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Exploring the structure and stability of β-dipeptide – A quantum chemical and molecular dynamics study

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Density functional theory (DFT) calculations followed by molecular dynamics study has been performed to analyze the structure and stability of β-dipeptide structures in aqueous medium. From DFT study, three local minima with folded conformations and one local minimum with unfolded conformation have been identified. In gas phase, the most stable β-dipeptide has a folded conformation with a weak hydrogen bonding. The interaction of water molecules, approximated from the first solvation shell, also confirms the folded conformation to be the most stable structure. The DFT optimized β-dipeptide conformers have been simulated in explicit water to evaluate the tendency of folded and unfolded state formation. Simulations confirmed the transition of the structure from folded to unfolded and vice versa and further indicated the former to happen rapidly within a few pico second time scale.

Keywords: Peptides, Conformers, DFT, Ab initio, Molecular dynamics

1 Introduction

Beta peptides, which consist entirely of β-amino acids, have been a subject of intense research, since the first structures were elucidated[1]. β-peptides have attracted much attention due to their potential use as the non-degradable peptide mimetics and the possibility to tune the conformation of the peptide by altering the side chain composition[2-9]. Small β-peptides, as few as six amino acid residues, fold into turns[10-15] helices[10,12,16-22] and sheet- like structures[11,14-16] analogous to the secondary structures of protein. At first, the study on the secondary structures of β-peptide was carried out on the polymers derived from β-amino acids (the so called Nylon-3 derivatives) and poly (β-alanine)[2,3]. Each β-amino acid has three backbone rotatable bonds (ϕ, ψ and μ) compared to α-amino acid (which has only two), making β-peptides more flexible and equivalent to α-peptide. Because of this greater flexibility, easy formation of secondary structures for β-peptides is totally unexpected and hence the understanding of β-peptide folding acquired much interest in research.

The process of peptide folding is a critical step towards the understanding of protein folding and would greatly facilitate the design of peptides with predetermined structures and properties for biotechnological applications[4]. Dynamics simulation method like molecular dynamics (MD) has been used to characterize the particular folded states of peptides in solution[23,24]. Various molecular dynamics simulation studies have been carried out to predict the folding patterns of β-peptides[6-8]. The possibility of simulating the reversible folding in solution and the transition between folded and unfolded states for a β-heptapeptide have been studied by Dura *et al.*[9] A very few studies on the conformational features of β-peptides have been reported using theoretical models.[25] Gellman *et al.*[26] reported the IR and NMR study of conformation preference of β-dipeptide. Wu *et al.*[27] studied different β-peptides and located conformational minima with low energies and conformations significant for secondary structures.

Despite many efforts, several issues on folding and unfolding of β-peptides are still needed to be resolved. Hence here we attempt to study the folding and unfolding behavior of the β-dipeptide[27], which is a non-natural glycine-dipeptide analogue with an additional methylene in the backbone, by applying state-of-the-art techniques such as quantum chemical (QC) and molecular dynamics (MD) simulation. We made a quantum chemical study on the interaction of various conformers of the chosen β-dipeptide with five water molecules included explicitly in the first shell region of

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about ~2.5 Å around the dipeptide. Subsequently MD study on the folded and unfolded states of the optimized β-dipeptide conformers in explicit water by exploring the time behavior of their end-to-end distance, main chain dihedral angle ϕ and their trajectories has been performed. Such a study on this β-dipeptide would in-turn be helpful in understanding the mechanism and dynamics of various peptides which continues to be a central problem in molecular biology.

2 Method of Calculation

As mentioned earlier, the calculation is comprised of two parts. First the QC study on the complexation of the conformers of β-dipeptide with five water molecules and second the MD simulation to infer the folded and unfolded patterns of the optimized conformers. For convenience, herein after we name the considered β-dipeptide as glydimet in the discussion.

2.1 Quantum chemical calculation

The geometries of isolated conformers of glydimet with five molecules of H_2O were optimized at HF/6-31G** and B3LYP/6-31G** levels of theory. Topological analysis were carried out to get the charge density $\rho(r)$ and Laplacian of charge density $\nabla^2\rho(r)$ for the bonds using Bader's Atoms in Molecules (AIM) theory[28]. The chemical hardness values for the conformers of isolated and complex β-dipeptide systems were calculated at HF/6-31G** level of theory. NBO analysis[29] was performed to understand the charge transfer of hydrogen bonding orbitals in the complexes. All the calculations were done using the Gaussian 03W program package[30].

