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Study of nonplanarity of peptide bond using theoretical calculations

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Abstract

The conformational dependence of nonplanarity of the peptide bond of formylglycinamide has been studied using ab initio and density functional theory methods. Hartree–Fock self-consistent field theory (HF), Møller–Plesset perturbation theory (MP2) of ab initio and B3LYP level of theory of dft method have been used employing 6-31++G** basis set. The MP2 method predicts better results than HF and B3LYP levels of theory for conformational stability dependence of nonplanarity. Systematic dependence of planarity deviation has been observed in MP2 theory. The chemical hardness values successfully predict the conformational region, but fail to obey maximum hardness principle. It is concluded that the most reliable dft method could not successfully predict the planarity of peptide bond in comparison with electron correlated method of ab initio method.

Keywords: Ab initio; Density functional theory; Formylglycinamide; Nonplanarity; Peptide bond; Maximum hardness principle

1. Introduction

Protein molecules are the basis for many studies in a number of research fields such as drug design and functional genomics. This research critically depends on

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the quality of the coordinates, which represents bond lengths, bond angles, planarity of certain groups and the standard deviation of their values about the observed mean. Engh and Huber [1] have performed complete study using the Cambridge structural database (CSD) [2] for the geometrical information.

Various researchers have extensively studied [3–7] the planarity of peptide group, using X-ray crystal structures and NMR spectroscopy. Mac Arthur and Thornton [8] made a complete survey on the planarity of peptide bond in peptides and proteins using CSD database. It has been concluded that the deviations from the planarity can be tolerated with a standard deviation in the angle up to 6° about a mean value for the trans peptide, that is less than 180°. Later, Rick and Cachau [9] have derived similar observations from the analysis of protein structures in the protein data bank (PDB) [10]. They concluded that, the torsional rotation of the peptide bond is environment dependent and different secondary structure elements in proteins are characterized by different degrees of the nonplanarity of ω angle. Recently, Ramek et al. [11] have studied the conformational dependence of nonplanarity of the peptide bond; and concluded that, the systematic deviation has been observed but fails to predict planarity deviation dependence on the conformational preference. They have taken small peptide system (For-Ala-Ala-NH_2) for their study. Moreover, establishing correlation between peptide main chain and planarity provides a continuous challenge for experimentalists and theoreticians alike. For theoreticians, uncertainties arise, for example, from the problem of ideal size, type of a peptide model to be used for the computation, the required minimum level of ab initio theory, and the incorporation of important structural factors such as nonplanarity of the amide group. The correlation between conformation and planarity will be useful in studying secondary structure of protein.

Most of the earlier studies on nonplanarity have considered the real systems such as peptides and proteins and taken their data from CSD and PDB. The analysis of ω angles and their distributions in the existing database of protein structure depend on the refinement of the method used. It has been estimated that even in the best-resolved X-ray protein structures the backbone torsion angles are subject to a minimum error of 10° [5]. The determination and refinement of protein structure by X-ray crystallography requires therefore the use of known structural information in order to supplement the experimental data. Some of the theoretical studies have been reported on the planarity using semi empirical and ab initio methods [11–14]. Majority of previous theoretical studies whether "empirical," or quantum-mechanical, the peptide bond was considered as planar and trans. However, not much study on planarity has been done using high accurate and well-defined quantum chemical methods. This is due to computational tractability, and it is difficult to study the real protein system using the quantum chemical methods. Therefore, one can take simple model system that has the characteristics of real protein systems for the study. Further, it is a very challenging problem to study the nonplanarity using the theoretical methods [14]. Theoretical results are sensitive to both basis set effects and electron correlation. The ab initio calculations [15] on amino acids have been published during the past decade, which demonstrates the general utility of quantum chemical procedures in studies of such molecules. Recently, density functional theory methods

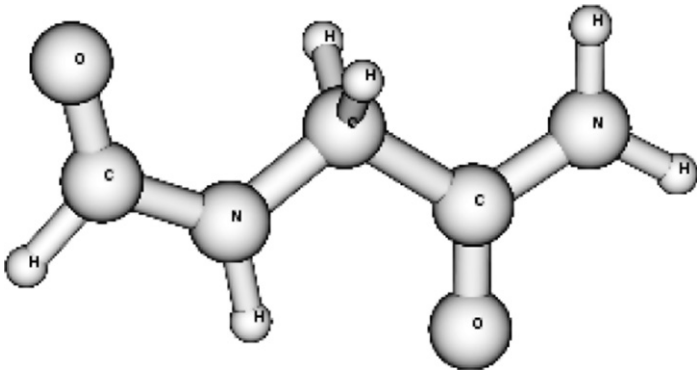

Fig. 1. Molecular structure of formylglycinamide is taken in this study.

have become powerful tool to study the biomolecules, an alternate to high cost ab initio methods. More number of dft studies [16–19] have been performed on biomolecules and it can be confirmed the validity for these methods.

