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Full Length Research Paper

Coupled Cyclo hexa peptide nano ring system drug carriers; study the stability and electrical field

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To design self-assembly nanocarrier to maintain a particular biological function is the main goal of bionanobiology. Biodegradable and biocompatible materials are more preferred to prevent the polymer remaining in the body, in the preparation of particles for drug delivery purpose. An advantage of particles that are produced based on proteins is that, not only they are safe in biological purposes, but also they contain functional -COOH and -NH_2 groups, the effective cross linking agents. It is important to make the couple nano ring system more stable with a nanoplymer with biocompatibility, low cost, high performance and lightweight such as poly(lactic acid). The heterocyclic nanorings were designed with three constant members of glycine and three variable amino acid members. The effect of Poly-L-lactate chain was introduced as the main biodegradable, and easy to produce and use nano support. All systems were analyzed physicochemically by computational methods. Temperature as the mail surrounding r effect is considered in this investigation. Geometrical changes in order to increase temperature may cause the rings near each others, to form a new geometrical optimization and attract each other more. The results considered that, different utilization for various drugs structure, with any type of hydrophobicity or hydrophilicity, any dipole moment, suitable couple rings based on the obtained results, could be designed. Poly electrolytes such as polylactic acid (PLA) make the systems more strong, to deliver a pack of drugs, for example in production of arterial stents.

Key words: Hetero cyclic hexa peptide nanoring, polylactic acid, drug delivery, biocompatible, biodegradable, quantum mechanics.

INTRODUCTION

Many drug delivery systems have been designed and developed to improve safety transport, targeting and get the higher efficacy of therapeutic agents. Liposomes (Sapra and Allen, 2003; Allen and Cullis, 2004; Medina et al., 2004), lipid surfactant micelles (Huh et al., 2005; Torchilin, 2005, 2006), polymeric vesicles (Discher and Eisenberg, 2002), micro/nano-encapsulation (Savic et al., 2003), dendrimers (Dufes et al., 2006), nanoparticles (Feng, 2004; Gu et al., 2007) and carbon nanotubes (Liu et al., 2007) are the most common forms of carriers.

The main principle of utilization of such delivery vehicles is to provide a protective and hydrophobic system that can molecularly solubilize and circulate in the blood stream. Some of these systems are successful in delivering chemotherapeutics, but some challenges remain in their biocompatibility, biostability and toxicity of the vehicles after degradation (Sahoo and Labhasetwar, 2003; Moses et al., 2003).

In drug delivery technology, self-assembling peptides are more considered, because of chemical/physical characteristics and biological functions. Self assembling peptides have a great potential as delivery constructs for nanomedicine application (Fung et al., 2007; Hsieh et al., 2002; Daviset al., 2006).

A suitable nano drug delivery vehicle should avoid toxicity and present no immunogenicity, control pharmacokinetics and pharmacodynamics, possess bio-recognition and enhance drug efficacy (Allen and Cullis, 2004; Kopecek, 2003; Hubbell, 2003) (Table 1). Cell penetration and targeting are the most intelligent aspects of peptide drug delivery (Aina et al., 2002; Hawiger, 2002; Schwartz and Zhang, 2000).

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Table 1. Non-ideal properties of drugs and their therapeutic implications (Allen and Cullis, 2004).

Problem	Implication	Effect of DDS
Poor solubility	A convenient pharmaceutical format is difficult to achieve, as hydrophobic drugs may precipitate in aqueous media. Toxicities are associated with the use of excipients, such as Cremphor® EL (the solubilizer for paclitaxel in Taxol).	DDS such as lipid micelles or liposomes provide both hydrophilic and hydrophobic environments, enhancing drug solubility.
Tissue damage on extravasation	Inadvertent extravasation of cytotoxic drugs leads to tissue damage, e.g., tissue necrosis with free doxorubicin.	Regulated drug release from the DDS can reduce or eliminate tissue damage on accidental extravasation.
Rapid breakdown of the drug *in vivo*	Loss of activity of the drug follows administration, e.g., loss of activity of camptothecins at physiological pH.	DDS protects the drug from premature degradation and functions as a sustained release system. Lower doses of drug are required.
Unfavorable pharmacokinetics	Drug is cleared too rapidly, by the kidney, for example, requiring high doses or continuous infusion.	DDS can substantially alter the PK of the drug and reduce clearance. Rapid renal clearance of small molecules is avoided.
Poor biodistribution	Drugs that have widespread distribution in the body can affect normal tissues, resulting in dose limiting side effects, such as the cardiac toxicity of doxorubicin.	The particulate nature of DDS lowers the volume of distribution and helps to reduce side effects in sensitive, non target tissues
Lack of selectivity for target tissues	Distribution of the drug to normal tissues leads to side effects that restrict the amount of drug that can be administered. Low concentrations of drugs in target tissues will result in suboptimal therapeutic effects.	DDS can increase drug concentrations in diseased tissues such as tumors by the EPR effect. Ligand-mediated targeting of the DDS can further improve drug specificity.

These systems can deliver therapeutic proteins, small molecules and bioactive peptides (Hsieh et al., 2002; Davis, 2006; Hawiger, 1999; Schwartz and Zhang, 2000).

Both hydrophobic and hydrophilic therapeutics could be delivered based on the unique amphiphilic structure and ability to self-assembly. The excellent characteristic of these systems, are that, there are no report on detectable immune response when these peptides are exposed to animal cells (Holmes et al., 2000).

Sequence modification and design for cell penetration and targeting makes this system more benefitable. There are some categories of drugs which have the different problems in transfer to body. Hydrophobic potential and poor water solubility (Gupta et al., 2006; Kwon, 2003), fast drug degradation, Cytotoxicity of drugs, unfavorable pharmacokinetics and poor biodistribution (Allen and Cullis, 2004) are the other problems which will be solved by cyclic peptide nano carriers. To prevent the polymer remaining in the body, in the preparation of particles for drug delivery purpose, biodegradable materials are more preferred. These materials are divided into two categories: biological polymers such as albumin and synthetic polymers. An advantage of particles that are made based on proteins is that they contain functional -COOH and -NH2 groups, which can be used for mild cross linking (Gorbitz, 2002).

It is important to make the couple nano ring system more stable to reduce the repulsion effect formed in interaction of drug-carrier, or make the half life of the system more stable. Numerous polymer biomaterials have been used to maintain these purposes. Such polymers have acceptable biocompatibility, biodegradability and absorbability (Chen et al., 2007).