2.2 Molecular dynamics simulation

A nanosecond (ns) MD simulation for the system containing the above optimized isolated structures with water added explicitly in a rectangular box using TIP3P water model[31] was carried out with boundary condition at 300 K. The temperature of the system was slowly increased to reach 300 K and maintained to a NVT ensemble. As a result, the mass density in the box was 1.0 g/cm^3. The non-bonded cut-off distance 10.0 Å was employed. The trajectories in each step and the transition state region of structures during simulation were investigated for the change in conformation from folded to unfolded and vice versa. All the MD simulations were performed by applying ff99 amber force field[32] using the AMBER program package.[33]

3 Results and Discussion

3.1 Quantum chemical studies

Wu *et al.*[27] have located six conformational minima for glydimet both in gas and solution phases. Here in our study, during optimization, out of all the six conformers 5a, 5b, 5c, 5d, 5e, and 5f (named by Wu *et al.*), the stationary points for the conformers 5d and 5f were not obtained. Hence, we considered only the optimized minimum energy conformers 5a, 5b, 5c, and 5e for further analysis. For our convenience, we have denoted the conformers as A, B, C and D (Fig. 1) and those with water

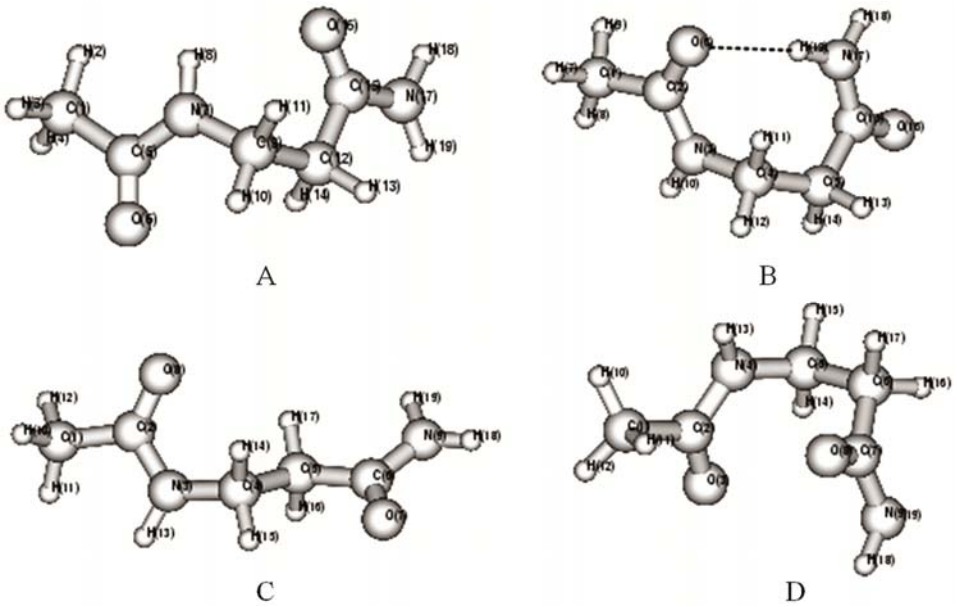

Fig. 1 — Isolated structures of conformers 5a, 5b, 5c, and 5e (designated as A, B, C and D) of β-dipeptide structures optimized at B3LYP/6-31G** level of theory.

molecules as AW, BW, CW and DW (Fig. 2) for further discussion.

Due to interaction with water molecules, the dipole moment, relative energy and chemical hardness of the conformers were found to vary considerably (Tables 1 and 2). In the isolated form, conformer A is found to be more stable, with the dipole moment of 3.238 Debye at HF/6-31G** (Table 2) and 4.837 Debye at B3LYP/6-31G** levels of theory (Table 2), which is in consistent with the work of Wu *et al.*[27] Although there is a strong intramolecular hydrogen bond in B, enthalpically conformer A is more stable. The key reason for this is the latter's unfavorable dihedral angle ψ(23º) that causes about 1.5 kcal/mol destabilization[34]. Also, conformer C can be derived from A by rotating the dihedral angle μ from gauche to anti, however, it is found to be less stable than A by 2.859 kcal/mol at B3LYP/6-31G** level of theory. Conformers B and D differ only by dihedral angle ψ,

Table 1 — Dipole moment (units of Debye), relative energy (units of kcal/mol) and chemical hardness (units of eV) of isolated and complex glydimet structures calculated at HF/6-31G** level of theory.

