

## The effect of polylactic acid support in stability and electrical field of heterocyclic coupled hexa peptide nano systems: A novel strategy to drug delivery

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### ABSTRACT

Biological materials, recently, are the building blocks of several self-assembling peptide and protein systems. The main challenge in molecular self-assembly is to design molecular building blocks that can undergo spontaneous organization. These cyclic peptides were produced by an alternating even number of D- and L-amino acids, which interact through non-covalent interactions to an array of self-assembled nanotubes. Physicochemical properties of structure of some peptide nanorings in couple form, with the support of a biocompatible and biodegradable polylactic acid (PLA) have been calculated 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 in water medium at 310 K. Four rings, *Cyclo* [-(D-Gly-L-Gly)<sub>2</sub>] (A), *Cyclo* [-(D-Gly-L-Ala)<sub>2</sub>] (B), *Cyclo* [-(D-Gly-L-aminoGly)<sub>2</sub>] (C), *Cyclo* [-(D-Gly-L-hydroxyGly)<sub>2</sub>] (D), are designed in a couple form and geometrically optimized near by the 1, 3 and 6 polylactic acid (PLA) support, with non-covalent interaction. Analyzing the geometrical position of polylactic acid chain, around the coupled nano system, results the PLA is preferred to stand in the distance of 4 Å of AA, 2-5 Å far AB and 12 Å far both BC and AD. The stability of some systems, could not be affected in the wide range of distances such as, AC in 1-10 Å, BB in 3-12 Å, CC in 4-12 Å and both CD and DD in the 2-12 Å. DD nano system presents the best in all conditions where CC, BD and AD couples stand in the second rank BC and AC stand after. The stability of AA, AB and BB are less. Although no effect in behavior of nano systems are seen, increasing the number of supports make them more stable. Coming near and go far, the PLA affects the dipole moment of system, deeply.

**Keywords:** Cyclo hexa peptide nano ring, Drug delivery; Quantum mechanics; Polylactic acid, Gibbs free energy; Dipole moment

### INTRODUCTION

Nanotechnology provides the tools for the investigation of biological systems, on biology offers inspiration models as well as bio-assembled nanomachines to nano dimension technology. Investigative methods of nanotechnology have made an effective way into fundamental biological processes. Self-assembly, cellular processes, and systems biology are the main targets. Nanotechnology offers new technology for the utilization of biosystems and provides a broad technological platform for applications such as bioprocessing and molecular medicine [1-9].

Biological materials, recently, are the building blocks of several self-assembling peptide and protein systems that form nanotubes, helical ribbons and fibrous scaffolds. Peptides and proteins have also been selected to bind metals, semiconductors and ions, the design of new materials for a wide range of applications in nano-biotechnology is one of the main goals of this interdisciplinary sciences [7-14]

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### The basis of molecular self-assembly

The main challenge in molecular self-assembly is to design molecular building blocks that can undergo spontaneous organization. Well-defined and stable structure supported with non-covalent bonds, is the base of this technology. Typically, hydrogen bonds, ionic bonds, water-mediated hydrogen bonds, hydrophobic and van der Waals interactions are well known non-covalent bonds. The collective 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 [2-9].

### 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 non-covalent 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 nanocompartments and application in material sciences [8-29].

### Biodegradable polymer, PLA

Poly(lactic 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 this

impurity. D-lactic acid units are incorporated into L-PLA to optimize the crystallization kinetics for specific fabrication processes and applications. 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 most commonly found. 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 [30, 31].

## THEORETICAL BACKGROUND

### Hartree-Fock (Self-Consistent Field, SCF) method

This method is based on determination of the spatial orbitals  $\psi_i$  of the many-electron determinantal wave-function based on reducing coupled non-linear differential equations for the optimum forms of the molecular orbitals by use of the variational method. The Hartree-Fock Hamiltonian operator is defined in terms of these orbitals through the operators of coulomb and exchange repulsion. The general procedure for solving the orbitals self-consistent with the potential field they generate, is the fundamental of Hartree-Fock equations. The self-consistent field method is achieved through a trial-and-error computational process. In the case of open-shell systems it should distinguish between the spin-restricted Hartree-Fock (RHF) method and spin-unrestricted Hartree-Fock (UHF) method. In the former approach a single set of molecular orbitals is present, some being doubly occupied and some being singly occupied with an electron of spin. In the UHF approach different spatial orbitals are assigned to electrons with  $\alpha$  and  $\beta$  spins and the orbitals  $\psi_i$  doubly occupied in the RHF method are replaced by two distinct orbitals  $\psi_i(\alpha)$  and  $\psi_i(\beta)$  [32].

