Bulgarian Chemical Communications, Volume 49, Special Issue J, (pp. 99 – 105) 2017

A density functional theory study on the heterocyclic cyclodecapeptide and its linear analogs in water and octanol solvents

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Submittted May 20, 2017; Revised August 21, 2017

The density functional theory (DFT) calculations at B3LYP/6-31+G(d,p) level were used to study the structures of heterocyclic cyclodecapeptide (HCD), composed of nine glycine amino acids and one threonine, and its linear analogs in water and octanol solvents. The linear analogs of HCD was designed in silico. The calculations in the solvents of water and octanol with dielectric constants of 78.35 and 9.86, respectively were carried out by the SCRF method. Based on the HOMO-LUMO Gap (HLG) analysis, it was found that the linear structure was more stable and less reactive than the cyclic structure. Also, the difference between the energy gaps for the linear peptides in water and octanol, as well as for the cyclic peptides in these solvents were modest. The chemical hardness, chemical potential, electrophilicity, chemical softness, and the maximum amount of electronic charge were determined, and the results showed that the cyclic structure was more reactive than the linear structure. Moreover, it was observed that the studied peptides were more reactive in octanol. The reduced density gradient (RDG) analysis showed that in the water solvent the steric effect for the cyclic peptide was more pronounced. Also, there was no van der Waals' interaction for the cyclic form in water, while this kind of interaction was weak for the linear structure. Furthermore, in octanol solvent, the van der Waals' interaction was very weak for both cyclic and linear structures. The steric effect and hydrogen bonding for the linear form is more than the cyclic one in octanol.

Keywords: Cyclic peptide, Linear peptide, RDG analysis, energy gaps, solvent, hydrogen bonding, chemical softness

1.INTRODUCTION

The structure and reactivity of free molecules are very different from those in the solvent environment, and therefore, the solvation effect plays an important role on biomolecules. The solute interaction with the solvent molecules may affect the stability of different configurations, as well as the kinetics and thermodynamics of the involved reactions [1]. Proteins are important macromolecules having a central role in all biological processes [2, 3]. The protein-solvent interactions are responsible for the activity of proteins associated with their structure, conformational stability and folding. Therefore, the study on the interactions between solvents and peptides/proteins is crucial for providing some significant information about folding mechanisms and structural changes [4-7]. Solvent molecules, for example, can form intermolecular hydrogen bonds [8].

There are some theoretical investigations on the role of different solvents in peptides. For instance, Khurana et al. performed a molecular dynamic simulation study on the self-assembling of two cyclopeptides and their dimers, cyclo [(- L-Trp-D-N-MeLeu) 4-]$_2$ and cyclo [(- L-Trp -D- Leu) 4-]$_2$, in water and nonane as polar and non-polar solvents, respectively. They showed that the dimers are stable only in the non-polar solvent during 10 nanoseconds of simulation [9]. The study of quantum chemistry and molecular simulations for the effect of solvent on the glycylalanine and cyclo glycylglycine dipeptides was done by Yogeswari et al. According to their results, increasing the dielectric constant of the medium led to the more stability of the structure, and therefore, the geometry was affected by the solvent[8].

It has been found that cyclopeptide can form complexes with molecules. For example, Kubik et al. discovered that different cyclohexapeptides can make bonds with anionic, cationic and natural molecules by the systematic changes of peptide subunits [10]. The theoretical calculations determined that cyclodecapeptide can distinguish between enantiomers of 1-phenyl-1-propanol. Hence, it was suggested that cyclopeptides can be suitable hosts for molecular recognition and chiral separation [11].

In this study, we used water, as a polar solvent, and octanol, as a non-polar solvent, in order to study the effect of solvents on peptides. For this purpose, a cyclic peptide, composed of nine glycine amino acids and one threonine, along with its linear analogs were chosen to study the interactions
between the solvents and peptides by the density functional theory. The RDG analysis was used to study the weak interactions in the studied systems. Also, the chemical hardness, chemical potential,

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electrophilicity, and chemical softness were evaluated and the reactivity of the linear and cyclic peptides in both solvents were compared.