Conformers	Dipole moment		Relative energy		Chemical hardness	
	Isolated	Complex	Isolated	Complex	Isolated	Complex
A	3.238	1.952	0	0	7.852	7.934
B	4.854	4.958	1.869	3.609	7.915	7.249
C	3.098	9.134	2.519	7.714	8.008	7.760
D	2.813	4.185	3.529	6.067	7.891	7.932

Table 2 — Dipole moment (Debye), relative energy (kcal/mol) and interaction energy (Δ*E*) (kcal/mol) of isolated and complex glydimet structures calculated at B3LYP/6-31G** level of theory.

Conformers	Dipole Moment		Relative Energy		ΔE
	Isolated	Complex	Isolated	Complex	Complex
A	4.837	3.897	0	6.189	-0.078
B	4.823	3.581	0.314	0	-0.032
C	2.333	3.172	2.859	4.501	-0.076
D	2.262	1.785	3.690	1.318	-0.070

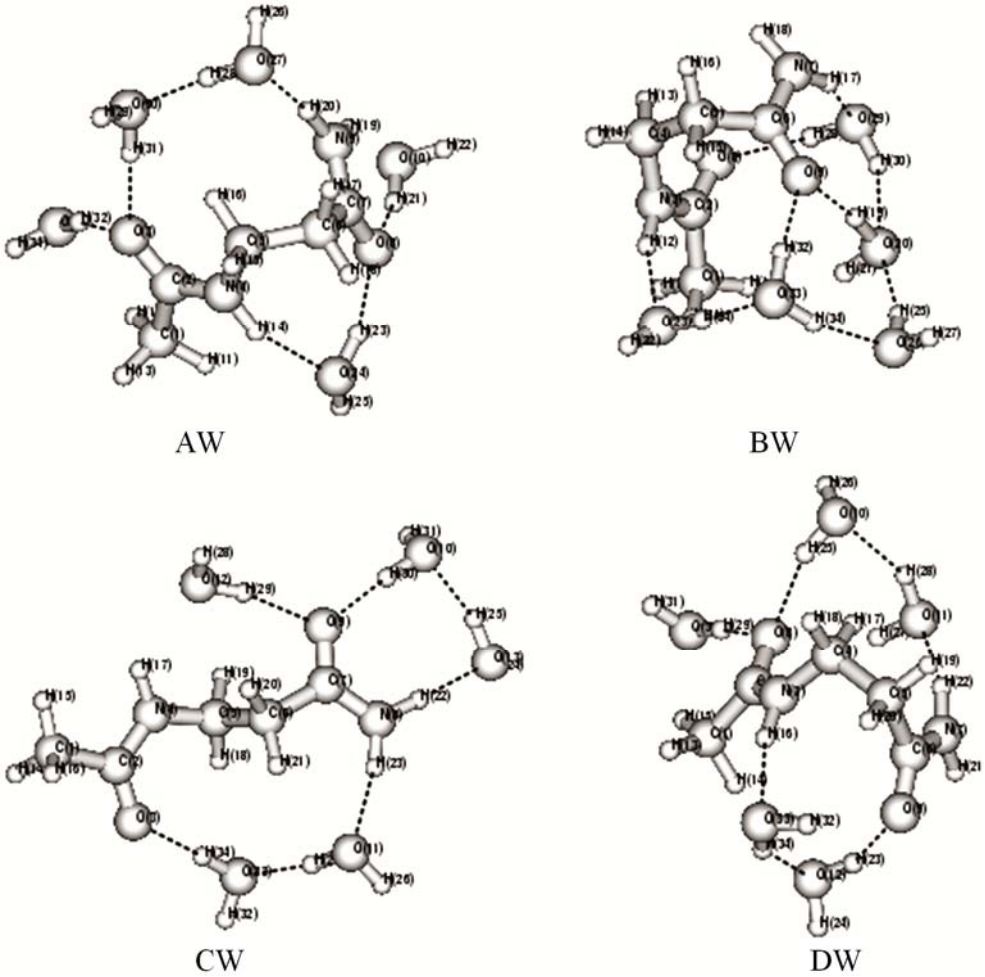

Fig. 2 — Structure of glydimet…H_2O complexes (designated as AW, BW, CW, and DW) optimized at B3LYP/6-31G** level of theory.

and D is quite high in energy because of the absence of intramolecular hydrogen bond. We have modeled the interaction of beta-dipeptide conformers with water by adding five water molecules explicitly around the first solvation shell. Although complex AW is the most stable structure at HF/6-31G** level of theory, DFT method shows conformer BW to be the most stable one where the number of peptide fragments involving in H-Bond is more compared to other complexes. The orders of stability of isolated and complexes were found to be: A > B > C > D and BW > DW > CW > AW, which can be inferred from the graphs (Fig. 3(a,b)).

