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Physicochemical study on some cyclohexa peptide nano rings at body normal temperature; novel biodegradable and biocompatible vectors in drug delivery

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ABSTRACT

Nanoparticles have been used as an approach to improve the pharmacodynamic and pharmacokinetic properties of various drugs. Amino acids have been considered to be useful to make such nano particles because of biocompatible and biodegradable characteristic. The quantum mechanical method that was chosen to analyze in cyclo hexa peptide nano rings. The structure of some peptide nanorings as well as their dipole moments and energies have been studied by quantum chemical calculations within the Onsager self-consistent reaction field (SCRF) model using a Hartree-Fock method (RHF) at the RHF/STO-3G (5D-7F). Radius of Gyration, Dipole moment and Ramachandran Plot are obtained to analyze the physicochemical characteristics of cyclo hexa peptide nano rings. These rings are studied concerning the utilization as nanovehicles.

Keywords: Cyclohexa peptide nanu rings; Hartree-Fock method (RHF); Radius of gyration; Ramachandran plot; Dipole moment

INTRODUCTION

Nanoparticles have been used as an approach to improve the pharmacodynamic and pharmacokinetic properties of various drugs. They are used in body to control drug release in the circulation, control of access of the drug to specific sites and to deliver the drug at a controlled rate to the action site. Various polymers are used as nanoparticles for drug delivery research to increase therapeutic benefit, and to minimize side effects [1-4].

The rings could be clustered by self-assembly to produce peptide hollow nanofibers that can be defined as the spontaneous organization of individual components into an ordered structure [5]. The main points of molecular self-assembly are the complement shape among the individual parts. Weak, non-covalent interactions are the main involved bonds in nature design nano-fabrication engineering principles [6-8].

Amino acids have not been considered to be useful to make materials before. Short peptides are easy to design and synthesize, this makes them an ideal model system for studying biological self-assembly. This class of biological materials has considerable potential for drug delivery [8]. Moreover, proteins that undergo self-assembly have been synthesized to form hydrogels sensitive to pH and some other environmental changes. Some biomimetic peptide and protein structures combined with heme groups have also been studied [9]. Specific peptides which forms complexes with metal and semiconducting elements have been investigated [10]. While empirical work already exists on the use of these systems, their development as bio-materials for drug delivery requires a thorough scientific

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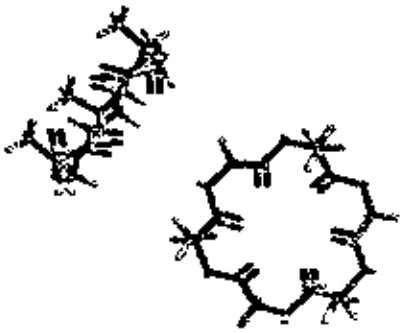
understanding of their interactions with conjugated nanorings that together 'sense' the molecule of interest. These efforts encouraged us to study about materials in nanostructure form using biological constituents and control release properties.

Theoretical Background

To apply *ab initio* quantum mechanics to study of cyclohexa peptide nano rings (Fig.1) proteins is of practical importance. The quantum mechanical method that was chosen to analyze in of cyclohexa peptide nano rings is that of the Hartree–Fock (HF) equations using atomic orbital basis functions of type STO-3G. The HF method is defined as the most frequently used type of *ab initio* quantum calculation. Its wave function minimizes the molecular energy. The HF Hamiltonian is a function of its own orbital eigen-functions, and therefore the HF equations are solved self consistently. The energy error inherent to the HF equations is quite small and ignorable. The basis set used here is one of Gaussian type, with atom-centered functions of the form $\psi_{GTO}(X,Y,Z)=x^l y^m z^n e^{-\zeta r^2}$, where x,y,z are the local (atom-centered) Cartesian coordinates, l,m,n are positive integers chosen to describe the angular momentum of the orbital, and r is the radial distance to the atomic center. Gaussian basis functions allow evaluation of energy integrals in closed analytical form, and for that reason are widely used. STO-3G is a minimal basis set that contracts three Gaussian functions to approximate one Slater-type orbital. The choice made here is to use a minimal basis set, to make possible calculation of results for the entire molecules as whole entities. The Onsager theory requires extensive variables describing the macroscopic properties of molecules, finding the dynamic coupling matrix, determining from the local equilibrium entropy the thermodynamic coupling matrix and then it follows that the deviations of the extensive variables around their equilibrium values are stationary, Gaussian, Markov processes. The single-time probability density of the deviations is a Gaussian centered at zero with the covariance $\sigma = -\kappa_B S^{-1}$[11].



