3LYP / 6-31G* level of theory is given in Figure 2. From this figure we compare the optimum energy value of the dipeptides obtained by HF / 6-31G* and DFT – B3LYP / 6-31G* methods and conclude that by DFT – B3LYP / 6-31G* method better results can be obtained. The choice of DFT method is also due to its wide spread success for the calculation of large molecules. Therefore, we decided to choose density functional approach for the present structural investigation of dipeptides.

The eight dipeptides were constructed with different combinations in which *glycine* is fixed at the N-terminus position. The C-terminus position is named as X-position. In these dipeptides the X-position is varied with different amino acids, which are connected to the fixed *glycine* end at N-terminus position. Eight different amino acids are chosen for X- position and they are *asparagine (Asn), aspartate (Asp), serine (Ser), cystine (Cys), tyrosine (Tyr), valine (Val), phenylalanine (Phe),* and *glycine (Gly).* All these are taken as neutral species. The
structural parameters were analyzed after optimization of all the dipeptide molecules at DFT level with B3LYP correlation function applying 6-31G* basis set.

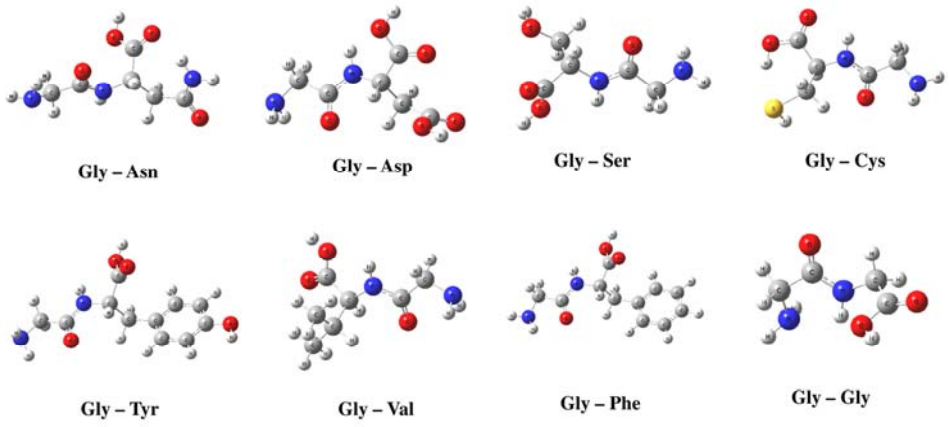


Figure 1. Optimized structures of the dipeptides studied.

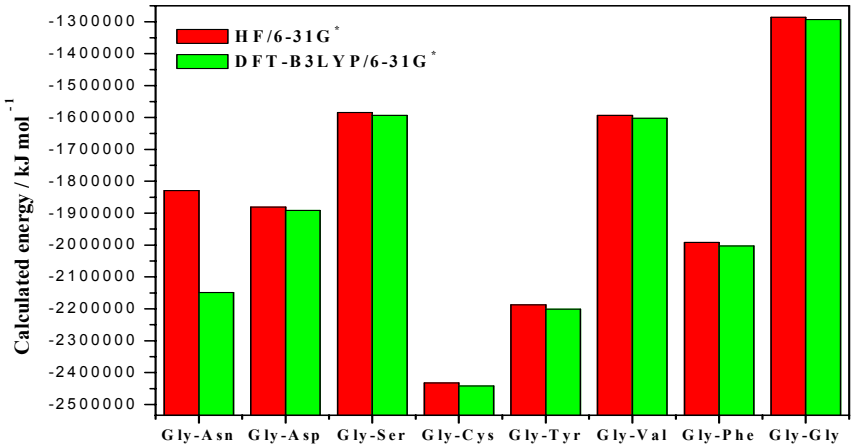


Figure 2. Plot of calculated energy of the dipeptides by HF and DFT – B3LYP method applying 6-31G* basis set.