The chemical hardness is an important quantity which is used to characterize any chemical and biological systems. It was observed that the hardness of all conformers doesn't obey the Principle of Maximum Hardness (MPH) rule. The hardness value increases during the complexation for conformers A and D, whereas, for the other two it decreases. During the complexation, hydrogen bonds of type (i) residue as a proton donor N-H…O and C-H…O and (ii) water as a proton donor O-H…O were noted in all the complexes (AW, BW, CW and DW). One of the most important known characteristics of H-X bond within X-H…Y system is its elongation in length compared to the free H-X bond. After interaction, the X-H bond distances of complexes were found to elongate, except for the C-H…Y H-bond. This variation may be associated with the transfer of charge from proton acceptor to remote part of the proton donor molecule[35], which correlates well with the improper hydrogen bond. For this reason, in the case of residue as a proton donor, two types of hydrogen bonds namely: (i) proper hydrogen bond X-H…Y (where X and Y are electronegative atoms in which there is an interaction between lone pairs orbitals of the proton acceptor 'Y' with antibonding orbitals of the proton donor 'X') and (ii) improper hydrogen bond (Z-X-H…Y, where X is not necessarily the electronegative atom) were noticed. These two different views on hydrogen bonding are quite interesting and grabbed the attention of researchers[36,37]. Hence beta peptide systems are one of the ideal structures to study these types of hydrogen bonds. In addition, these H-bonds can also be explained based on the charge transfer mechanism and rehybridization of X atom[38]. Hence detailed topological and NBO analyses would assist to find the strength of charge transfer between interacting orbitals, by discriminating more precisely the proper and improper hydrogen bonding.

As discussed above, in the complexes AW, BW, CW and DW, the bonds of type N-H…O (where N-H residue acts as a proton donor) and O-H…O (where O-H bond of water acts as a proton donor) forms proper hydrogen bonding and C-H…O type bonds, where C-H residue acts as a proton donor possess improper hydrogen bond. Hence we have considered only the selected bonds that are sufficient enough to describe the proper and improper H-bonds for the topological and NBO analyses.

3.1.1 Topological analysis

Table 3 depicts the topological properties like electron density and Laplacian of electron density at the bond critical points of preferred N-H…O, O-H…O and C-H…O bonds of all complexes calculated at B3LYP/6-31G** level of theory. In the complexes, electron density $\rho(r)$ and Laplacian of electron density $\nabla^2\rho(r)$ were found to have a range

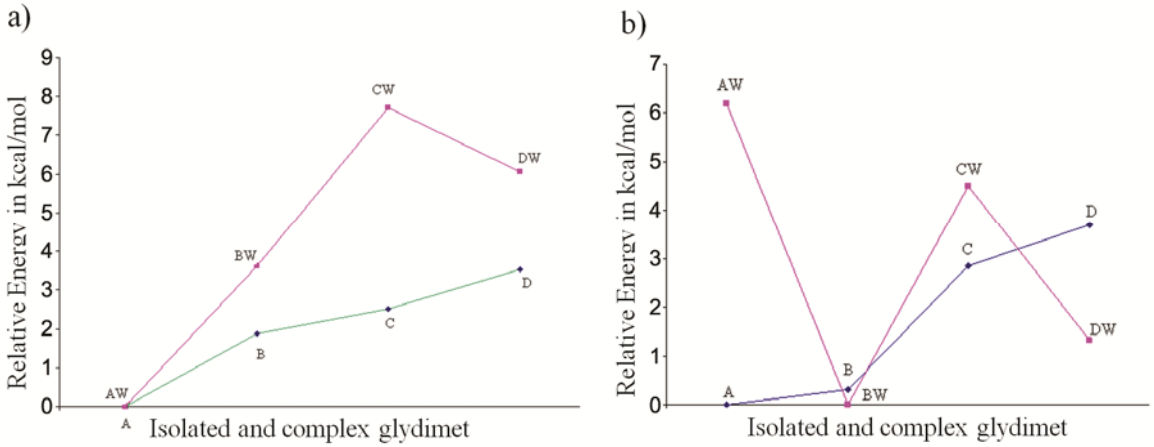

Fig. 3 — Relative energy of isolated and complex structures calculated at (a) HF/6-31G** and (b) B3LYP/6-31G** levels of theory.