2. COMPUTATIONAL DETAILS

Geometry of all structures were optimized by B3LYP/6-31+G(d,p) level of DFT approach implemented in Gaussian 09 package [12, 13]. The CPCM method was used for the solution phase study [14, 15]. The dielectric constants of 78.35 and 9.86 were used in the calculations for water and octanol, respectively. Reduced density gradient (RDG) function combined sign(λ2)ρ were used [16]. The topological properties were performed with the program of Multiwfn with the wave functions generated from B3LYP/6-31+G(d,p) results [17].

3. RESULTS AND DISCUSSION

3.1. Geometrical parameters

Fig 1 shows the optimized structures of cyclodecapeptide and its linear analogs

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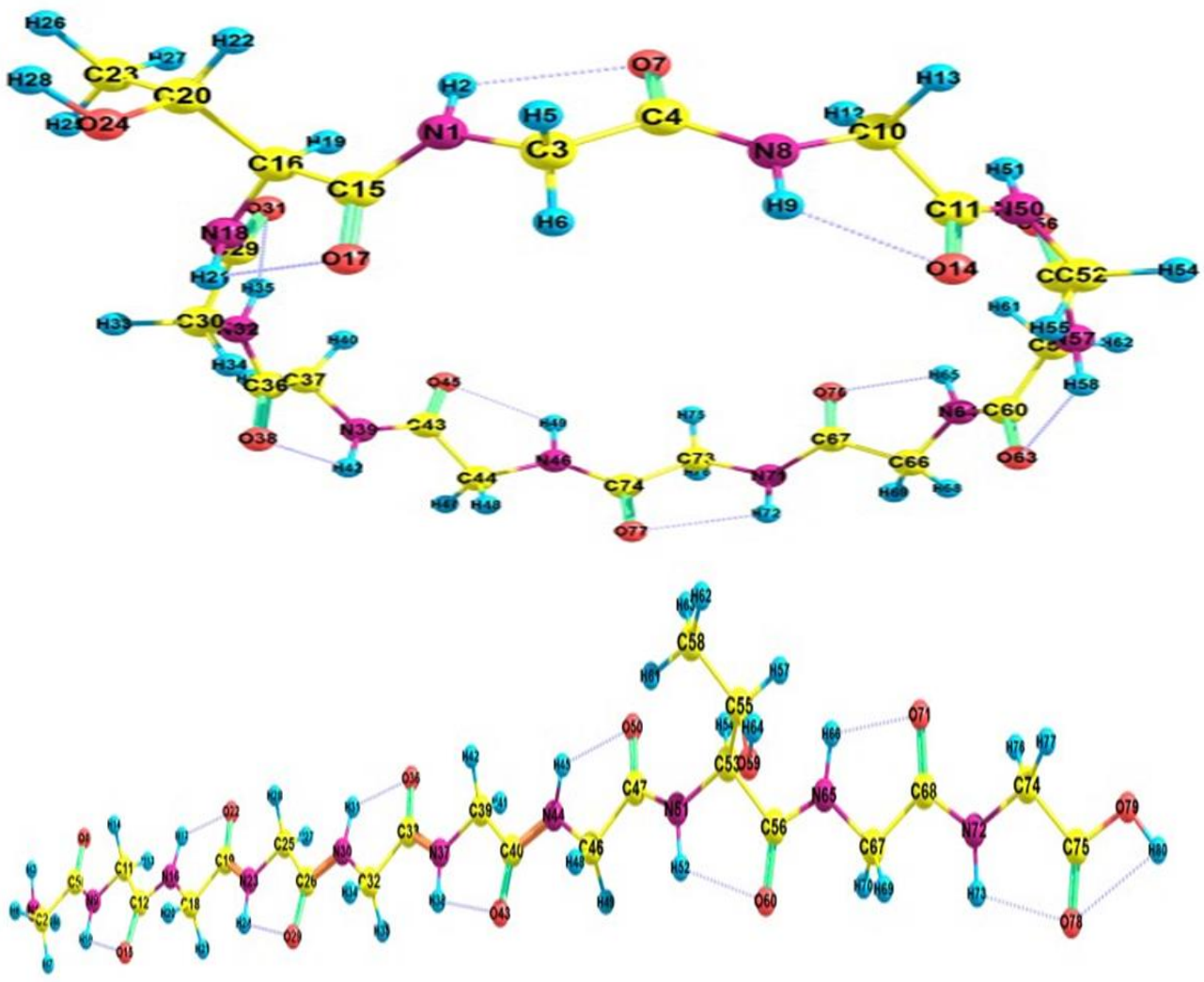

Fig 1. The optimized structures of cyclodecapeptide and its linear analogs. The yellow, purple and red colors are for carbon, nitrogen and oxygen atoms, respectively.