Therefore, in this paper, we are interested to examine the conformational dependence of nonplanarity of the peptide, formylglycinamide using ab initio and density functional theory methods. The selection of formylglycinamide (Fig. 1) is due to the peptide with the simplest side chain. Because Ramek et al. [11] have found that side chain in the amino acid residue would affect the planarity of the peptide. The validity of maximum hardness principle (MHP) [20] in this molecule has been tested using ab initio method (HF). The present investigation contains two steps; one is to correlate the deviations of ω angle in between the absence and presence of side chain in the peptide systems. Second, to find out the validity of dft method to study the nonplanarity of biomolecular systems.

2. Computational details

Ab initio and density functional theory methods have been used to study the nonplanarity of peptide bond in formylglycinamide. Hartree–Fock self-consistent field theory, second order Møller–Plesset perturbation theory [21] of ab initio method and Becke's three parameter [22] hybrid functional combined with gradient corrected functional of Lee et al. [23] of dft method employing 6-31++G** basis set have been used. Earlier studies have confirmed that this hybrid functional is much reliable for studying hydrogen-bonded systems. The structure has been optimized at different ϕ, ψ angles of the first peptide residue, and other parameters except the first peptide bond moiety have been kept frozen. The 2D conformational energy surface has been generated for different ϕ, ψ angles, because of the convenience for the comparison with peptide bond angle (ω) and C—N bond length. The numbering used to define the ϕ, ψ angles is shown in Table 1, that we have termed it as region numbers. The chemical hardness values have been calculated at HF level of theory implement-

Table 1
Assignment of region numbers with respect to ϕ_i and ψ_i dihedral angles

Region numbers	ϕ_i	ψ_i
1	0	0
2	0	30
3	0	60
4	0	90
5	0	120
6	0	150
7	0	180
8	0	210
9	0	240
10	0	270
11	0	300
12	0	330
13	0	360
14	30	0
15	30	30
16	30	60
17	30	90
18	30	120
19	30	150
20	30	180
21	30	210
22	30	240
23	30	270
24	30	300
25	30	330
26	30	360
⋮	⋮	⋮
169	360	360

ing 6-31++G** basis set. All the calculations have been performed using Gaussian 98W program package [24].

3. Results and discussion

The relative energy, C—N bond length, and peptide bond angle (ω) have been calculated for different ϕ and ψ angles, the minimum energy conformations have been predicted and are depicted in Tables 2–4. Figs. 2–4 show the potential energy surface map for the optimized structure of ϕ and ψ angle with respect to the relative energy, peptide bond angle (ω) and C—N bond length calculated at MP2 level of theory.

Generally the conformational stability of the system has been studied by the relative energy analysis. Hence, the relative energies have been calculated between the global minimum and different local minima. It shows that, the global minima exists at the region number 85 for $\phi = \psi = 180°$. The HF-SCF and B3LYP level of theory predicts 11 minimum energy conformations (one global minimum, five pairs of mir-

Table 2
Stable conformation points at different ϕ_i (in degrees) and ψ_i (in degrees), the peptide bond angle ω_i (in degrees), the C—N bond length R (in Å), deviation from planarity, relative energy (in kcal/mol) and chemical hardness (in eV) computed at HF level of theory implementing 6-31++G** basis set