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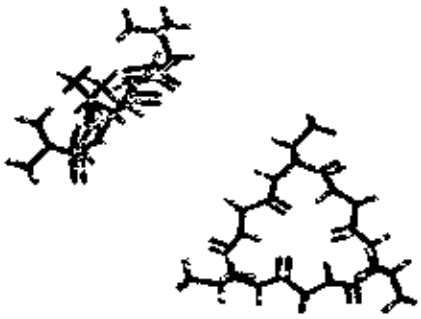

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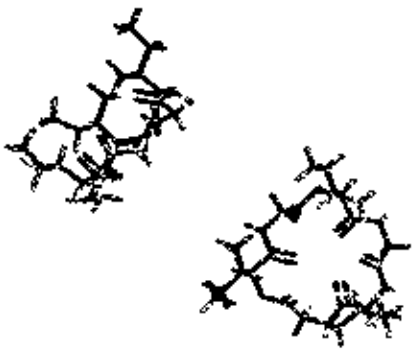

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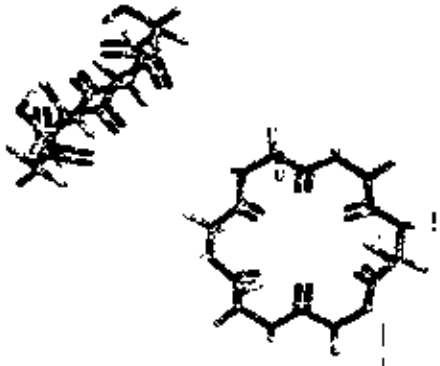

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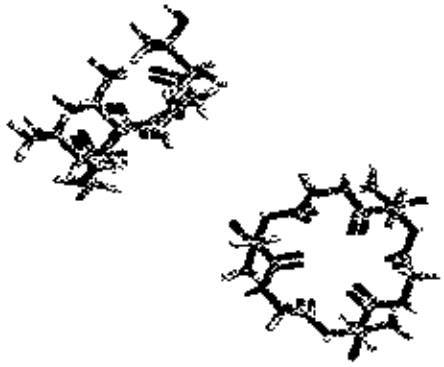

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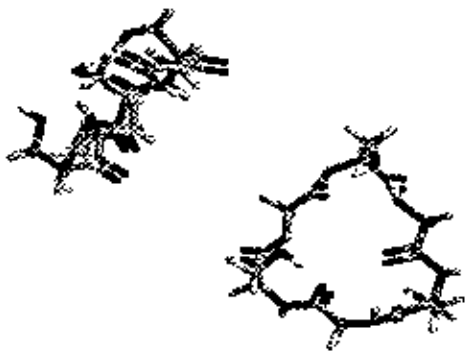

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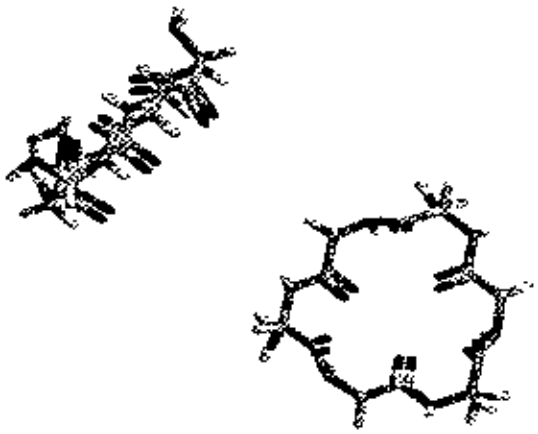