The total energies and dipole moments of the studied systems in the gas and solution phases are given in Table 1. According to Table 1, the interaction of cyclopeptide with the solvent reduces the energy of the system and increases its stability. The stability of the system in water is more than that in octanol. Also, the stability of the linear structure in octanol is less than that in the gas phase. The structural parameters of HCD and its linear analogs in the gas and solution phases are reported in Tables 2 and 3.

Table 1. Total energies, E/Hartree, and dipole moments, μm/Debye, for cyclodecapeptide and its linear analogs in the gas phase and solvents of water and octanol at the level of B3LYP/6-31+G(d,p)

Dimentions of box	Span time of simulation(ps)	Number of solvent	RMS	Dipol moment
Cyclo HCD	gas	-2234.131	0.0000631	2.134
Cyclo HCD	octanol	-2234.184	0.00000143	2.750
Cyclo HCD	water	-2234.190	0.0000257	3.166
Linear HCD	gas	-2310.566	0.00000268	21.919
Linear HCD	octanol	-2297.332	0.00000234	19.755
Linear HCD	water	-2310.632	0.00000409	24.424

Table 2. The structural parameters of HCD in the gas and solution phases at the level of B3LYP/6-31+G(d,p)

Bond length (A˚)	in the vacuum	Water	Octanol	Cyclo[$(Gly)_8$][19]	[11]
C15=O17	1.22968	1.23510	1.23494	1.233	-
C15-N1	1.35646	1.35352	1.35278	1.364	-
N1-H2	1.01503	1.01248	1.01331	1.030	-
N1-Cα3	1.45036	1.45209	1.45216	1.451	-
C20-O24H	1.42833	1.43420	1.43321	-	-
O24-H28	0.96575	0.96725	0.96701	-	-
C36-C37	1.53211	1.53011	1.53003	1.542	-
Vertical C16-C 66	12.226	12.60174	12.7358		13.1
Horizontal Cα44-C α10	11.7776	11.60308	11.58482		11.1
C3-C73	12.02788	12.63438	12.6069		11.9
C30-C59	11.9378	11.82143	11.7789		12.2
C37-C52	11.82371	11.25190	11.2226		11.2

As can be seen in Table 2, the bond lengths of C20-O24H and O24-H28 in the side chain of the threonine amino acid in water are longer than those in octanol. The bond lengths of C16-C66 increase in different environments in the order of octanol > water > gas phase. Also, the bond lengths of Cα44-Cα10 increase in different environments in the order of gas phase > water > octanol. In fact, the structure of the HCD in octanol is close to an elliptical structure.

The geometric structure of the cyclopeptide was influenced by the solvent. For example, the bond lengths of C15-N1 and N1-H2 became shorter and resulted in the increase of the corresponding bond strengths. The bond length of C15-N1 in water is shorter than that in octanol. Generally, the determined bond lengths for HCD was very similar to those reported for cyclo[(Gly-D-Ala)4] and cyclo[(Gly)8] [18, 19].

The geometric structure of the linear peptide was influenced by the used solvent. For example, the bond lengths of C33-N37 and N37-H38 became shorter and resulted in the increase of the corresponding bond strengths.