S. No.	Region numbers	ϕ_i	ψ_i	ω_i	R	Planarity deviation	Relative energy	Chemical hardness
1	85	180	180	179.91	1.342	0.09	0	5.89
2	98	210	180	191.15	1.345	−11.15	0.99	5.89
3	72	150	180	168.8	1.345	11.2	0.99	5.89
4	121	270	90	184.51	1.347	−4.51	2.31	5.95
5	110	240	150	190.63	1.348	−10.63	2.38	5.93
6	49	90	270	175.44	1.347	4.56	2.4	5.95
7	64	120	210	169.31	1.348	10.69	2.4	5.91
8	136	300	150	188.87	1.347	−8.87	5.65	5.92
9	34	60	210	171.1	1.347	8.9	5.71	5.91
10	28	60	30	187.74	1.353	−7.74	8.38	5.84
11	142	300	330	172.18	1.353	7.82	8.41	5.84

Table 3
Stable conformation points at different ϕ_i (in degrees) and ψ_i (in degrees), the peptide bond angle ω_i (in degrees), the C—N bond length R (in Å), deviation from planarity, and relative energy (in kcal/mol) computed at MP2 level of theory implementing 6-31++G** basis set

S. No.	Region numbers	ϕ_i	ψ_i	ω_i	R	Planarity deviation	Relative energy
1	85	180	180	179.94	1.355	−0.06	0
2	50	90	300	177.47	1.357	−2.53	0.4
3	121	270	60	182.46	1.357	2.46	0.45
4	98	210	180	193.56	1.359	13.56	0.64
5	72	150	180	166.37	1.359	−13.63	0.65
6	110	240	150	192.43	1.363	12.43	1.59
7	60	120	210	167.5	1.363	−12.5	1.61
8	136	300	150	188.48	1.358	8.48	3.68
9	34	60	210	171.49	1.358	−8.51	3.72
10	40	90	0	189.2	1.367	9.2	4.95
11	130	270	360	170.52	1.367	−9.48	4.98
12	28	60	30	187.96	1.365	7.96	5.42
13	142	300	330	171.97	1.365	−8.03	5.46

ror-image conformers, and one global minimum, four pairs of mirror-image conformers, and two local minima at HF and B3LYP levels of theory, respectively.). But MP2/6-31++G** level of theory predicts 13 conformations (one global, six pairs of mirror image conformers). Two more stable conformations have also been predicted by MP2 level of theory at region number 41 and 131. Császár [25] once reported that the different levels of theory predict different number of conformations in glycine. Ramek et al. [11] have predicted 47 optimized structures for *N*-formyl-L-alanyl-L-alanine amide at MP2/6-311G** level of theory within the range of 11 kcal/mol which is due to the presence of more number of flexible rotors. While studying the order of stability among the considered levels of theory, the second

Table 4
Stable conformation points at different ϕ_i (in degrees) and ψ_i (in degrees), the peptide bond angle ω_i (in degrees), the C—N bond length R (in Å), deviation from planarity, and relative energy (in kcal/mol) computed at B3LYP level of theory implementing 6-31++G** basis set

S. No.	Region numbers	ϕ_i	ψ_i	ω_i	R	Planarity deviation	Relative energy
1	85	180	180	179.95	1.355	−0.05	0
2	98	210	180	192.79	1.358	12.79	0.88
3	72	150	180	167.16	1.358	−12.84	0.9
4	50	90	300	176.9	1.356	−3.1	1.94
5	120	270	60	183.06	1.356	3.06	1.98
6	110	240	150	191.74	1.361	11.74	2.23
7	60	120	210	168.2	1.361	−11.8	2.24
8	35	60	240	173.43	1.359	−6.57	5.87
9	40	90	0	187.3	1.367	7.3	6.45
10	130	270	360	172.48	1.367	−7.52	6.48
11	28	60	30	187.05	1.366	7.05	7.88