The most attractive biomaterials, in view of their good biocompatibility, low cost, high performance and lightweight materials are considered (Eberhart et al, 2003; Peng et al., 1996).

Poly (lactic acid) (PLA) polymer is such a kind of biocompatible and biodegradable material having potential environmental and biomedical applications, where biodegradability and safe elimination of the polymer are required (Aou and Hsu, 2006; Xu et al., 2005).

The basis of molecular self-assembly

The main challenge in molecular self-assembly is to design molecular building blocks that can undergo spontaneous self organization. Well-defined and stable structure supported with non-covalent bonds, is the base of this technology. The accumulation of such interactions can produce very stable structures. Amino acids and

short peptides had not been defined to be useful for drug delivery purpose. The genetic engineering techniques in peptide synthesis and molecular engineered proteins have changed this view. Self-assembly of biomolecules is now, a new route to produce novel biomaterials and to complement other materials. Considerable points have been designed in the use of peptides and proteins as building blocks to produce a wide range of biological materials for universal applications (Dufes, 2006; Feng et al., 2004).

Peptide-based nanostructures

Peptide building blocks had been introduced for the assembly of nano-ordered material a decade ago when Ghadiri and co-workers were the first to describe a new class of biochemical nanotubes based on rationally designed cyclic polypeptides. These cyclic peptides were produced by an alternating even number of D- and L-amino acids, which interact through noncovalent interactions to an array of self-assembled nanotubes. The internal diameter of the nanotubes ranges between 7-8 Å and can be controlled by changing the number of the amino acids. Various applications were offered for these tubular structures. One of the first applications was based on their membrane interactions. The cyclic peptide nanotubes are toxic antibiotic agents to bacteria. Other potential applications include drug delivery, as these structures can serve as nanocontainers and application in material sciences (Dufes et al., 2006; Feng et al., 2004; Gu et al., 2007; Liu et al., 2007).

Polylactic acid (PLA), the biodegradable supporter polymer

Polylactic acid (PLA) is a rigid thermoplastic polymer that can be semicrystalline or totally amorphous. L(-)-lactic acid (2-hydroxy propionic acid) is generally, the natural and most common form, but D(-)-lactic acid is produced by microorganisms or through racemization and impurity. Lactic acid is the basic building block for PLA. It is a highly water-soluble, three-carbon chiral acid that is naturally occurring and is the most commonly found acid. It is used as an acidulant in foods, as a building block for biodegradable polymers, and is converted to esters and used as a green solvent for metal cleaning, paints and coatings. The physical characteristics of PLA are to an excellent dependent on its transition temperatures, such as density, heat capacity and mechanical properties. PLA can be either amorphous in the solid state, or semicrystalline. It depends on the stereochemistry and thermal history (Xu et al., 2005; Bowman, 2008).

METHODS

The term “ab initio” is defined as the computational methods that are derived from theoretical principles. This is an approximate quantum mechanical calculation. Hartree-Fock (HF) calculation is the most common type of ab initio calculation. In such method, primary approximation is the central field approximation. Columbic electron-electron repulsion is taken into account by integrating the repulsion term. This reveals the average effect of the repulsion, but not the repulsion interaction. One of the advantages of this method is that it breaks the many-electron Schrödinger equation into many simpler one-electron equations. If the molecule has a singlet spin, then the same orbital spatial function can be used for both a and b spin electrons in each pair. This is called the restricted Hartree-Fock method (RHF) (Bowman, 2008).

To apply ab initio quantum mechanics to the study of heterocyclic hexa nano peptide rings proteins is of practical importance. The quantum mechanical method that was chosen to analyze in heterocyclic hexa nano peptide rings is that of the Hartree-Fock (HF) equations using atomic orbital basis functions of type STO-3G. The RHF method is defined as the most frequently used type of ab initio quantum calculation. Its wave function minimizes the molecular energy (Tsai, 2002).

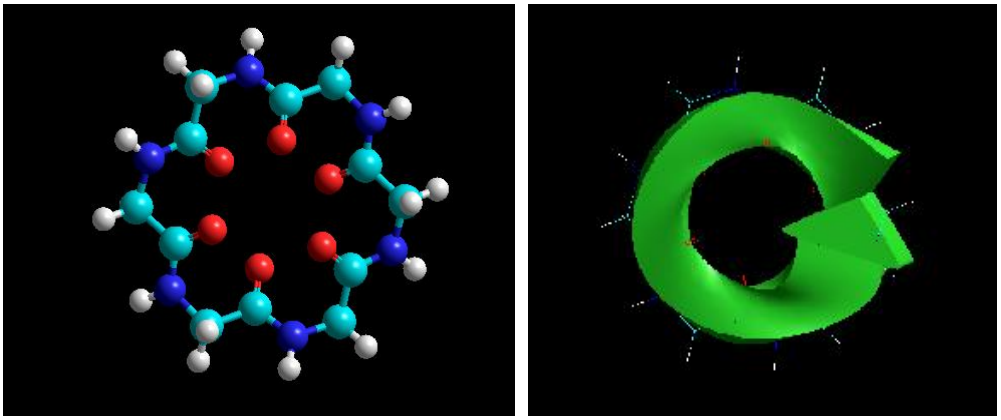
In the present research, the structure of some peptide nanorings as well as their dipole moments and energies have been studied by quantum mechanical calculations within the Onsager self-consistent reaction field (SCRF) model using a Hartree-Fock method (RHF) at the RHF/STO-3G (5D-7F) level. The structures are designed by Hyperchem^{TM} 6.01 software and the geometry of cyclo hexa peptide nanorings are fully optimized in water solution at 290, 310 and 315 K with Gaussian 03 package. The Gaussview 03 was the software used to design different distance interval between nanorings. The entire calculations are performed at Hartree-Fock (HF) levels on a Pentium IV/2.8 GHz personal computer using Gaussian 03 W program package, invoking geometry optimization (Tsai, 2002; Young, 2001; Graveland-Bikker et al., 2006; Frisch, 2003; Caplan et al., 2000). 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 (Tsai, 2002).

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 in the central field approximation and the wave function is described for only 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 molecule and a classical medium. In the Gaussian programs, a simple approximation is used in which the volume of the solute is used to compute the radius of a cavity which forms the hypothetical surface of the molecule.