Table 3. The structural parameters of the linear peptide in the gas and solution phases at the level of B3LYP/6-31+G(d,p)

Bond length (A˚)	In vacuum	Water	Octanol
C47=O50	1.23349	1.21219	1.21167
C33-N37	1.34845	1.33278	1.3332
N37-H38	1.01639	0.99682	1.51940
N37-Cα39	1.44694	1.44079	0.99681
C55-O59H	1.42888	1.40941	1.44060
Cα32-C33	1.53217	1.51929	1.40887

3.2. Molecular orbitals (HOMO and LUMO)

The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of a molecule have a decisive role in the chemical stability[20]. HOMO reflects the ability to donate an electron, while LUMO represents the ability to accept electrons. The energy gap between HOMO and LUMO determines chemical reactivity, optical polarizability and chemical softness–hardness of molecules [21]. While the HOMO energy is directly related to the ionization potential, LUMO energy depends directly to the electron affinity. The energy difference between HOMO and LUMO, called the energy gap, is an important factor on the stability of structures [22]. The higher the difference between HOMO and LUMO, the more stability can be seen for the system. Higher stability of a molecule is indicative of its lower chemical reactivity[23]. The energy values of HOMO and LUMO along with the energy gap for the studied systems are reported in Table 4. According to Table 4, the energy gap for the linear structure is higher than the cyclic structure, and therefore, the linear peptide is more stable than the cyclic one. The difference between the energy gaps for the linear peptides in water and octanol, as well as for the cyclic peptides in these solvents are modest. The lower the energy gap, the more easily electron transfers from HOMO to LUMO, and hence a change can be seen in the electronic properties of the molecules.

3.3. Chemical hardness-softness, chemical potential, and electrophilicity

Molecules with high energy gaps are known as hard molecules and those with low energy gaps as soft molecules. Soft molecules are more easily polarized than hard molecules because they require low energies to be excited. The global hardness, η, electronic chemical potential, μ, global softness, S, and the maximum amount of electronic charge, ΔN_{max}, [24] can be determined as follows:

$$\eta = (I - A)/2 \quad (1)$$

$$\mu = -(I + A)/2 \quad (2)$$

$$S = 1/2\eta \quad (3)$$

$$\Delta N_{max} = -\mu/\eta \quad (4)$$

where I and A are ionization potential and electron affinity, respectively. According to Koopman's theorem, η = (ELUMO-EHOMO) / 2 and μ = (EHOMO + Elumo) / 2 [3, 25, 26] Also, Parr et al. [27] described the electrophilicity index, ω, as

$$\omega = \mu^2/2\eta \quad (5)$$

The global hardness, electronic chemical potential, global softness, electrophilicity index and the maximum amount of electronic charge were calculated and reported in Table 5. Accordingly, changing the cyclic structure to linear one resulted in the increase of hardness and chemical potential and decrease of electrophilicity index and softness. Moreover, there is not a significant difference between the hardness as well as chemical potential for the peptides in water and octanol.

Table 4. The energy values of HOMO and LUMO along with the energy gap for the linear and cyclic peptides in the solvents of water and octanol and in the gas phase

	Cyclo gas (ev)	Cyclo octanol (ev)	Cyclo water (ev)	Linear gas (ev)	Linear octanol (ev)	Linear water (ev)
Homo	-0.26443	-0.26660	-0.26643	-0.22844	-0.39289	-0.39339
Lumo	-0.01622	-0.01359	-0.01340	-0.04165	0.06351	0.06412
Gap energy	0.24821	0.25301	0.25303	0.18679	0.4564	0.45751

Table 5. The values of global hardness, electronic chemical potential, electrophilicity index, global softness, and maximum amount of electronic charge for the linear and cyclic peptides in water and octanol as well as in gas phase.

		Hardness [η=(I-A)/2](ev)	Chemical Potential [μ=-(I+A)/2] (ev)	Electrophilicity [ω=μ2/2η] (ev)	Softness [S=1/2η] $(ev)^{-1}$	ΔNmax (a.u.)
Cyclo HCD	gas	3.377021	-3.81838	2.158715	0.148059	1.1307
Cyclo HCD	octanol	3.442328	-3.81213	2.110824	0.145251	1.10743
Cyclo HCD	water	3.4426	-3.80723	2.105237	0.145239	1.10592
Linear HCD	gas	2.541371	-3.67471	2.656733	0.196744	1.4459
Linear HCD	octanol	6.20955	-4.48138	1.617087	0.080521	0.7217
Linear HCD	water	6.224652	-4.47988	1.612086	0.080326	0.7197

3.4. Analysis of weak interactions

The reduced density gradient (RDG) was used to distinguish between hydrogen bonds with other weak interactions [16]. The electron density, ρ, from which all the chemical properties can be achieved [28], is the key quantity in the density functional theory (DFT). The reduced density gradient, which is obtained from electron density and its derivatives, is a dimensionless quantity for describing the fundamental deviations from a homogeneous electron distribution [28-30].