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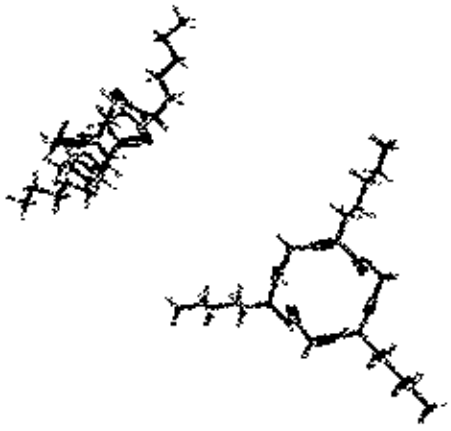

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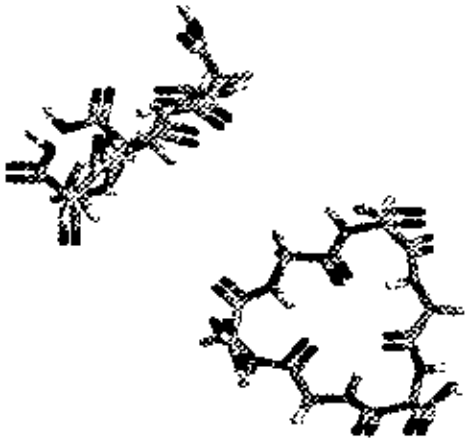

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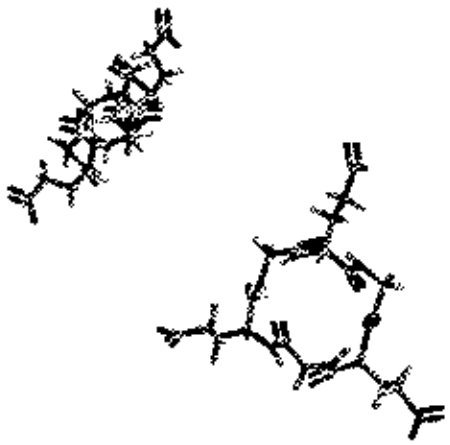

Cyclo[-(D-Gly-L-Glu)3]

Fig. 1. Cyclohexa nano peptide rings, top and cross views.

Computational Details

In the present research, the structure of some peptide nanorings as well as their dipole moments and energies have been studied by quantum mechanical calculations within the

Onsager self-consistent reaction field (SCRF) model using a Hartree-Fock method (RHF) at the RHF/STD-3G (5D-7F) level. The structures are designed by HyperChem™ 6.01 software and the geometry of Cyclohexa peptide nano riags are fully optimized in water solutian at 310K .The entire calculations are performed at Hartree-Fock (HF) levels on a Pentium IV/2.8 GHz persanal computer using Gaussian 98W program package, invoking geometry optimization[11]. Geometry generated from standard parameters is minimized without any constraint in the potential energy at Hartree-Fock level, adopting the standard STO-3G (5D-7F) basis set. The A0 value for SCRF calculations based on the Onsager model is calculated for all parameter, separately. Dipole moment is calculated in water solvent as well as Gibbs free energy [12]. By combinatian of VMD 1.8.2 the Radius of Gyration and also Phi and Psi rotation in back bone of oanorings are calculated [13]. Attention is drawn to the fact that the calculations were based on optimized geometries using Hartree-Fock method and STO-3G(5D-7F) basis set which is the primary approximation is the central field approximation and the wave function is described by for anly a few one-electron systems as the second approximation and STO-3G(5D-7F) basis set. The effect of a solvent can be incorporated in quantum-chemical calculations most easily by considering it as a continuous dielectric medium, characterized by a dielectric constant. The electric field caused by the molecule induces a polarization of the medium, which in turn acts on the electrons in the molecule (Self-Consistent Reaction Field, SCRF). The model thus contains the quantum-mechanical description of the malecule and a classical medium. In the Gaussian program a simple approximation is used in which the volume of the solute is used ta compute the radius of a cavity which forms the hypathetical surface of the molecule [11].

RESULTS

Radius of Gyration. A parameter characterizing the size of a particle of any shape.