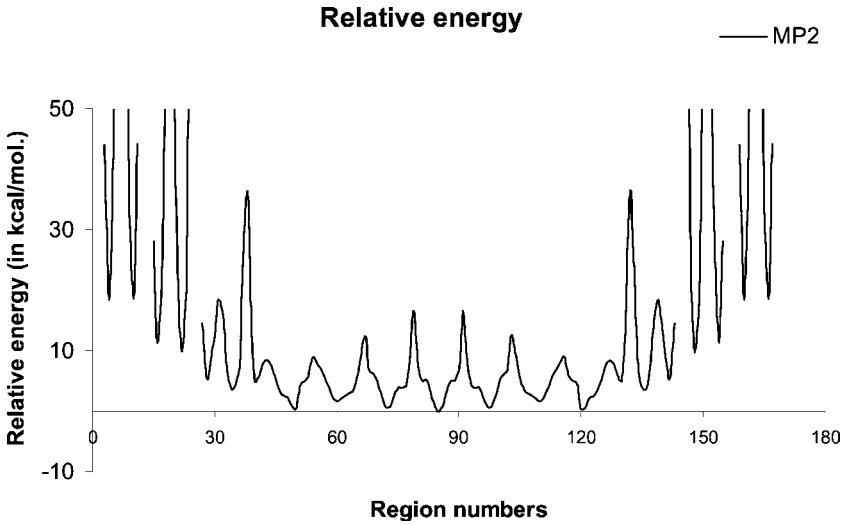

Fig. 2. Torsional dependent of relative energy at MP2 levels of theory.

stable conformation predicted by the MP2 level of theory is found to be the sixth stable conformation at HF and fourth stable conformation at B3LYP levels of theory. The third stable point will be 4th and 5th at HF and B3LYP levels of theory, respectively. There are several factors determining the position of backbone conformers, this includes the effects of one particle basis set deficiency, the extent of electron correlation, and the effect of geometry optimization. However, this is acceptable, because these conformations are having low energy barriers, so the order of stability is different between the levels of theory. Earlier Császár [17] and Barone et al. [16] have confirmed that the order of stability is different in between the levels

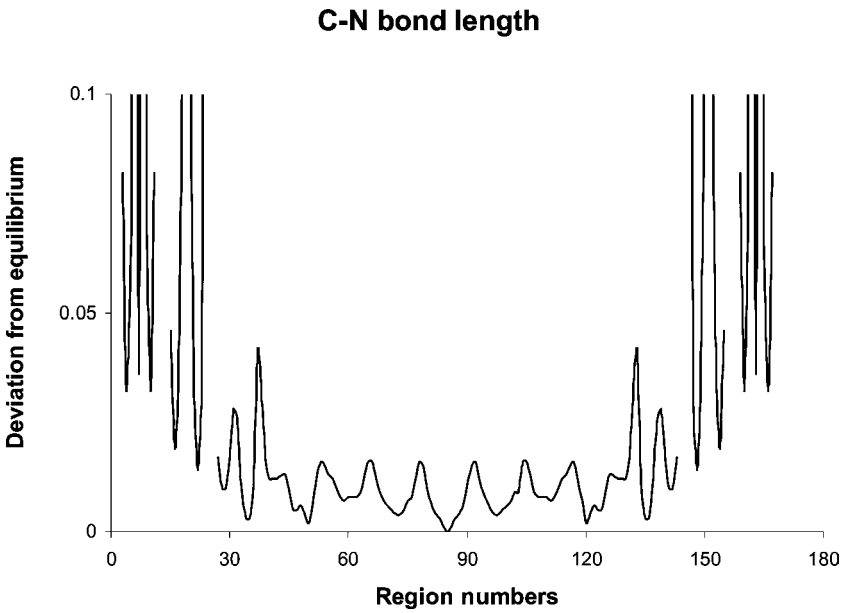

Fig. 3. Torsional dependent of C—N bond length at MP2 levels of theory.

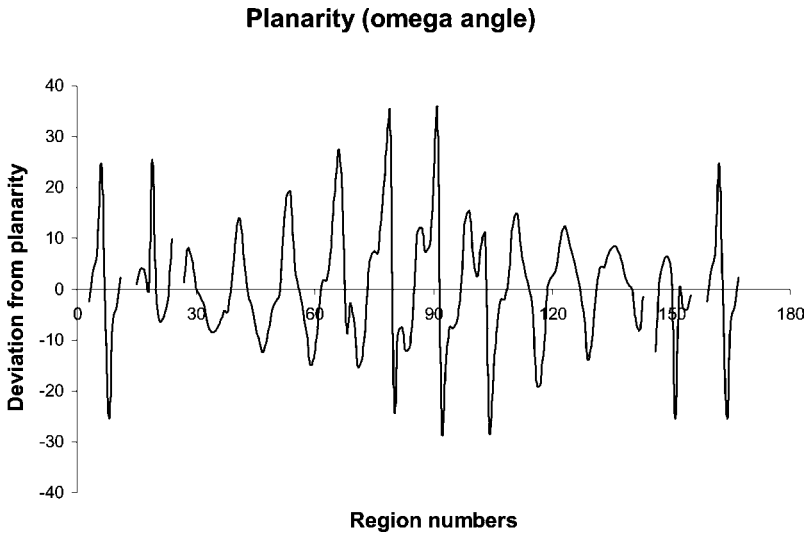

Fig. 4. Torsional dependent of Planarity at MP2 levels of theory.

of theory, because the energy difference between two conformations in glycine is very low. Hence, even at the higher level of theory, the order of stability of the conformers is changed for different basis set.