Table 1: Calculated energy (kJ mol^{-1}) of the eight dipeptides studied

Dipeptide combination	HF / 6-31G*	DFT – B3LYP / 6-31G*
Gly – Asn	-1828803	-1839262
Gly – Asp	-1880889	-1891436
Gly - Ser	-1584770	-1593757
Gly - Cys	-2432025	-2441867
Gly - Tyr	-2187556	-2200507
Gly - Val	-1593238	-1602761
Gly - Phe	-1991990	-2002933
Gly - Gly	-1285774	-1293063

3. Results and Discussion

3.1 Bond Length and Bond Angle

Five bond lengths (C4–C6, C6–O7, C6–N8, N8–C10 and N8–H9) for the amide planes were considered for eight combinations. All the bond length data are listed in Table 2 (the atom numbering is like the numbering indicated in Figure 3). All the bond lengths are in Å unit. It is observed on studying the five bond lengths (mentioned earlier) of the amide plane of eight dipeptides that the maximum deviation in bond length is only 0.008 Å. So, we can say that the bond length is not

changed much with the variation of the X – group for all the dipeptides studied in this paper.

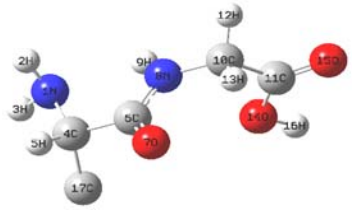


Figure 3. Geometrical scheme with the atom numbering for the dipeptides studied.

Six bond angles (in °) related to amide plane were investigated; those are ∠CCO (4-6-7), ∠CCN (4-6-8), ∠OCN (7-6-8), ∠CNC (6-8-10), ∠CNH (6-8-9) and ∠HNC (9-8-10), listed in Table 3 with respect to atom numbering (Figure 2). The maximum deviation of bond angle of amide plane *i.e*. ∠HNC (9-8-10) is 3.525°. This may be due to the variation in the – R group of the amino acids connected to *glycine i.e*. X–group.

It is clear that there is a very little difference in bond length with the variation of X–group but in case of bond angles some variation is observed, this is probably due to the steric interaction of local species or those directly bonded to the atom which is connected to the α-carbon atom and H–bonding (discussed in section 3.3)

3.2 α – Carbon Geometry

For peptide structure the geometry around *α*–carbon atom plays very important role in the overall structure of protein if they vary significantly throughout a series of amino acid residues. Slight deviation should have a big impact as the protein consists of thousands of residues. Ideally bond angle around carbon atom is 109.5°. But due to the streogenic nature of *α*-C atom the ideal nature is not expected. In this part the emphasis will be on how the bond angle around *α*–carbon changes when the X–group amino acid is changed with *Asn, Asp, Ser, Cys, Tyr, Val, Gly and Phe.* Appreciable changes in the angles would suggest that the same geometry is not retained by *α*–carbons and should be considered in larger protein structure prediction. The bond angles were measured for both the residues of eight dipeptides *i.e*. for fixed amino acid residue and varying residue (X – group) for each combination. Each dipeptides studied in the paper have two *α*–C centers, C4 and C10 (shown in Figure 2). Therefore *α*–carbon bond angle studied here are ∠$HC_{\alpha}N$ (24-4-1), ∠$HC_{\alpha}H$ (24-4-5), ∠HC_{α} plane (24-4-6), ∠$RC_{\alpha}C$ (12-10-13), ∠$RC_{\alpha}H$ (12-10-11) and ∠RC_{α} plane (12-10-8). The angles formed between the first atom of the – R group and each of the other three substituents on *α*–carbon were examined. *α*–carbon bond angles (°) are given in Table 4. The left portion of the table contained

the *glycine* residues of the dipeptides which remained fixed at the N - terminus position all along the whole study and the right side of Table 4 has the X-amino acid residues. The range of angles for *glycine* residue is not very large.