from 0.011 to 0.046 a.u and 0.024 to 0.125 a.u, respectively, and they agree well with the previously reported values (0.002 - 0.34 and 0.016 - 0.13 a.u).[39] A close observation shows that the electron density $\rho(r)$ and Laplacian of electron density $\nabla^2\rho(r)$ for proper hydrogen bonds N-H…O and O-H…O of all the β-dipeptide complexes are higher than the improper hydrogen bond C-H…O.

Table 3 — Bond critical points (a.u.) of H-bond (H…Y) glydimet…H_2O complexes (AW, BW, CW and DW) calculated at B3LYP/6-31G* level of theory.

Bond	H---Y	
	ρ	$\nabla^2\rho$
AW complex		
C_1-H_{12}...O_{20}	0.013	0.039
O_{10}-H_{21}...O_8	0.036	0.110
N_9-H_{20}...O_{27}	0.040	0.097
BW complex		
C_1-H_{10}...O_{23}	0.011	0.037
O_{33}-H_{32}...O_9	0.046	0.125
N_7-H_{17}...O_{29}	0.035	0.092
CW complex		
C_5-H_{18}...O_{17}	0.009	0.033
O_{17}-H_{34}...O_8	0.039	0.119
N_7-H_{17}...O_{12}	0.034	0.088
DW complex		
C_1-H_{19}...O_{11}	0.007	0.024
O_{10}-H_{25}...O_8	0.013	0.044
N_3-H_{16}...O_{33}	0.035	0.089

3.1.2 NBO analysis

To substantiate the presence of hydrogen bond and to get more information about the charge transfer mechanism, NBO analysis was carried out. The calculated occupation number for X-H antibond orbital, lone pair electron bond orbital Y, X-H bond length for isolated and complexes, and stabilization energy of selected N-H…O, O-H…O and C-H…O bonds of all the four complexes AW, BW, CW and DW at B3LYP/6-31G** level of theory are listed in Table 4. After complexation, the occupation number of σ*(X-H) antibonding orbitals has increased considerably for N-H…O and O-H…O H-bonds as a result of transfer of charge from n(O) lone pair orbitals thereby elongating X-H bond length with stabilization energies >8 kcal/mol. As discussed earlier, in the case of C-H…O H-bond, the contraction of C-H bond length even after the charge transfer from n(O) to σ*(C-H) orbitals is noted, which accounts for improper hydrogen bonding. The reason for this contraction is because of the secondary effect, i.e., in the case of C_5-H_{18}…O_{17} bonding in CW complex (Fig. 2), the atom nearer to C_5 is N_3, which is electronegative and attracts the H_{18} atom towards itself, thereby resulting in C_5-H_{18} contraction. Also, in the case of C_1-H_{12}…O_{20}, C_1-H_{10}…O_{23}, and C_1-

Table 4 — NBO analysis of isolated and complex glydimet structures - bond length r(X-H) (Å) of proton donor, occupation numbers (a.u.) of the antibonds, bonds, and the donor➠acceptor stabilization energies E_{ij}^2 (kcal/mol) calculated at B3LYP/6-31G** level of theory.

Bond	Donor				Acceptor		E(2)(Y) → σ (X-H)
	r (X-H)		σ *(X-H))		n (y)		
	A	AW	A	AW	A	AW	
C_1-H_{12}...O_{20}	1.093	1.092	0.005	0.014	1.999	0.985	2.74
O_{10}-H_{21}...O_8	0.950	0.985	0.001	0.039	1.977	1.942	12.08
N_9-H_{20}...O_{27}	1.006	1.028	0.010	0.054	1.999	1.948	21.34
	B	BW	B	BW	B	BW	
C_1-H_{10}...O_{23}	1.093	1.093	0.007	0.012	1.999	1.991	1.96
O_{33}-H_{32}...O_9	0.950	0.976	0.001	0.039	1.978	1.964	12.75
N_7-H_{17}...O_{29}	1.018	1.033	0.039	0.061	1.999	1.944	21.34
	C	CW	C	CW	C	CW	
C_5-H_{18}...O_{17}	1.098	1.092	0.140	0.015	1.999	1.999	0.53
O_{17}-H_{34}...O_8	0.950	0.989	0.001	0.055	1.863	1.858	16.33
N_7-H_{17}...O_{12}	1.008	1.093	0.011	0.055	1.999	1.948	19.63
	D	DW	D	DW	D	DW	
C_1-H_{19}...O_{11}	1.090	1.095	0.007	0.009	1.999	0.993	1.08
O_{10}-H_{25}...O_8	0.950	0.980	0.001	0.033	1.976	1.945	8.54
N_3-H_{16}...O_{33}	1.092	1.033	0.017	0.062	1.998	1.942	20.52