While studying the conformational dependence of C—N bond length, it can be noted that all the levels of theory have predicted the systematic deviation of C—N bond length. This shows that if the C—N bond length increases, the relative energy also increases, which means the rigidity (or) charge transfer decreases as the stability of the conformation decreases. Barone et al. [16] have studied the significance of C—N bond length and the importance of quantum chemical method to study the planarity. They concluded that the C—N bond in peptide plays an important role in deciding the planarity of the system. Moreover, the C—N bond length is a crucial measure for the double bond character of the peptide. In the present study, HF level of theory calculated the C—N bond length as 1.342–1.353 Å and MP2 level of theory as 1.355–1.365 Å, and it varies ~0.01 Å, at B3LYP level of theory which is in agreement with Fogarasi and Szalay [14] study on the peptide system. In their study they have accurately calculated the C—N bond length as 1.354 Å using CCSD method. The higher value of C—N bond is partly the consequence of the nonplanar geometry. From the structural point of view, the C—N bond length 1.35–1.36 Å indicates clearly the partial double bond, the corresponding experimental values in methanimine (H_2C=NH) and methylamine (CH_3–NH_2) are 1.273 and 1.471 Å, respectively. [26,27] The well-known explanation is that π-electron conjugation between the CO double bond and the nitrogen lone pair strengthens the C—N bond, leading to partial double bond character, which is lost during rotation.

While considering the conformational dependence of planarity, the HF and B3LYP methods, could not predict the conformational dependence of planarity deviation. This indicates that, there is no similar order is found in between the relative energy and planarity deviation angle. But the Møller–Plesset perturbation method predicts the conformational dependence of planarity for the first three conformers. HF and B3LYP levels of theory predict the second and third stable conformations have large deviation from the planarity i.e., the second and third stable conformations are at the region number 98, 72, and have the planarity deviation −11.15°, 11.2°, and 12.79°, −12.84° at HF and B3LYP levels of theory, respectively. At the MP2 level of theory the second and third stable conformations have the planarity deviation is −2.53° and 2.46° at the region numbers 50 and 121, respectively. Eventhough MP2 level of theory shows conformational dependence, there is not much correlation found between the ω angle and relative energy. Because, at MP2 level of theory (Fig. 4), the conformation observed at the region number 99, may have the secondary interaction between the C=O and —CH groups. This may be the reason for low relative energy and higher deviation, such type of secondary interaction is also found in the region number 111, in those regions the secondary interactions decide the planarity.

The maximum deviation of ω angle observed in the present study is −11.15° to +10.69°, −13.63° to +13.56°, and −12.84° to +12.79° for HF, MP2, and B3LYP levels of theory, respectively. In the case of *N*-formyl-L-alanyl-L-alanine amide, [11] it can be predicted approximately −30° to +30° at MP2/6-311G** level of theory. Experimental results [3] show that the ω angle deviation for cyclotetraglycine is 14° to 24°, from an ideal value of 180°, whereas ω angle deviation 10.2° was observed in the crystal structure of glycyl-L-alanine [28]. It has been noted that the highest

deviation was observed in Ramek et al. [11] study due to the presence of side chain. Perczel and Császár [29] once reported that the side chains in amino acids would largely affect the conformations of the systems. This is again confirmed by the present study as well as in Ramek et al. [11] study also. Since the deviations from planarity are small in the present investigation, so it is not easy to judge whether the ω values in the model system correspond to individual real deviation in actual structure. Due to the presence of simplest side chain, more number of secondary interactions has been restricted, that will decrease the deviation of angle. Furthermore, the presence of side chain causes a perturbation in the electronic distribution of the adjacent —CO-NH- bonds, reflecting their presence in the deviation. In the case of dialkyl glycines, [8] the Thorpe–Ingold distortion of the C^{α} geometry may affect the peptide bond geometry in a more subtle manner. Moreover, the potential energy barrier is very low in between the conformers. This may be one of the reasons for the mismatch between the order of planarity deviation and relative energy. The dft method considered in this study, fails to predict the order of stability in comparison with MP2 level of theory. Therefore, one may use highly correlated methods, such as CCSD to obtain the correct order of dependence for planarity.