Table 2: Bond length (Å) [calculated] for amide plane for all combination of dipeptides studied

X-amino acids	C4-C6	C6-O7	C6-N8	N8-C10	N8-H9
Asn	1.526	1.225	1.368	1.451	1.011
Asp	1.538	1.226	1.367	1.457	1.010
Ser	1.529	1.225	1.366	1.457	1.010
Cys	1.526	1.229	1.361	1.447	1.014
Tyr	1.540	1.226	1.367	1.459	1.011
Val ¤	1.539	1.227	1.364	1.457	1.010
Phe	1.529	1.226	1.364	1.458	1.010
Gly	1.533	1.224	1.363	1.439	1.014
Average Maximum deviation	1.532 0.008	1.226 0.003	1.365 0.003	1.453 0.006	1.011 0.003

For *Val* ¤: C4 will be C3 and C6will be C4

Therefore the geometry around *α*–C atom (C4) does not change very much with the variation of X-group. This is due to the fact that the bulkiness of the –R group of the amino acid residues (X - group) have a little effect as this resides in a distance. The geometry around *α*–C atom (C10) of the X-group is varied, which is reflected specially in the bond angle of ∠$RC_{\alpha}C$ (12-10-13). This is because the varying –R group is in the nearest position and have an impact on the bond angle around C10. All the data are listed in Table 4 suggest that the geometry around *α*–carbon atoms are not retained throughout an amino acid sequence, so this factor must be taken into account for consideration in case of larger peptides.

Another interesting fact in Table 3 is the geometry of the two *glycine α*–C atoms, when both of them are present in *Gly–Gly* combination. This comparison reveals differences in bond angles about the *α*–carbon atoms of the two positions in the

Table 3: Bond angles (°) [calculated] for amide plane for all combination of dipeptides studied

Dipeptide combination	∠CCO (4-6-7)	∠CCN (4-6-8)	∠OCN (7-6-8)	∠CNC (6-8-10)	∠CNH (6-8-9)	∠HNC (9-8-10)

Gly - Asn	122.03	116.01	121.93	120.28	119.09	118.49
Gly - Asp	122.12	115.57	122.30	120.98	119.33	117.94
Gly - Ser	121.50	115.51	122.91	122.00	119.88	117.70
Gly - Cys	121.73	116.00	122.23	121.22	121.68	115.22
Gly - Tyr	121.88	115.30	122.80	121.76	119.71	117.57
Gly – Val [§]	121.76	115.46	122.75	121.61	119.99	118.18
Gly - Phe	121.45	115.68	122.78	121.38	119.77	117.70
Gly-Gly	121.43	114.11	122.44	121.73	115.50	121.57
Average Maximum deviation	121.74 0.378	115.45 0.553	122.77 1.677	121.37 0.632	119.37 2.312	118.04 3.525

[§] For *Val*: C4 will be C3 and C6 will be C4

dipeptide in spite of the fact that both positions are occupied by the same amino acid residue. This difference can be explained by the fact that there is a significant difference between the N of the amine group for the first amino acid and the N of the plane (previously of amine group) of the X-amino acid and similarly with the carboxyl carbon.

Table 4: Calculated α-carbon bond angles (°) in both amino acid residues of the eight dipeptides studied

X – *amino acid*	Bond angles (°)					
	Glycine			X – amino acids		
	$\angle HC_\alpha N$ (24-4-1)	$\angle HC_\alpha H$ (24-4-5)	$\angle HC_\alpha$ plane (24-4-6)	$\angle RC_\alpha C$ (12-10-13)	$\angle RC_\alpha H$ (12-10-11)	$\angle RC_\alpha$ plane (12-10-8)
Asn	114.812	106.584	105.701	111.307	109.817	109.787
Asp	108.904	106.158	107.706	110.891	107.577	111.879
Ser	114.790	106.500	105.913	111.382	109.047	110.995
Cys	114.843	106.553	105.955	113.724	107.734	110.366
Tyr	109.372	106.188	109.830	111.826	109.246	111.811

Val	108.816	106.185	107.649	111.603	107.134	112.269
Phe	114.765	106.481	105.940	111.767	109.098	111.679
Gly	108.445	106.611	106.178	106.815	107.498	111.831
Average	111.843	106.407	106.859	111.164	108.394	111.327
Maximun deviation	3.000	0.204	2.917	2.560	1.423	0.942

For *Asp* H24 will be H23 ; *Ser* H24 will be H21; *Cys* H24 will be H21; *Tyr* H24 will be H31; *Val* H24 will be H6; *Phe* H24 will be H30 and *Gly* H24, C13, H11 will be H17, C11, H13 respectively.