RESULTS

The L and D contains cyclo hexa nano peptide that was designed (Figure 1). This nanoring because of the chemical arrangement of the amino acids in consequent D and L position, present a beta- pleated sheet like structure (Figure 1b).

Three available positions were selected to be substituted with the certain chemical groups; most of them



(a) (b)

Figure 1. The demonstration of schematic *cyclo* [-(D-Gly-L-Gly) 3] (a) and the β pleated sheath strand form of mentioned ring (b).

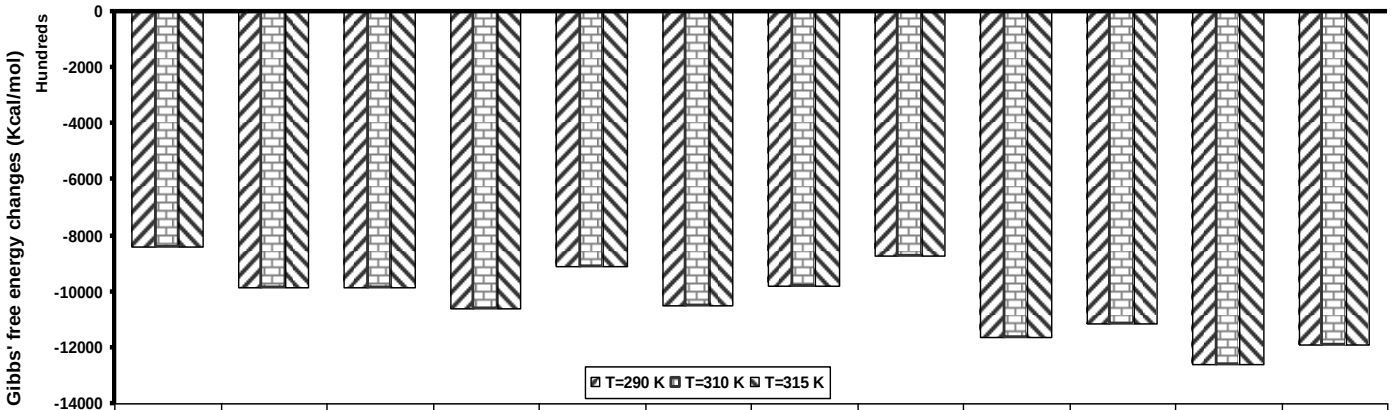
Table 2. The heterocyclic nano rings (*cyclo* [-(D-Gly-L-Amino acid) 3]).

Side chain (Rx)	Residue	Cyclohexapeptide
-CH3	Alanine	Cyclo[-(D-Gly-L-Ala)3]
	Proline	Cyclo[-(D-Gly-L-Pro)3]
-CH-(CH3)2	Valine	Cyclo[(D-Gly-L-Val)3]
-CH(CH3)-CH2-CH3	Isoleucine	Cyclo[(D-Gly-L-Ile)]
-OH	α -Hydroxyglycine	Cyclo[(D-Gly-L- α -Hydroxyglycine)3]
-CH(OH)-CH3	Thereonine	Cyclo[(D-Gly-L-Thr)3]
-CH2OH	Serine	Cyclo[(D-Gly-L-Ser)3]
-NH2	α -Aminoglycine	Cyclo[(D-Gly-L- α -Aminoglycine)3]
-(CH2)4-NH2	Lysine	Cyclo[(D-Gly-L-Lys)3]
-COOH	α -Carboxyglycine	Cyclo[(D-Gly-L- α -Carboxyglycine)
-CH2-CH2-COOH	Glutamic acid	Cyclo[(D-Gly-L-Glu)3]
-CH2-COOH	Aspartic acid	Cyclo[(D-Gly-L-Asp)3]

contain the amino acid side chains (Table 2). All rings were examined in three critical temperatures of 290, 310 and 315K, which belong to laboratory, normal body and fever temperature. In all calculations the water was the main medium, because of its biological importance. No significant difference in free energy was observed in a nanoring, where the temperature changed. Although, in comparison of various groups the maximum stability by the amount of -1187931.69 kcal/mol referred to *Cyclo* [-(D-Gly-L-Glu)$_3$], the minimum of -840929.68 kcal/mol belongs to *Cyclo*[-(D-Gly-L-Ala) $_3$] (Figure 2).

In water medium, the minimum dipole moment in Debye unit was referred to *Cyclo* [-(D-Gly-L-Ala)$_3$] by the amount of 0.0845 and the maximum of 19.40 for *Cyclo* [-(D-Gly-L-Lys)$_3$] (Figure 3).

Four rings of *Cyclo* [-(D-Gly-L-Gly)$_3$], *Cyclo* [-(D-Gly-L-Ala)$_3$], *Cyclo* [-(D-Gly-L- aminoGly)$_3$] and *Cyclo* [-(D-Gly-L-hydroxyGly)$_3$] were named, A, B, C and D to facilitate the following analysis. A-A, A-B, A-C, A-D, B-B, B-C, B-D, C-C, C-D and D-D, couple heterocyclic nanoring were designed. The distance between all couple individual rings were changed from 1 up to 10 Å and both the stability and dipole moment were calculated, to find the best distance and maximum of thermodynamics stability. In A-A system, the distance of 3 Å was shown the best. 2-4 Å and 9 Å were also positioned in the acceptable stability. To evaluate the A-B system, 2 Å was the best. Other points except for the 1, 5 and 8 Å are acceptable.



	Cyclo[-(D-Gly-L-Ala)3]	Cyclo[-(D-Gly-L-Pro)3]	Cyclo[-(D-Gly-L-Val)3]	Cyclo[-(D-Gly-L-Ile)3]	Cyclo[-(D-Gly-L- a-(OH)Gly)3]	Cyclo[-(D-Gly-L-Thr)3]	Cyclo[-(D-Gly-L-Ser)3]	Cyclo[-(D-Gly-L- a-(NH2)Gly)3]	Cyclo[-(D-Gly-L- Lys)3]	Cyclo[-(D-Gly-L- a-(COOH)Gly)3]	Cyclo[-(D-Gly-L-Glu)3]	Cyclo[-(D-Gly-L-Asp)3]
T=290 K	-840929.68497	-983949.75165	-986050.09142	-1058609.0321	-907360.20715	-1052456.9568	-979907.28370	-870569.99134	-1161564.9205	-1116757.2288	-1260422.1716	-1187931.6918
T=310 K	-840933.38408	-983953.68106	-986054.44627	-1058613.6423	-907363.77449	-1052461.1328	-979911.07192	-870573.58691	-1161569.9587	-1116761.3841	-1260427.0146	-1187935.8352
T=315 K	-840934.32909	-983954.68569	-986055.56071	-1058614.8233	-907364.68562	-1052462.2021	-979912.04078	-870574.50557	-1161571.2482	-1116762.4465	-1260428.2521	-1187936.8950

Figure 2. Comparison the three energy levels of heterocyclic nanorings in three different temperatures of room, normal body fever temperatures.