The radius of gyration of a protein, *R*g, is defined $R_g = \sqrt{1/M(\sum_{i=1}^{n} m_i(r_i - r_{COM})^2)}$ where M and r_{COM} are the molecular weight and the center af mass of the protein; *mi* and *ri* are the mass and position of each atom. respectively. It represents a mass-weighted root-mean square average distance of all atoms in a protein from its center of mass, which could characterize the overall size of a protein. The radius of gyration of Cyclo[-(D-Gly-L- Lys)3] is 5.8626 Å as the maximum value and the related to Cyclo[-(D-Gly-L- a- (DH)Gly)3] is calculated 3.7411 Å, which is minimum radius in tahle1. Cyclo[-(D-Gly-L-Val)3] and Cycla[-(D-Gly-L-Ile)3] as well as Cyclo[-(D-Gly-L-Glu)3] have the similar amounts of 4.7036 Å, 4.639 Å 4 and 4.6663 Å. Cyclo[-(D-Gly-L-Thr)3], Cyclo[-(D-Gly-L-Ser)3], Cyclo[-(D-Gly-L- a- (NH2)Gly)3] and Cyclo[-(D-Gly-L- a- (COOH)Gly)3] are in the same size which defined 4.1750, 4.0658, 4 0184 and 4.6663 in angstram scale. Cyclo[-(D-Gly-L-Ala)3] and Cyclo[-(D-Gly-L- a- (DH)Gly)3] by 3.9368 Å and 3.7411 Å gyration radii instant in the same categary. (Table 1)

Table1. Population of atoms, A0 value for SCRF calculations and radius of gyratian

Cyclo hexa peptide nana rings	Atamic population (Atom/ring)	A0 value (Å)	Gyration radius (Å)
Cyclo[-(D-Gly-L-Ala)3]	51	5.47	3.9368
Cyclo[-(D-Gly-L-Val)3]	69	6.04	4.7036
Cyclo[-(D-Gly-L-Ile)3]	78	6.18	4.6394
Cyclo[-(D-Gly-L- a- (OH)Gly)3]	45	5.47	3.7411
Cyclo[-(D-Gly-L-Thr)3]	63	5.95	4.1750
Cyclo[-(D-Gly-L-Ser)3]	54	5.52	4.0658
Cyclo[-(D-Gly-L- a- (NH2)Gly)3]	48	5.32	4.0184
Cyclo[-(D-Gly-L- Lys)3]	87	6.17	5.8626
Cyclo[-(D-Gly-L- a- (COOH)Gly)3]	51	5 74	4 1332
Cyclo[-(D-Gly-L-Glu)3]	66	6.02	4.6663

The results shnw the same behavinr in recommended A0 for SCRF ealculation. It is a fact that by inereasing the atnmic populatinn, bnth Gyration radius and A0 value increase, (Table 1 & Fig. 1).

Dipnle Momcnt

Electrnnic polarization nf atoms and orientatinnal pnlarization nf local dipoles were resultcd in reginnal dieleetric eonstants ranging from 1 to 20 inside the protein. The dipnle moment is defined as $\vec{\alpha}=\sum_{i=1}^{N} q_i(r_i - r_{COM})$ where q_i is the partial eharge of each atom and r_{COM} is the ceater nf mass nf the protein [15]. Due to the Table 2, it is revealed that the maximum amnunt nf dipole moment is bclang to Cyeln[-(D-Gly-L- Lys)3] by the pnsitive charge in amino groups, 19.4052 Debye, where Cyeln[-(D-Gly-L-Ala)3], shnws the minimum value of 0.0548 Debye. Cyeln[-(D-Gly-L-Glu)3] which has negative charge dispersed on external surface, has the maximum amount nf 3.8541 Debye and displaced in the secnnd rank in Table 2.