The reduced gradient properties have been studied in the course of developing accurate functionals [31].

By localizing low-density, the weak interactions in a molecular system can be identified using low-gradient regions. However, the density values alone cannot determine more specific interaction types. High-density regions are related to strong interactions, while the regions with low densities associate to the weakest interactions, such as van der Waals [16].

Different types of strong interactions can be distinguished by the sign of the Laplacian of the density, $\nabla_2\rho$. The Laplacian is often decomposed into a sum of contributions along the three principal axes of maximal variation. These components are the three eigenvalues λi of the electron-density Hessian matrix[32, 33]:

$$\nabla_2 \rho=\lambda1 + \lambda2 + \lambda3, (\lambda1 \leq \lambda2 \leq \lambda3) \quad (6)$$

The chemical bonding has been studied in detail by the analysis of these components.

Yang et al. developed an approach to study the weak interactions in real space based on the electron density and its derivatives [30]. The reduced density gradient (RDG) is a fundamental dimensionless quantity as:

$$RDG(r)=1/[2(3\pi^2)]^{(1/3)} [\nabla\rho(r)]/ [\rho(r)] ^{(4/3)} \quad (7)$$

Different regions with low electron density and low RDG value show the weak interactions. The density values of the low-gradient spikes (the plot of RDG versus ρ) are indicative of the interaction strength. The attractive interactions, such as dipole-dipole or H-bonding, can be distinguished from large negative values of sign (λ2), whereas large positive values of sign (λ2) are indicative of the nonbonding interactions, such as strong repulsion or steric effect in a cage. Moreover, the near-zero values indicate very weak interactions, such as van der Waals interactions[30]. The weak interaction types can be analyzed by the plots of the RDG versus the electron density _ multiplied by the sign of λ2.

The weaker dispersion interactions are related to the surfaces with very low density values (i.e., $\rho< 0.005$ au). The stronger noncovalent interactions, including H-bonding (negative λ2) and steric clashes (positive λ2), can be mapped by the surfaces with slightly higher density values (i.e.,$0.005 < \rho< 0.05$ au). Fig 2 shows the RDG plots for the studied systems.

Generally, hydrogen bonds, van der Waals interactions, and strong repulsions are colored in blue, green, and red, respectively. Herein, the weak interaction analysis was carried out with the Multiwfn3.2.8 package.36