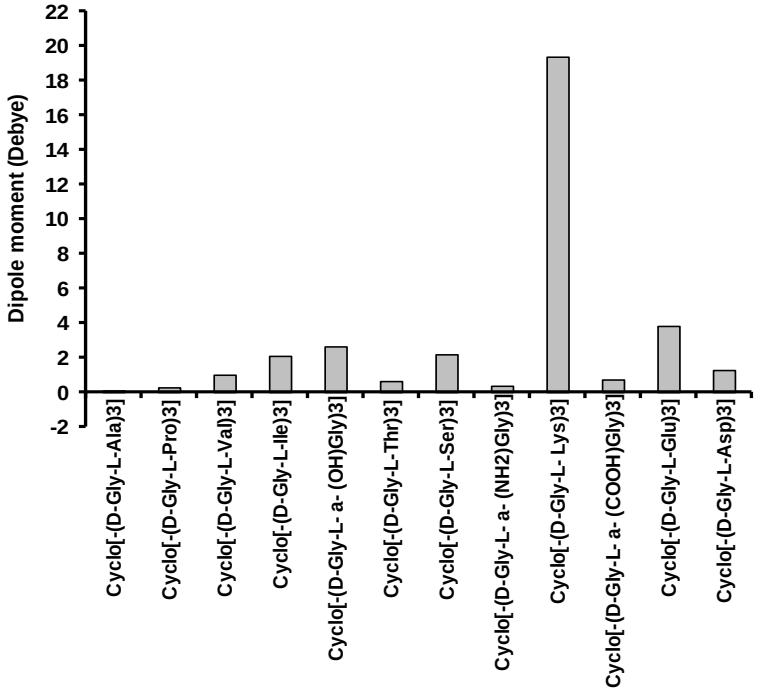


Figure 3. Dipole moment analysis of heterocyclic nanorings in water medium.

In spite of the fact that B-B and A-D systems were shown the most stable point in 1 Å, but this stability referred to joint of two rings, therefore it is better to evaluate the 5Å to B-B and the distance interval of 2-10Å, except for the 5Å to A-D system. Analyzing the A-C couple system, some complexity in structure occurred below the 6 Å, because of high risk 6 Å. It is preferred to choose the 9th point of distance as the best. The same problem happened to B-C, under the 4 Å of distance and the 9 Å was reported as the most stable point. Because

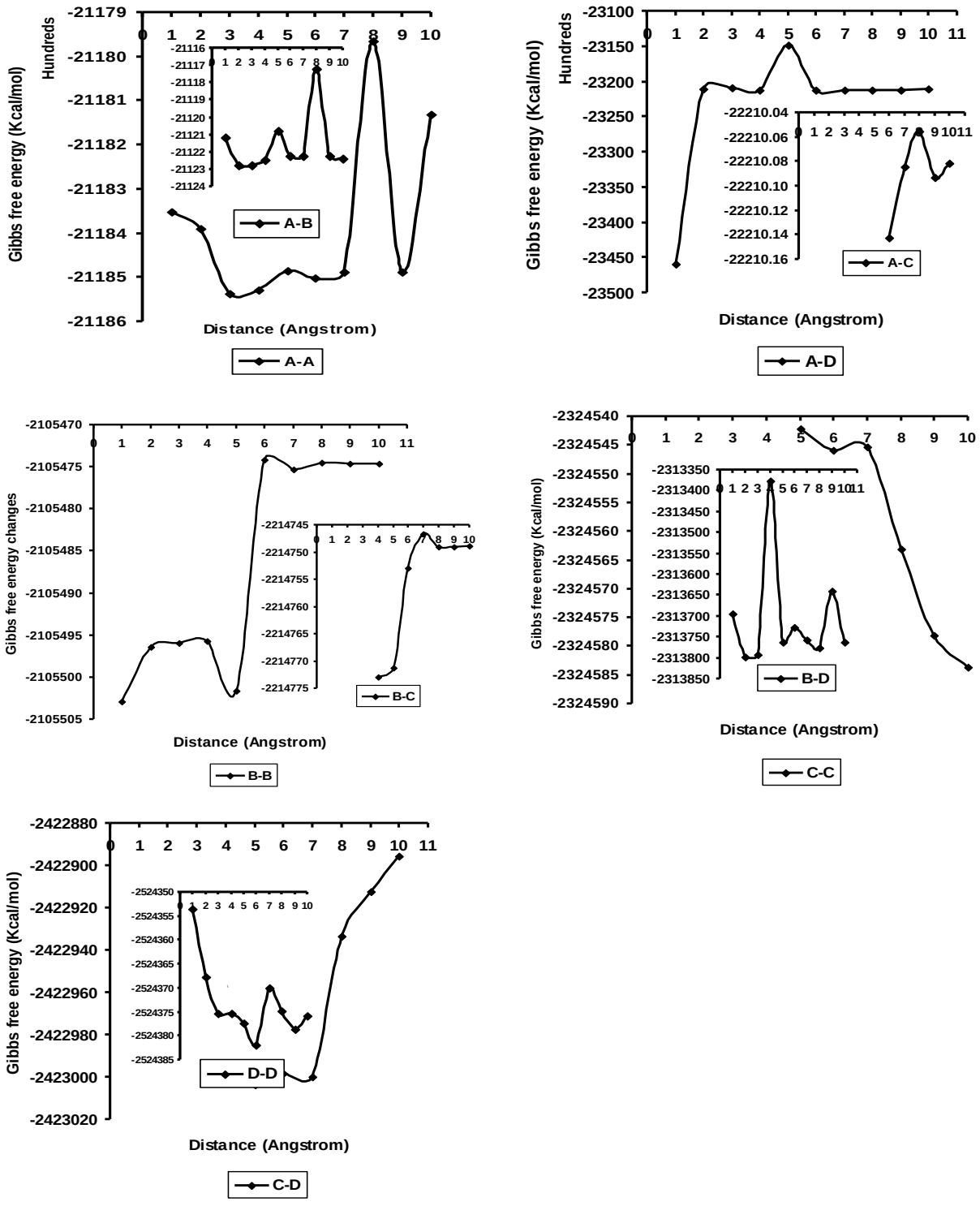


Figure 4. Gibbs free energy changes due to distance interval, between certain heterocyclic nanorings.

of the structural problems, the C-ring never showed good behavior in making the rings, this problem was observed clearly in combination of C-C and C-D rings (Figure 4). Analyzing the dipole moments, some rings could not reach to final result, because of the structural tight junction that happen to system. The dipole moment amounts of rings were presented in Table 3. It is better to consider these amounts, in the stable distance of each

Table 3. Dipole moment changes on Debye, due to the changes in distance between two heterocyclic nanorings.