3.3 Dihedral Angle

Planarity of the amide plane and information about peptide bond are the key factors for investigation of the peptide molecules. Dihedral angle of the dipeptide bond can supply that information. The dihedral angle between atoms C10 and H9 with respect to atoms C6 and N8 [peptide bond: C6–N8] is important for consideration and will be named as 'D'. The dihedral angle 'D' should be 180° if the amide plane is planar. The other important dihedral angles which supply valuable information about the planarity of the peptide bond are: (i) the angle between atoms N8 and O7 with respect to the bond joining C4 and C6 referred as 'D_1' (ii) the angle between atoms C4 and C10 with respect to the bond joining atoms N8 and C6 *i.e.* the peptide bond, referred as 'D_2' (iii) the angle between atoms C4 and H9 with respect to the peptide bond *i.e.* the bond joining atoms N8 and C6, referred to as 'D_3'. For a planar structure all the above said dihedral angles should be 180°, 180° and 0° for D_1, D_2 and D_3 respectively.

All the investigated dihedral angles *i.e.* D_1, D_2 and D_3 are listed in Table 5. From the data it is clear that none of them have the perfect angle (180° or 0°, wherever required) to give structural planarity. Therefore none of the eight dipeptides studied have a planar amide plane. All other dihedrals exhibit deviations from their expected values with the large difference seen in 'D'. Deviation of dihedral angle ~ 16° (Table 6, deviation from 180°) is reported, pointing towards the fact that the geometry around the amide plane nitrogen *i.e.* N8 is not planar. Along with the calculated deviation from 180° in 'D' Table 6 presents the value of φ for the peptide bond [N8-C10] joining *glycine* with each of the X–amino acids. Table 6 also illustrates the trend of the values of φ with the change of – R group of X–amino acid residues. Similar study had been done by our group and Keefe *et. al.* where different amino acid was (fixed) at N–terminus position and varied the C–terminus position with eight other amino acids. After a thorough study with different *Gly*–X combination we conclude the hydrogen bonding (H–bonding) between amide plane

hydrogen H9 and oxygen O14 of carboxylic acid terminus of dipeptide plays the major role for determining the values of 'D'. *Asparagine* (at C–terminus position) of *Gly–Asn* combination shows stronger deviation of 'D' (Table 6). In this case, O18–H22, O19–H21 and O7–H3 distances are ~ 1.9 Å, 2.4 Å and 2.2 Å respectively, clearly indicating towards good H–bonding and hence a deviation of 'D' ~ 16°) is observed. The dipeptides studied in this paper do not show any general trend in the deviation of 'D' values from 180°. We feel the observed change in the 'D' as well as φ values can be cumulative effect of the sterric hindrance (R group of X–amino acid residue) and possible H–bonding. The interatomic distances (between O and H) are compatible to weak hydrogen bonding in peptide systems.

Table 5: Dihedral angles (°) [calculated] of the amide plane for the dipeptides studied

X – amino acid	Dihedral angles (°)			
	D_1(180)	D_2 (180)	D_3 (0)	D (180)
Asn	178.62	-171.53	-8.37	-163.16
Asp	179.39	-171.79	-7.13	-164.66
Ser	177.24	-177.22	10.26	172.50
Cys	178.46	-170.09	-6.37	-163.71
Tyr	-179.39	174.41	5.83	168.57
Val	178.60	-174.86	-0.18	-174.68
Phe	176.93	-179.38	13.07	167.53
Gly	-179.33	172.63	4.90	167.72