$H_{19}…O_{11}$bonds in AW, BW and DW complexes, the nearest atom to C_1 is another less electronegative carbon atom, which is responsible for the contraction of C-H bond. As a supporting information, the stabilization energy of such C-H…O bond is found to be very low (<3 kcal/mol) when compared to the proper hydrogen bonds.

3.2 Molecular dynamics simulation

A 1ns MD simulation at 300 K in an explicit water solution was performed for the conformers optimized at B3LYP/6-31G** level of theory. The main objective of MD simulation is to identify the transition of the structure from folded to extended conformation and vice versa and also the time taken for the transition. Out of all the optimized conformers, A, B, and D correspond to fold and C to an extended conformation. In order to reduce space, conformer A and C are considered for MD simulation and the selected trajectories are shown (in Fig. 4) along with the numbering of atoms.

3.2.1 Examination of the folded conformations

The distance between the terminal atoms N_2-C_1 in the main chain as a function of time for the conformer A is shown in Fig. 5(a). It is noted that starting from

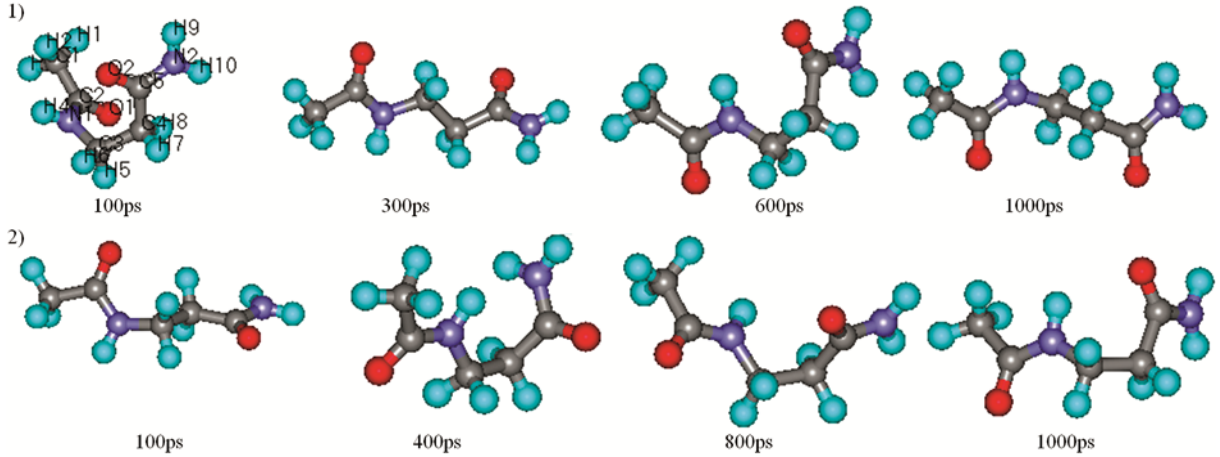

Fig. 4 — Trajectories of (1) *conformer A* and (2) *conformer C* simulated for1000 ps in explicit water at 300 K.