Distance (A)	Dipole moment (Debye)								
	A-A	A-B	A-C	A-D	B-B	B-C	B-D	C-C	D-D
1	8.19	5.57	n.i.	4.92	14.52	n.i.	4.31	n.i.	3.28
2	5.06	4.34	n.i.	2.27	0.32	n.i.	5.47	n.i.	4.76
3	3.59	4.04	n.i.	5.13	3.17	n.i.	5.29	n.i.	2.25
4	3.71	10.64	n.i.	5.08	5.24	11.03	191.66	n.i.	2.88
5	6.65	n.i.	n.i.	10.06	5.91	19.19	3.56	14.99	3.20
6	5.41	5.31	35.73	3.76	8.54	29.74	n.i.	13.09	2.79
7	7.09	4.99	41.06	2.90	8.63	40.67	1.68	13.38	2.59
8	n.i.	n.i.	50.67	3.57	6.57	44.51	4.51	13.81	2.73
9	6.62	5.48	55.12	3.63	6.54	52.24	6.77	9.45	2.73
10	4.15	13.45	63.59	4.04	6.57	59.73	5.25	6.05	2.77

n.i., not identified.

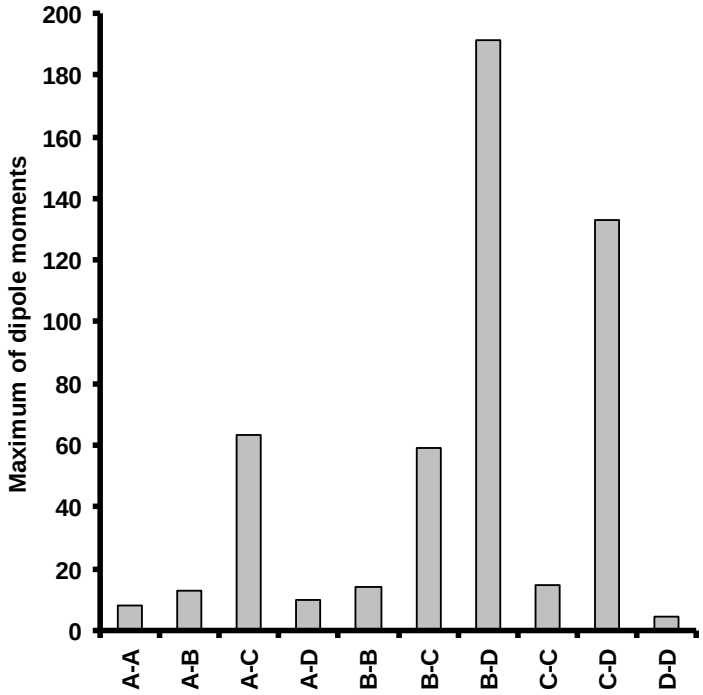


Figure 5. Comparison of maximum dipole moments between double rings in, certain thermodynamic stability point.

system. The B-D system showed the maximum of dipole moment of 19.66 Debye, the C-D system as well as the B-D had a high amount in the second rank. A-B and B-C rings, analyzed and positioned at the third rank (Figure 5).

To make the systems more stable, utilization of poly electrolyte with the property of assembly, to heterocyclic nano couple rings were suggested. Poly-L-lactate, PLA, is one of the safest and easier to produce and utilize poly electrolyte.

Based on the architecture of rings, there are some free locations ready to accept the PLAs. Three situations were planned in this phase, respecting the PLAs concentration. Low, medium and high concentrations of PLA were added to surround the system (Figure 7a, b and c).

The stability of systems was calculated considering the Gibbs free energy. All systems could be analyzed in the distance interval of 1-12 Å, except for BC-L-LA, that made a tight junction with PLA below 6 Å of length.