The conformational stability of the molecule has been studied using maximum hardness principle (MHP). The chemical hardness is defined as

$$\eta = 1/2\left(\mathrm{d}^2E/\mathrm{d}N^2\right)_{V(r),}$$

where E is the total energy: $V(r)$ is the external potential, and N is the number of electrons, in a finite difference approximation, with the assumption that the energy

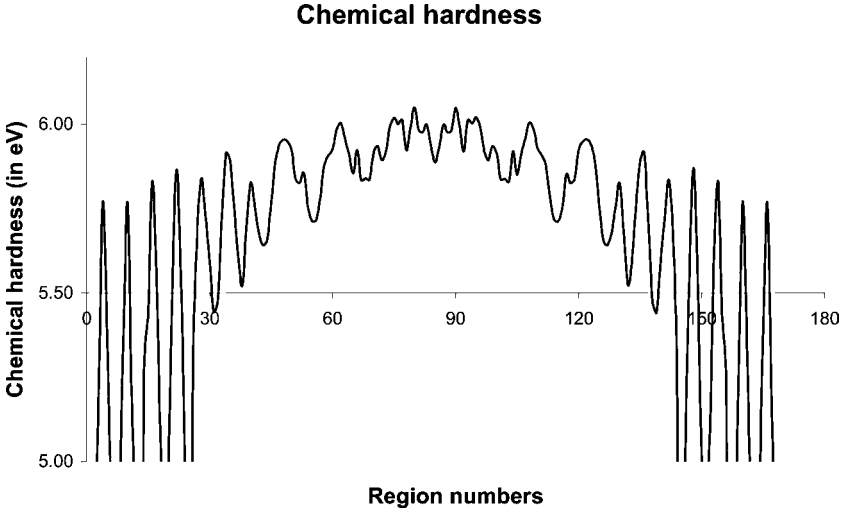

Fig. 5. Torsional dependent of chemical hardness at HF level of theory.

varies quadratically with the number of electrons. This can be expressed with an orbital basis as

$$\eta = \frac{I - A}{2},$$

where I is the ionization potential and A is the electron affinity of a system. The chemical hardness values have been calculated for the different torsional dependence conformations (Fig. 5) at HF level of theory implementing 6-31++G** basis set. In the present investigation, it has been found that chemical hardness has been calculated from the orbital energies. The orbital energies are accurately calculated by HF level of theory. In the present study, we have found that the Maximum hardness principle fails to predict the order of stability for the conformations and it has been noted that correlation exists between relative energy and chemical hardness. The chemical hardness value varies between 5.50 and 6.00 eV for stable conformation region. At the same time, the large distortion is found in the region 0–35 and 140–180. This distortion can arise from pyramidalization at the amino nitrogen atom as well as simple twist about the peptide bond. The chemical hardness values also support that the regions above mentioned are disallowed region for the stable conformations as it has been observed by the relative energy. So the chemical hardness produce the systematic deviation with respect to ϕ–ψ space and it successfully predicts the conformational region. Since some of the conformations have very low energy barrier, so the chemical harness values could not find the order of stability as like relative energy.

4. Conclusions

In summary, HF and B3LYP levels of theory predicts similar results for conformational stability of the formylglycinamide molecule, but MP2 method provide better results than the above two methods. This indicates that correlation term should be essential to study the complex conformational stability of some biological systems. The C—N bond length calculated by all the theories, produce comparable results. The systematic dependence of planarity deviation have been noted at MP2 level of theory, but HF and B3LYP level of theory have not predicted systematic dependence on planarity. Moreover, the steric effects will decide planarity in some conformations. Again it is confirmed that the peptide bond deviation is also depends upon the side chain. From this study, it is confirmed that one can use the highly correlated methods or well defined exchange correlation functionals to study the planarity of the peptide bond for biological systems. The chemical hardness values successfully predict the conformational region, but fail to obey MHP. Finally, it has been concluded that B3LYP level of theory of dft method could not successfully predict the planarity of peptide bond, in comparison with electron correlated method of ab initio method.

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