3.4 Potential Energy Scan (PES) for Glycine: Barriers to Rotation

The potential energy scan is performed on *glycine*. Two separate rigid potential energy surface scan has been done: (i) by rotating the carboxyl group *i.e*. – COOH group and (ii) by rotating the – NH_2 group of the *glycine* amino acid. After the rotation of different groups the minimum energy conformation is obtained and we can get valuable structural information about protein. At first the geometry of *glycine* was optimized at DFT-B3LYP level with 6-31G* basis set. A rigid potential energy surface scan was performed on the optimized geometry of *glycine* with the same method (DFT - B3LYP / 6-31G*) by rotating the – COOH group between – 180° to +180° with the increment of 10° [dihedral angle of atom O8 and N1 with respect to the bond C3-C4, Figure 4]. Here, the – COOH group is rotated between -

180° to +180° with an interval of 10° keeping the rest of the *glycine* molecule fixed. Similar kind of rigid potential energy scan was performed for – NH_2 group of *glycine* within the range of +180° to -180° with an interval of 10° [dihedral angle of atoms H2 and C4 with respect to bond N1-C3]. The energy curves for – COOH and – NH_2 group rotation of *glycine* are given in Figure 4 and 5.

Table 6: Deviation [calculated] from 180° in 'D' and the corresponding value for φ for the peptide bond [10C-8N] in the eight dipeptides studied

X-amino acids	- R group	'D'(deviation from180°)	φ (°)
Asn	$-CH_2CONH_2$	16.84	-68.258
Asp	- CH_2COOH	15.34	-156.063
Ser	- CH_2OH	-7.49	-146.896
Cys	- CH_2SH	16.29	-159.434
Tyr	- $CH_2Ph(OH)$	-11.42	-149.046
Val ¤	- $CH(CH_3)_2$	5.32	-148.434
Phe	- CH_2Ph	-12.47	-150.927
Gly	- H	-12.27	-14.437

¤ For *Val* C6 will be C4

The energy curve for – COOH group rotation of *glycine* is given in Figure 4. The curve has two maxima named 'A' and 'B'. For conformation 'A' the dihedral angle (N1-C3-C4-O8) is – 90° and for conformation 'B' the same dihedral angle is 90°. Both the conformations are of same energy ($E_A = E_B$ = -746845 kJ mol^{-1}). During the rigid PES of – COOH group, the highest energy conformers ('A' and 'B') for *glycine* arise due to the *gauche* conformation between N (of – NH_2 group) and two O atoms (of – COOH group). As, these highly electronegative atoms (N and O) are in close vicinity, the repulsion is maximum. Again the high energy value of 'A' and 'B' is supported by the fact that there is no scope of hydrogen bond because the N–H and O–H bond distances are pretty large (Table 7). Two energy wells are also identified in the curve (Figure 4) named 'C' and 'D'. For conformation 'C' the dihedral angle (N1-C3-C4-O8) is –20 º and for conformation 'D' the same dihedral

N–H / O–H	Bond distance (in Å)	
	Conformation 'A'	Conformation 'B'
8O-2H	2.9	3.6
8O-10H	3.6	2.9
7O-2H	3.5	3.1
7O-10H	3.1	3.5
1N-9H	4.0	4.0

O--H	Bond distance (in Å)	
	Conformation 'C'	Conformation 'D'
8O-2H	2.4	2.6
8O-10H	2.6	2.4

electronegative atoms are sufficiently apart from each other to minimize repulsion. This lowering in energy is supported by hydrogen bonding (Table 8). The barrier of rotation is ~ 4 kJ mol^{-1} for conformation 'C' and 'D'. The lowest energy conformers are 'F' and 'G' having the same energy (E_F = E_G = -746858 kJ mol^{-1}). For conformation 'F' the dihedral angle (N1-C3-C4-O8) is –180° and for conformation 'G' the same dihedral angle is 180°. For both the conformations the lowest energy can be established by strong hydrogen bonding between O7, H2 and O7, H12 (for both 'F' and 'G' conformation, O7-H2 and O7-H12 distance is 2.7 and 2.7 Å respectively). Structures of 'A', 'B', 'C', 'D', 'F' and 'G' conformers are given in Figure 5.