The interval lengths between 2-5 Å for AB-L-LA, 2-12 Å

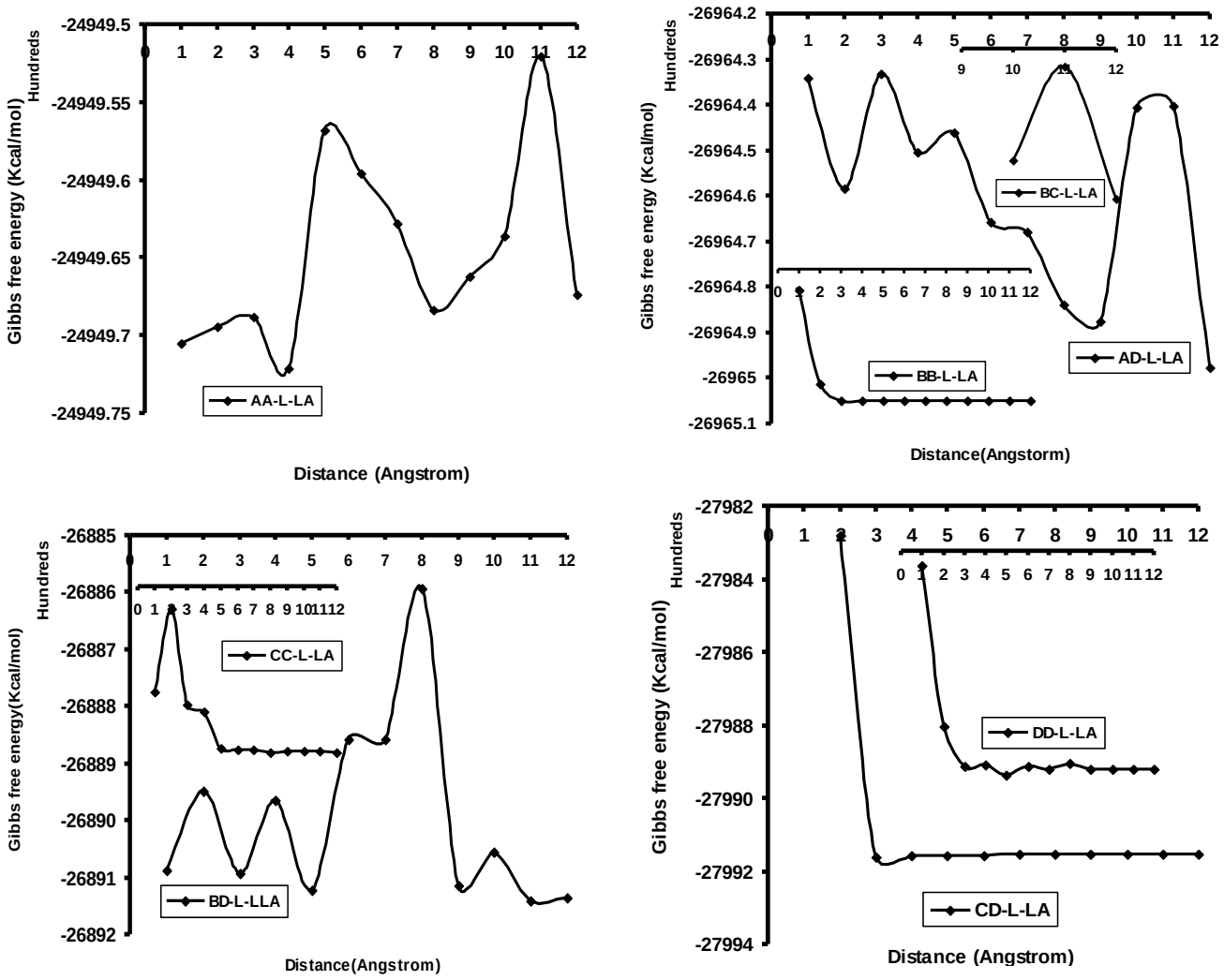


Figure 6. Stability analysis due to changes in distance between double rings in the maximum stability, and Poly-L-Lactic acid as a support.

for BB-L-LA, 5-12 Å for CC-L-LA, 3-12 Å for both CD-L-LA and DD-L-LA and 2-10 Å in AC-L-LA were reported as the more stable systems. BC-L-LA and AD-L-LA were stable in point of 12 Å as well as 4 Å in AA-L-LA and 3, 5, 9, 11 and 12 Å for BD-L-LA (Figure 6).

Dipole moment of system were reported in Table 4, the results reveal that the distance between PLA and the couple ring systems, could interfere the electric fields in systems (Table 4).

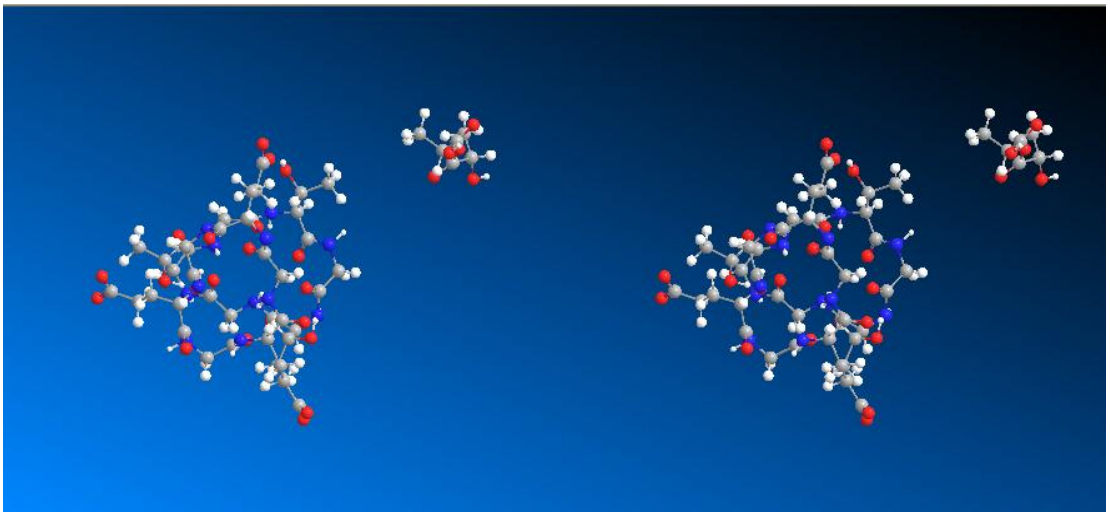
Comparing the systems in contraction with PLA as a biodegradable support, where 1, 3 and 6 PLA surrounds them revealed that DD-(n)LLA affected more than others, where CC-(n)LLA, BD-(n)LLA and AD-(n)LLA, stay in the second stage (Figure 8).

In a certain distance of stability to add 1, 3 and 6 PLA, causes the various changes in electrical fields (Table 5).The more PLA added, the more stability of system was observed, due to the Figure 9.

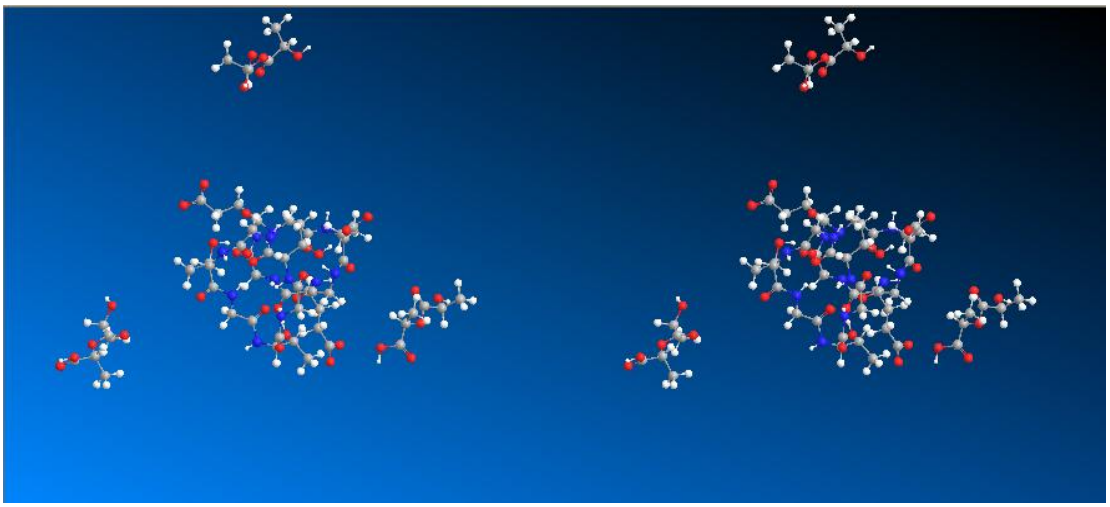
DISCUSSION

One of the main targets of nanobiology sciences, is to design a self-assembly nanovehicles to hold a biological function. A nanodevice can contain one or more self-assembled nano building block with a variety of different geometries. Several self-assembled peptide and protein nanotubes have been observed experimentally. The recent project involves optimal mapping of candidate protein building block.