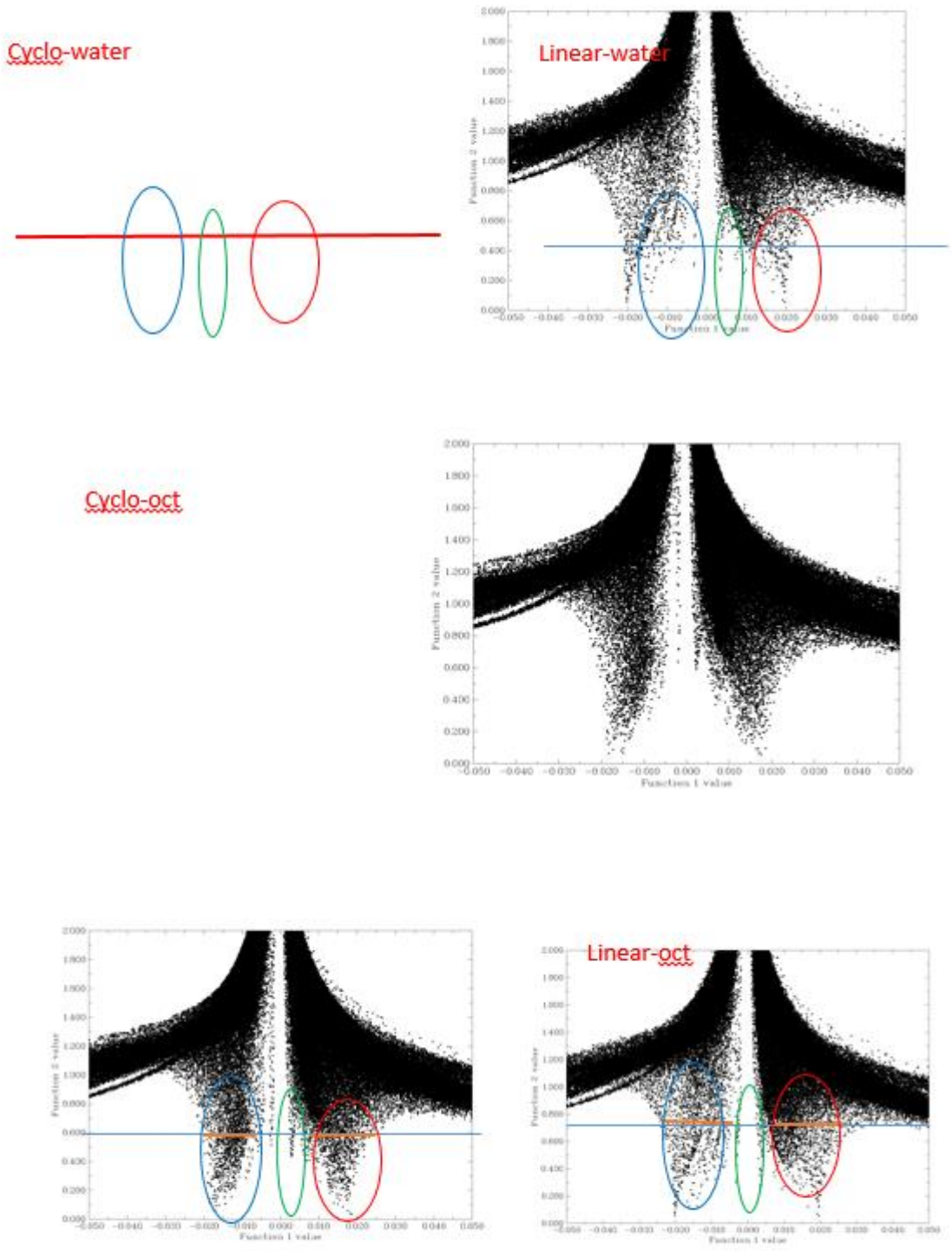

Fig 2. The RDG plots versus electron density: blue, green, and red circles are identified as hydrogen bonding, van der Waals interaction, and steric effects, respectively.

According to Fig 2, in the water solvent, the cyclic peptide shows more steric effects than the linear form, and the electron density in the middle is very low showing that the van der Waals interaction is very weak for the linear peptide. Also, there is no van der Waals interaction for the cyclic peptide. Furthermore, in the octanol solvent, the van der Waals' interaction is very weak for both cyclic and linear structures. The steric effect and hydrogen bonding for the linear form is more than the cyclic one in octanol.

4. CONCLUSIONS

According to the amount of energy obtained, both the cyclic and linear peptide structures were more stable in water than octanol. A higher energy gap

was seen for the linear structure, and therefore, this form of peptide was more stable than the cyclic structure. Also, the difference between the energy gaps for the linear peptides in water and octanol, as well as for the cyclic peptides in these solvents were modest. The higher chemical potential, electrophilicity index, and the maximum amount of electronic charge along with the lower energy gap and chemical hardness for the cyclic structure than the linear one showed its more reactivity. Moreover, it was observed that the studied peptides were more reactive in octanol.

In the water solvent, the cyclic peptide showed more steric effects than the linear form, and the electron density in the middle was very low showing that the van der Waals interaction was very weak for the linear peptide. Also, there was no van der Waals interaction for the cyclic peptide. Furthermore, in the octanol solvent, the van der Waals' interaction was very weak for both cyclic and linear structures. The steric effect and hydrogen bonding for the linear form was more than the cyclic one in octanol.

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