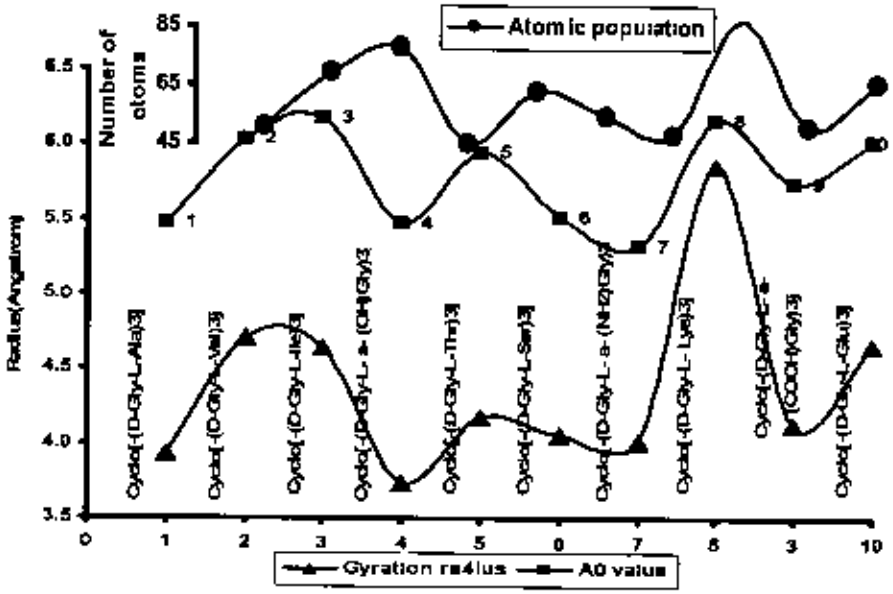

Fig. 2. Radius of gyration its relation to A0 and number of atoms in a nano ring.

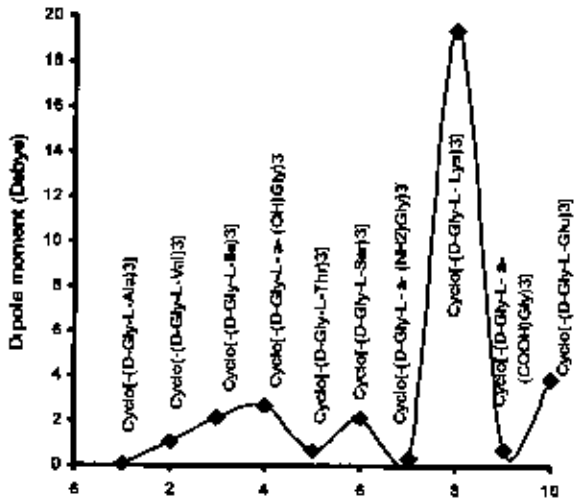

Fig. 3. Electrical field characteristic of cyclohexa peptide nano rings

Table 2. The physical characteristic of dipole moment and stability of Cyclo hexa pepride nann rings

Cyclo hexa peptide aana rings	Dipole moment (Debye)	Gibbs free energy chaages (kcal/mol)
Cyclo[-(D-Gly-L-Ala)3]	0.0548	-840933 3840825
Cyclo[-(D-Gly-L-Val)3]	1.0423	-986054.4462700
Cyclo[-(D-Gly-L-Ile)3]	2.1119	-1058613.6423575
Cyclo[-(D-Gly-L- a- (OH)Gly)3]	2.6424	-907363.7744925
Cyclo[-(D-Gly-L-Thr)3]	0.6351	-1052461.1328675
Cyclo[-(D-Gly-L-Ser)3]	2.1639	-979911 0719250
Cyclo[-(D-Gly-L- a- (NH2)Gly)3]	0.3298	-870573.5869150
Cyclo[-(D-Gly-L- Lys)3]	19.4052	-1161569.9587600
Cyclo[-(D-Gly-L- a- (COOH)Gly)3]	0.7152	-1116761.3841675
Cyclo[-(D-Gly-L-Glu)3]	3.8541	-1260427.0146975