Here, the heterocyclic nanorings were designed with three constant members of glycine and three variable members. The effect of side chains were analyzed on stability and electrical fields of such heterocyclic nanorings. All rings are biodegradable and biocompatible due to the amino acid based. The Poly L-lactate chain was introduced as the main biodegradable and easy to produce and use nano support. Increasing the temperature



(a)



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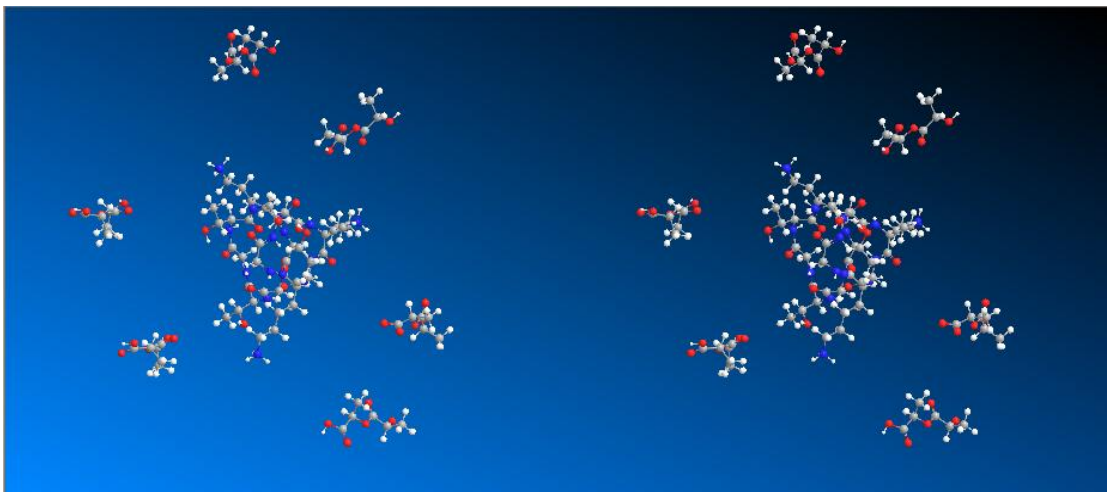

(c)

Figure 7. Stereo view of couple heterocyclic nanoring in combination of 1 (a), 3 (b) and 6 (c) polylactic acid.

Table 4. The effect of distance between polylactic acid and double nanorings system, on dipole moment.

Distance (Angstrom)	Dipole moment (Debye)									
	AA-L-LA	AB-L-LA	AC-L-LA	AD-L-LA	BB-L-LA	BC-L-LA	BD-L-LA	CC-L-LA	CD-L-LA	DD-L-LA
1	22.00	2.31	n.i.	24.69	9.87	n.i.	6.10	68.68	n.i.	4.98
2	22.54	2.42	35.43	21.96	11.72	n.i.	n.i.	41.66	65.59	4.87
3	23.35	2.20	28.15	18.58	8.36	n.i.	n.i.	92.14	61.92	4.64
4	25.57	2.55	31.48	27.01	8.09	n.i.	56.82	39.75	62.70	4.30
5	26.16	2.55	40.52	28.35	8.03	n.i.	6.96	18.28	63.70	4.16
6	26.10	2.20	34.72	23.93	8.01	n.i.	n.i.	88.86	63.59	4.18
7	25.95	2.19	35.98	24.45	8.00	n.i.	n.i.	101.32	63.75	4.41
8	25.70	2.20	37.38	32.04	8.00	n.i.	n.i.	86.31	63.77	4.32
9	26.07	2.19	21.31	35.27	8.01	n.i.	n.i.	56.09	63.79	4.20
10	26.74	2.16	38.76	47.54	8.01	n.i.	n.i.	110.27	63.79	4.14
11	71.36	2.18	38.38	48.78	8.01	n.i.	n.i.	117.21	63.87	4.18
12	27.01	2.20	38.10	44.27	8.02	41.14	8.36	64.12	63.89	n.i.

n.i., not identified.