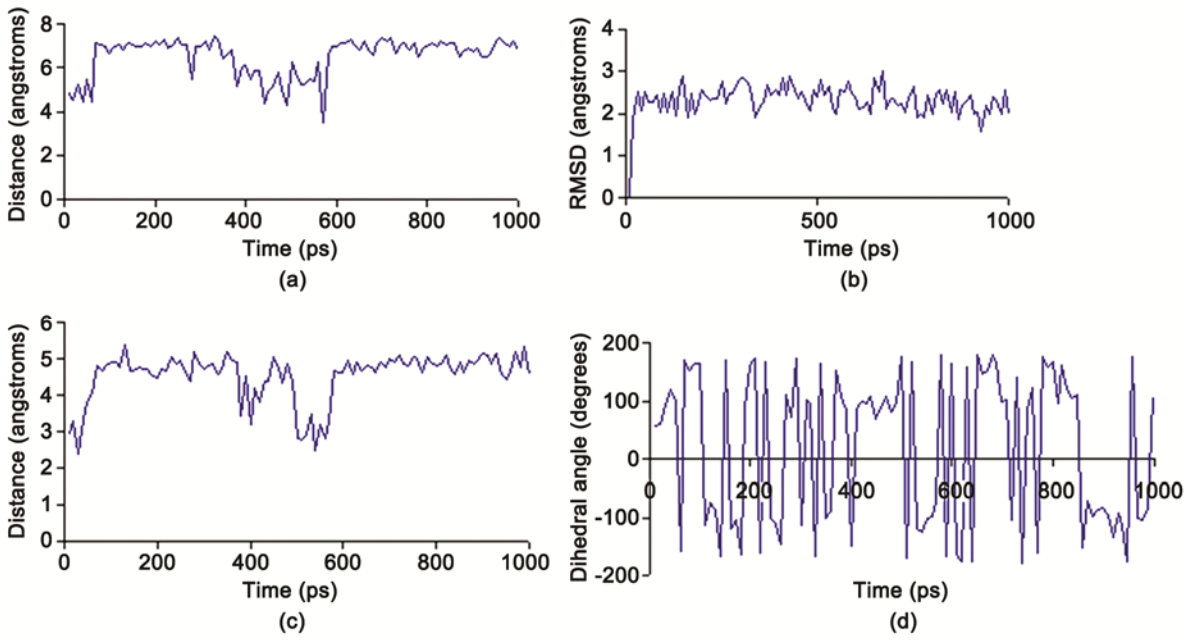

Fig. 5 — (a) C_1-N_2 (Å) distance (b) rmsd (Å) (c) intramolecular H bond distance of O_2-H_4 (Å) (d) dihedral angle ϕ (°) of the *conformer A* during 1000 ps simulation.

the folded conformation, the conformer has initially folded several times, and at around 60 ps, it goes to extended form, i.e., to conformer C with 7 Å of N_2-C_1 distance. Then the system continued to fluctuate around the extended conformation for the following period of ≈ 350 ps. However, one event of unfolding and folding was noticed between time periods 350 ps and 500 ps approximately (Fig. 4) after which the peptide continues to be in the fully extended conformation till it reached 1000 ps.

Figure 5(b) shows the root mean square atom positional deviation (rmsd) of all the atoms of conformer A as a function of time. The average rmsd of the structure is of the order of 2.316 Å. From the examination of the structures extracted from the trajectory (Fig. 4), it is clear that conformations having an rmsd less than or equal to 2.300 Å correspond to the initial folded conformation and rmsd greater than 2.300 Å represent the extended conformation. Conformer A is a six membered ring C6 structure with a very weak intramolecular hydrogen bonding (O_2...H_4) of 2.458 Å distance. This hydrogen bond was also analyzed at each step during the simulation and Fig. 5(c) shows the O_2...H_4 distance as a function of time for the conformer A. The weak hydrogen bond (≤3 Å), which prevails at around 60 ps, and between 350 and 500 ps, correspond to the folded conformation as mentioned earlier. In the remaining simulation, the bond length O_2...H_4 is very large (≥3 Å), which correspond to the unfolded conformation of the conformer A. The behaviour of main chain dihedral angle ϕ of conformer A during simulation is given in Fig. 5(d). It should be noted that the occupancy of ϕ around 60 ps and between 350 and 500 ps is similar to that of the initially optimized structure of A, i.e., the folded conformation. Also analysis of ϕ in the extended conformation region reveals that each conformer did not occupy a single state conformation but flipped between positive and negative values periodically.

Conformer B, a C8 hydrogen bonded structure with O_1...H_{10} bond distance of 2.123 Å, initially fluctuates in a folded region and quickly after 3 ps flips off to the extended conformation with an average rmsd of 2.304 Å. Since the behaviour of N_2-C_1 and rmsd of all the atoms for folded structures B and D are found similar to conformer A except for their time to reach unfold pattern, we have excluded the graphs and trajectories of B and D for discussion. Starting from folded conformation, the structure D folded several times and slowly at around 110 ps it reaches an extended conformation with 2.319 Å average rmsd.