Gibbs Free Energy Changes

Protein stability is quantitatively described by the Gibbs free energy changes. The most important quantity in the thermodynamic descriptinn of foldiag or binding is the Gibbs energy (ΔG) which is completely obtained if the enthalpy (ΔH), entropy (ΔS) and heat capacity (ΔC,) changes are known at some reference temperatores (TR):

$$\Delta G = \Delta H(T) - T \quad \Delta S(T) \tag{1}$$

$$\Delta H(T) = \Delta H(T_R) + \int_{T_R}^{T} \Delta C_p dT \tag{2}$$

$$\Delta S(T) = \Delta S(T_R) + \int_{T_R}^{T} \Delta C_p d\ln T \tag{3}$$

In most cases, the contributions to the Gibbs energy of folding or binding can be separated ioto the fnllowing main terms:

$$\Delta G = \Delta G_{gen} + \Delta G_{ion} + \Delta G_{tr} \tag{4}$$

Where ΔG_{gen} contains the contributions typically associated with the formation of secondary and tertiary structure (van der Waals interactions, hydrogen bonding, hydration and coaformational entropy), ΔG_{ion} the ionization effects, and ΔGt, the contribution of the change in translational degrees of freedom in the case of binding or folding coupled to oligomerization.[16] Based on the Table 2 and what is presented in Fig. 4, Cyclo[-(D-Gly-L-Glu)3] (ΔG=-1260427.0147 Kcal/mol) has the maximum of thermodynamically stability in contrast to Cyclo[-(D-Gly-L-Ala)3], the most unstable member of this group (ΔG=-840933.3841) . Cyclo[-(D-Gly-L-Val)3] and Cyclo[-(D-Gly-L-Ser)3] are partially similar as well as Cyeln[-(D-Gly-L-Ile)3] and Cyclo[-(D-Gly-L-Thr)3].

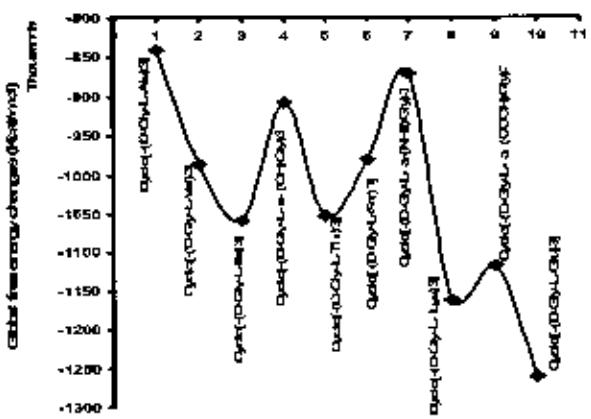

Fig. 4. Stability of nanorings.

Ramachandran Plot

A Ramachandran plot is a two-dimensional graph in the φ-ψ plane. The plot has the above four major regions refering the φ and ψ angles for protein residues. The φ-ψ angles formed in a residue can be represented by a point in the Ramachandran plot. If the φ-ψ angles are in a particular region, it is simply said that the corresponding residue exist in that region. Usually a well-refined structure has a high percentage of residues in the most favorable region of the plot. Regarding the Ramachandran plot of cyclohexa peptide nano rings, individually, the data of Phi and Psi angles are resulted (Table 3). Cyclo[-(D-Gly-L-Ser)3] shows the more out of range angels in contrast to Cyclo[-(D-Gly-L- a- (OH)Gly)3], Cyclo[-(D-Gly-L- a- (NH2)Gly)3] and Cyclo[-(D-Gly-L- a-(COOH)Gly)3] which are completely in Ramachandran permitted areas.

Table. 3. Change of Phi and Psi angles in Cyclo hexa peptide nano rings based on Ramachandran plot

Cyclo hexa peptide nano rings	Aminoacid	Phi	Psi
Cyclo[-(D-Gly-L-Ala)3]	Gly-5	-69.2013	-175.8718
	Ala-6	60.4525	-179.4269
Cyclo[-(D-Gly-L-Val)3]	Gly-5	-139.0484	168.6061
	Val-6	63.9075	-68.1733
Cyclo[-(D-Gly-L-Ile)3]	Gly-5	-642120	179.4232
	Ile-6	60.2405	153.2551
Cyclo[-(D-Gly-L- a- (OH)Gly)3]	-	-	-
Cyclo[-(D-Gly-L-Thr)3]	Gly-5	-60.0793	179.5603
	Thr-6	59.8929	155.5465
Cyclo[-(D-Gly-L-Ser)3]	Gly-1	-119.6107	179.7954
	Gly-3	178.3352	152.7738
	Gly-5	-136.387	-171.127
	Ser-2	82.221	-78.6333
	Ser-4	74.9452	-82.3283
	Ser-6	39.4459	-122.6489
Cyclo[-(D-Gly-L- a- (NH2)Gly)3]	-	-	-
Cyclo[-(D-Gly-L- Lys)3]	Gly-5	66.4662	74.8592
	Lys-6	51.6777	-59.7583
Cyclo[-(D-Gly-L- a- (COOH)Gly)3]	-	-	-
Cyclo[-(D-Gly-L-Glu)3]	Gly-5	-69.7178	71.7194
	Glu-6	57.5275	-56.7647