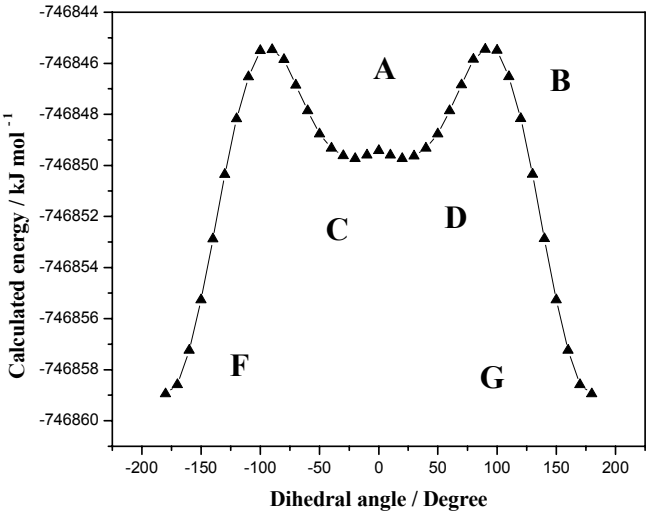
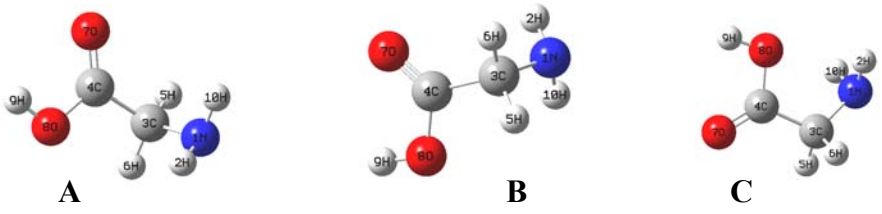
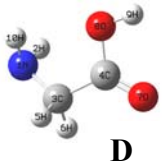


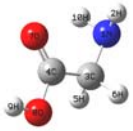
Figure 4. Plot of dihedral angle *vs.* energy (calculated) for the -COOH group rotation in g*lycine.*





D

F



G

Figure 5. Conformations of *glycine* at different positions ['A': ~ -90°, 'B': ~ 90°, 'C': ~ -20°, 'D': ~ -20°, 'F': ~ -180° and 'G': ~ 180°] of the plot (Fig 4) related to the PES study of *glycine* by rotating the –COOH group.

Figure 6 shows the energy curve for the rotation of – NH_2 group in *glycine* with all the other parts remaining rigid. The highest energy conformer of the energy curve is 'I' (E_I = -746814 kJ mol^{-1}) and the lowest energy conformer is 'H' (E_H = -746843 kJ mol^{-1}). For conformation 'I' the dihedral angle (H2-N1-C3-C4) is –120 º and for conformation 'D' the same dihedral angle is 50°. In the heighest energy conformer 'I', the N (of – NH_2 group) and two O atoms (of – COOH group) are in gauche conformation and there is no scope for hydrogen bonding. The O-H and N-H bon distances are given in Table 9. But in the low energy conformation the N (of – NH_2 group) and two O atoms (of – COOH group) are in partially staggered conformation. And pretty strong hydrogen bonding between O8 and H10 atoms (O8-H10 bond distance is 2.4Å). The barrier of rotation is ~ 29 kJ mol^{-1} for conformation 'H'. The highest (I) and lowest energy conformation (H) is given in Figure 7.