3.2.2 Examination of an extended conformation

In the final part of this MD study we investigated if the peptide could be folded to the native low energy conformation of a glydimet, from a fully extended conformation. To start with, the initial structure was chosen to be the extended conformer C. Figure 6(a) shows the N_2-C_1 distance of conformer C as a function of time. At about 240ps, the peptide adopted part of the low energy folded conformation of glydimet. After 240 ps, this peptide fully unfolded and refolded several times with extended conformation being stable initially up to ≈200 ps. Figure 6(b) shows the

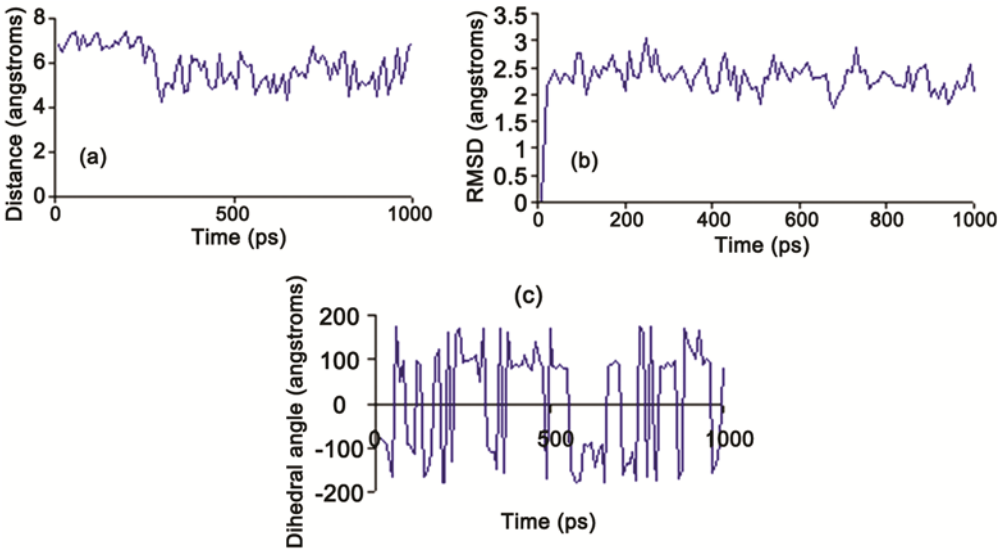

Fig. 6 — (a) C_1-N_2 (Å) distance (b) rmsd (Å) and (c) dihedral angle ϕ (°) of the *conformer C* during 1000 ps simulation.

rmsd of all the atoms of conformer C as a function of time and the average rmsd is found to be 2.303 Å. The comparison of the trajectory (Fig. 4) with rmsd shows that the conformation which has an rmsd less than or equal to 2.3 Å corresponds to an extended state and those greater than 2.3 Å match up with the folded conformation. Whenever the system attains an extended form the main chain dihedral angle value ϕ (Fig. 6(c)) flips toward the initial structure, whereas for other states it oscillates periodically between positive and negative values.

In summary, we have showed that it is possible to simulate the folding/unfolding of a peptide from a random conformation (that may either be folded or extended) within few pico seconds at 300 K. Molecular dynamics study[9] suggested that the transition time from a totally extended conformation to the experimentally folded conformation of a β-heptapeptide in methanol is less as the simulation temperature goes higher. In our study we have noted that the transition from a totally extended conformation to the low energy folded conformation of glydimet require less than 300 ps at 300 K. The transition from a folded to unfolded state was very rapid, and noted to be approximately 30 ps for a folded conformer with eight membered ring hydrogen bond $O_1...H_{10}$ i.e., conformer B, whereas the transition from extended to folded state was sluggish and took approximately 240 ps.

4 Conclusions

We have investigated the interaction of conformers of β-dipeptide with water applying quantum chemical methods. With the help of molecular dynamics simulation the transition of β-dipeptide from folded to unfolded states and vice-versa has also been studied. From quantum chemical calculations, it has been noted that the geometrical parameters of all the four isolated β-dipeptide conformers changes considerably during their interaction with water molecules. The analyses of topological and NBO parameters show that all the complexes of β-dipeptide satisfy the indicative criteria for different hydrogen bond interactions. During the simulation of β-dipeptide the process of folding and unfolding occurred rapidly, in which the transition from a folded to unfolded conformation happened within few pico seconds. This study suggest that the explicit simulation in solvent molecules to be a prerequisite to correctly predict the folding/unfolding states of peptides even at moderate temperatures. These results which illustrate the folding and unfolding patterns of β-dipeptides in water may contribute towards the understanding of the properties of β-peptides and their behavior in solution.

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