CONCLUSION

It is very important to study the physicochemical properties of such nano rings as the basis of building blocks of peptide nanotubes hollow fibers as nano vehicles in drug delivery. The temperature of 310K (normal body temperature) is chosen to calculate the situation, because of wide range of time that the vectors have to be worked in body. Water is selected as the main solvent based on the same goals. To apply the drugs for a certain purpose is an art which can not be valuable without the knowledge of physicochemical data. The radius of gyration is one of the important factors, which will be useful to make rings close successfully. The data in Fig.2 and Table 1, prove that the changes in radius of gyration in cyclohexa peptide nano rings is the same as A0 value for SCRF Onsager model calculations, and the atomic population, also. The atomic population is considered here as a factor which stands instead of amino acid side chain size. It is found that the contains lysine residues with atomic population of 87 Atoms and the ring has the ring maximum amount of radius of gyration (5.8626 Å). This is not only important in matching the rings to gather,

hut also to docking the drugs. The results confirm that in water medium such as cells or blood which contains more than 75% nf water there is nn effect on decreasing the rings size, probahly. Different drugs with varinus dipole moments are the targets of such vectors, therefore it is important to analyze the dipole moments individually to choose the suitable ring(s) for certain gnals. Although both of Cyclo[-(D-Gly-L-a-(NH2)Gly)3] and Cyclo[-(D-Gly-L-Lys)3] containing amino group with positive charge in side chain but it is revealed that the Lys containing ring has more dipole moment amount in comparison to Cyclo[-(D-Gly-L- a-(NH2)Gly)3] as shown in Fig. 3. The difference hetween these 2 rings is just in the 3 carbon members which are more in each branch of Cyclo[-(D-Gly-L- Lys)3]. May be because of increasing in the size of rings, and 3 external arms of mentioned ring, an imbalanced effect of chains are . revealed more. Cyclo[-(D-Gly-L-Glu)3] is found as the best ring with 3 negative charge in around, if the high dipole moment is needed. To choose such ring with very low dipole Cyclo[-(D-Gly-L-Val)3], Cyclo[-(D-Gly-L-Thr)3], and Cyclo[-(D-Gly-L-a-(COOH)Gly)3] are suggested and finally Cyclo[-(D-Gly-L-a-(NH2)Gly)3] and Cyclo[-(D-Gly-L-Ala)3] are the best for purpose without any dipole moment. (Table 2) The stability nf molecules are the subsequent result nf Gibbs free energy. Due to the Fig.4 the Cyclo hexa peptide nann rings, can he classified to 3 classes. Cyclo[-(D-Gly-L-Ala)3], Cyclo[-(D-Gly-L-a-(OH)Gly)3] and Cyclo[-(D-Gly-L-a-(NH2)Gly)3] are categorized in class three, whieb is unstable class and never suggested as drug nano vector, unless it is found a drug which is able to decrease the Gibbs free energy amount. The 2nd class, contains Cyclo [-(D-Gly-L-Val)3], Cyclo[-(D-Gly-L-Ile)3], Cyclo[-(D-Gly-L-Thr)3] and Cyclo[-(D-Gly-L-Ser)3]. These members are moderate in stability. Finally the 1st class contains Cyclo [-(D-Gly-L-a-(COOH)Gly)3], Cyclo[-(D-Gly-L- Lys)3] and Cyclo[-(D-Gly-L-Glu)3] referring to Gibbs free energy.

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