Table 9: N–H and O–H bond distances for conformation 'G'

N–H / O–H	Bond distance (Å)
8O-2H	3.3
8O-10H	3.8
7O-10H	2.8
7O-2H	3.2
1N-9H	4.3

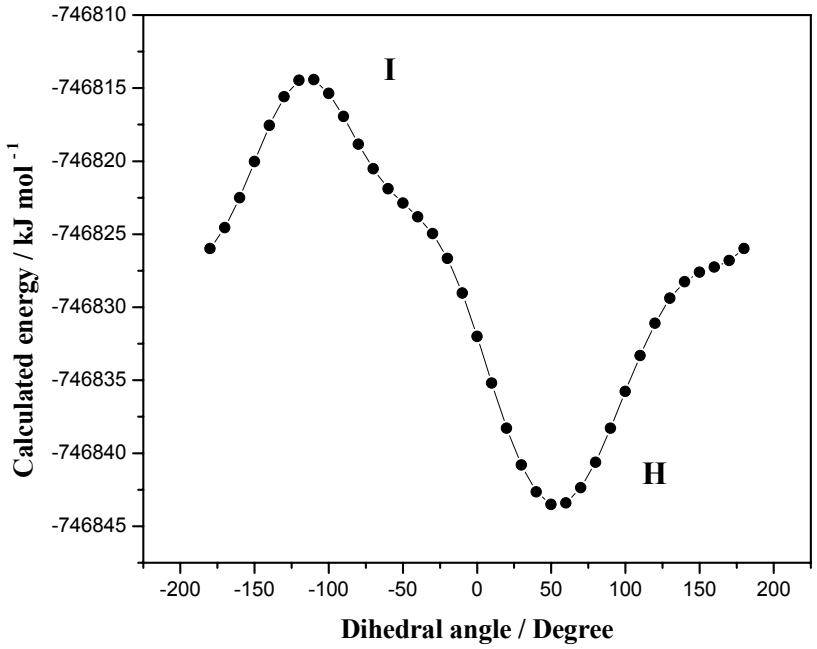


Figure 6. Plot of dihedral angle *vs.* energy (calculated) for the -NH_2 group rotation in g*lycine.*

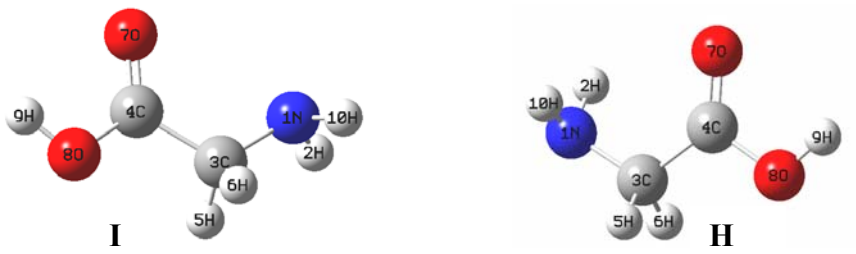


Figure 7. Lowest ['H': ~ 49°] and highest ['I': ~ -120°] energy conformations of *glycine* while rotating the -NH_2 group during the PES study of *glycine*.

4. Conclusion

Structural parameters investigated in this article give some idea on the conformational stability of amino acid sequences. This valuable structural information of small amino acid sequences enlightens the structural stability of a protein chain. Geometry optimization of the eight dipeptides studied in this article by applying DFT-B3LYP / 6-31G* level of theory offer better result than that

obtained by HF / 6-31G* method. After rigorous computation, the general bond length, bond angle data does not vary much. So we can say that the amide plane is more or less fixed. This data is a demonstration of the rigidity of the peptide backbone. This rigidity supports the idea that a proteins function is closely related to its shape. The rigid potential energy scan was done on *glycine* molecule by DFT method with B3LYP correlation applying 6-31G* basis set. The potential energy scans for *glycine* molecule by rotating – COOH and – NH_2 groups show energy barrier of ~ 4 and ~ 29 kJ mol^{-1} respectively indicating the fact that the structure is rigid. The protein structure is also rigid. This rigidity will be present not only in the backbone but also in the orientation of the – R group (for *glycine*, R = H). A consideration should be mentioned here is the methodology used for this study. During the rotation of – COOH and – NH_2 group (PES study) all the other parameters remained fixed. Conformation change in the other atoms, however, may exist as the groups rotate. This could possibly lower the barrier of rotation. As the large barrier is considered for all the rotations, it can be assumed that the lowering in energy due to conformational change would be negligible.

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