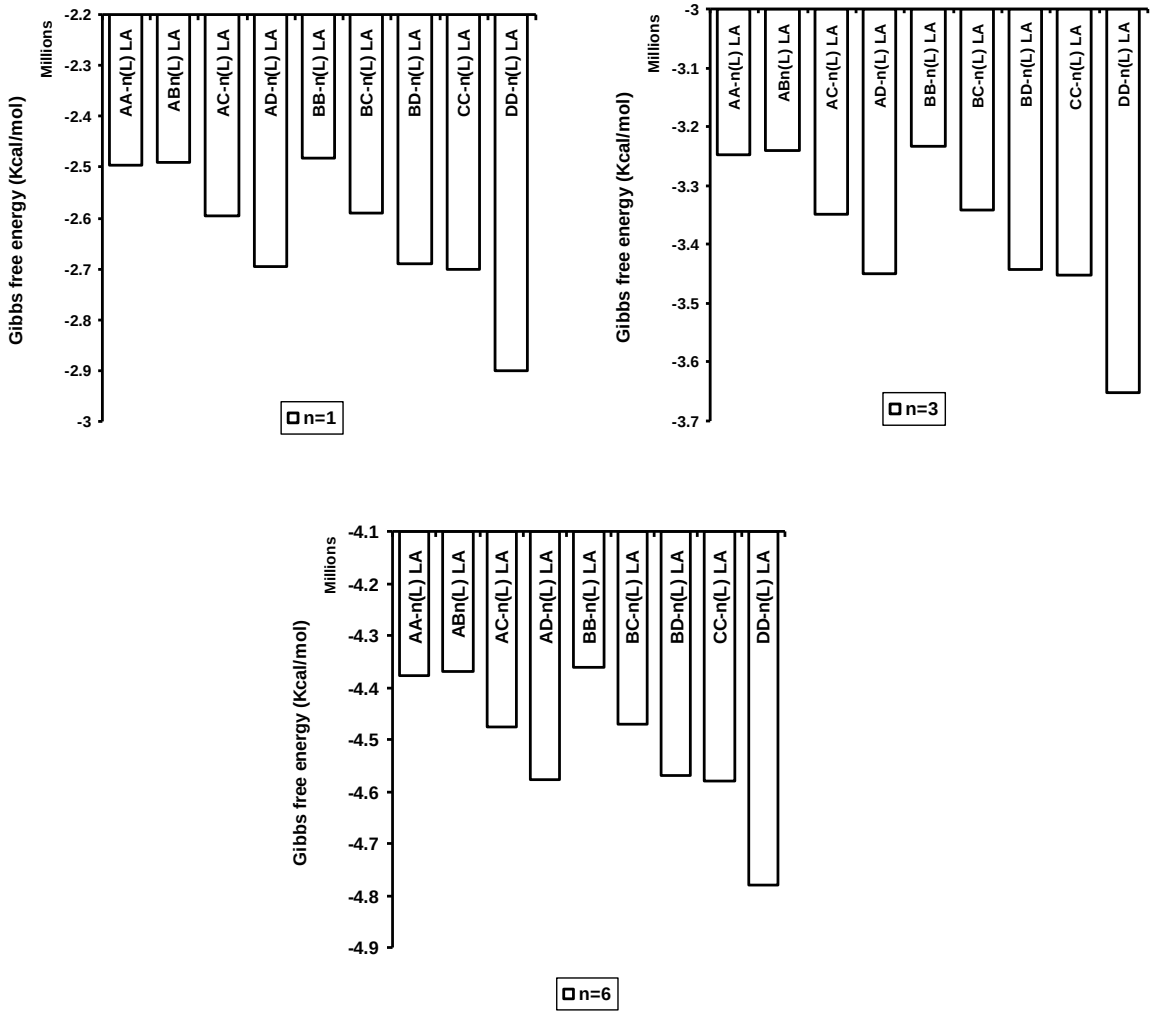

Figure 8. The effect of increasing polylactic acid support around the cyclo nano double rings systems in probable positions.

Table 5. Dipole moment changes after the effect of 1, 2 and 3 polylactic acid chain.

	Dipole moment (Debye)		
	n = 1	**n = 3**	**n = 6**
AA-n(L) LA	25.57	14.05	46.79
ABn(L) LA	2.42	2.69	5.45
AC-n(L) LA	40.52	84.74	41.29
AD-n(L) LA	44.27	12.42	22.70
BB-n(L) LA	8.36	8.49	10.05
BC-n(L) LA	41.14	35.71	35.54
BD-n(L) LA	8.36	43.19	41.59
CC-n(L) LA	86.31	32.23	12.38
DD-n(L) LA	4.16	4.27	7.13

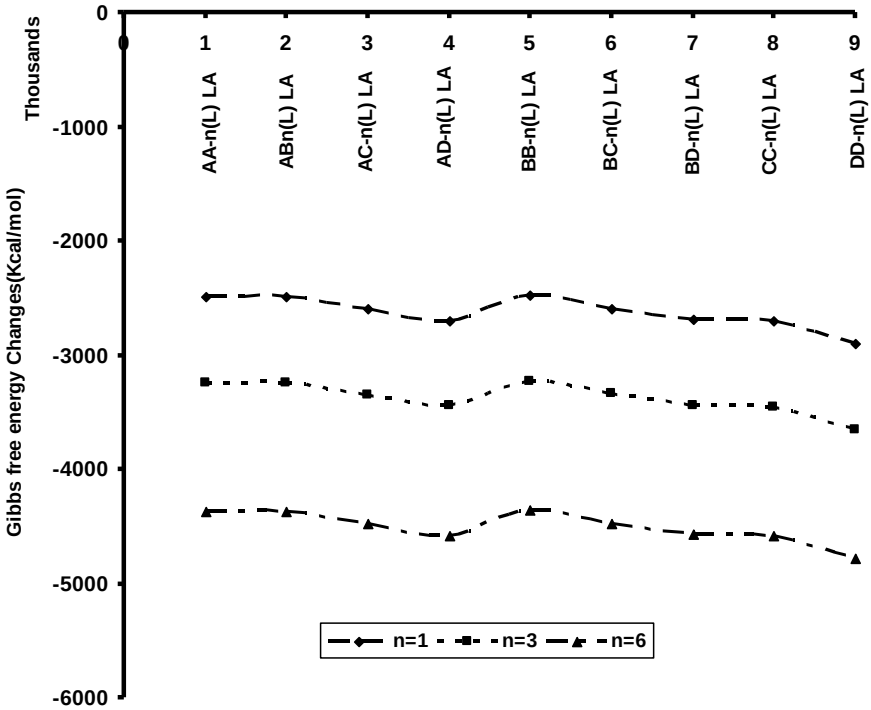

Figure 9. The effect of increasing poly lactic acid around the system.

temperature may cause more stability in the heterocyclic nanorings couple systems. Geometrical changes in order to increase temperature may cause the rings near each others, to form a new geographical optimization and attract each other more. *Cyclo* [-(D-Gly-L-lys)$_3$], not only has a long side chain in comparison to other ones, it has a positive charge. This ring is stable and it has the maximum amount of dipole moment. No continuous trends are seen in changing the distances between the rings. The results considered that, the effect of rings to each others are very complicated. The amine end rings residue in this study had some problems to join other rings in minimal distances. It is thought of that the electrostatic interaction of loan pairs in nitrogen of one ring and the partial positive charge of carbon in carbonyl group of another cause this group to come near and form the bands. In contraction of C ring to A and B, the dipole moments are increased by making the distances more far, but in other couples it depends on the situation. To different utilization for various drugs structures, with any type of hydrophobicity or hydrophilicity, any dipole moment, we can choose or design the suitable couple rings. Poly electrolytes such as PLA can make the systems more strong, to deliver a pack of drugs for

example in the production of arterial stents.

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