### Energy calculation and minimization

One of the basic properties of biomolecules is their energy content and level. Three theoretical

computational methods are included empirical (molecular mechanics), Semicempirical, and *ab initio* (quantum mechanics) approaches. Energy minimization results in geometry optimization of the molecular structure. *Ab initio* calculations are designed based on self-consistent field (SCF) methods, in which a set of orbitals is assumed and the electron-electron repulsion is calculated. This energy is then used to calculate a new set of orbitals, and used to calculate new repulsion energy. The process is continued until convergence occurs and self consistency is achieved. Semicempirical and *ab initio* calculations calculate the vibrational motions of selected atoms, search for transition states of reactant or product atoms, display the electrostatic potential, total spin density or total charge density, analyze and display orbitals and their energy levels, analyze and display the vibrational frequencies, analyze and display the ultraviolet-visible spectrum. An assumption of constant bond lengths and bond angles by carrying out folding simulation in vacuum simplifies the total energy expression to

$$E = E_{tor} + E_{vdw} + E_{elec} + E_p$$

where  $E_{tor}$ ,  $E_{vdw}$ ,  $E_{elec}$ , and  $E_p$  are torsion angle potential, van der Waals interaction, electrostatic potential, and pseudoentropic term that drive the protein to a globular state. The combination of try and error criteria with force field components may less sever the inadequacy in the simplified fitness functions. The prediction of secondary structure may be performed to reduce the search space. Thus, either idealized torsion angles or boundaries for torsion angles according to the predicted secondary structures can be used to constrain main-chain torsion angles. It is revealed that the incorrect structures have less stabilized hydrogen bond, electrostatic, and van der Waals interactions. A greater fraction of hydrophobic side-chain atoms exposed to the solvent and a larger solvent accessible surface is a property of the incorrect structures [32-34].

#### Dipole moment

Electronic polarization of atoms and orientational polarization of local dipoles were resulted in regional dielectric constants ranging from 1 to 20 inside the protein. Dipole moments can be calculated in two ways:

(i) as the expectation value of the dipole operator  $\hat{\mu}$  or

(ii) as the derivative of the electronic energy  $E(\lambda)$ , evaluated

for  $\lambda = 0$ , of the perturbed Hamiltonian

$$\hat{H}' = \hat{H} + \lambda \hat{\mu}$$

The dipole moment is defined as:

$$\mu = \sum_{i=1}^N q_i (r_i - r_{COM})$$

where  $q_i$  is the partial charge of each atom and  $r_{COM}$  is the center of mass of the protein [32]

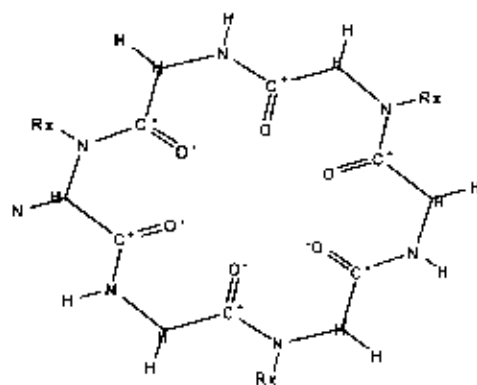
## COMPUTATIONAL DETAILS

Structure of some hetero cyclic hexa peptide nanorings in couple form in combination with the support of a biocompatible and biodegradable poly lactic acid, have been calculated 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 in water medium at 310 K. Hyperchem<sup>TM</sup> 8, software is used to design the structures. Gaussview03 is used to make the certain distinct distances. The entire calculations are performed at Hartree-Fock (HF) levels on a Pentium IV/2.8 GHz personal computer using Gaussian 98W program package, invoking geometry optimization. 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 AO 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. 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 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 [33-35].

## RESULTS

The heterocyclic hexa amino acid nano rings were designed and nomenclatured as in Figure 1.



Nanoring code	Rx	Heterocyclic nano ring
A	-H	Cyclo [-(D-Gly-L-Gly) <sub>2</sub> ]
B	-CH <sub>3</sub>	Cyclo [-(D-Gly-L-Ala) <sub>2</sub> ]
C	-NH <sub>2</sub>	Cyclo [-(D-Gly-L-aminoGly) <sub>2</sub> ]
D	-DH	Cyclo [-(D-Gly-L-hydroxyGly) <sub>2</sub> ]

Fig. 1. Structure of heterocyclic hexa peptide nanorings.

The polylactic acid as a biodegradable and biocompatible support were added to system and after energy minimization, the geometrical optimization were done on systems, as presented in Figure 2 as an example. After, all systems, optimized geometrically and the freq parameters, calculated as presented in following.

Analyzing the heterocyclic coupled nano carries systems near by the poly lactic acid cham, the stability of systems reveal the different behavior. The AA-L-LA system has the maximum of stability, where the PLA support stands in the distance of 4 Å. The minimum amount is defined in 11 Å. in AB-L-LA system 2-5 Å are the interval that is though the acceptable stability is obtained.

1-10 Å for AC-L-LA nano coupled system, 8, 9 and 11 Å for AD-L-LA, just 10 and 1 Å for BC-L-LA and 2-12 Å for BB-L-LA have

presented acceptable points. CC-L-LA, in the interval of 5-12 Å and

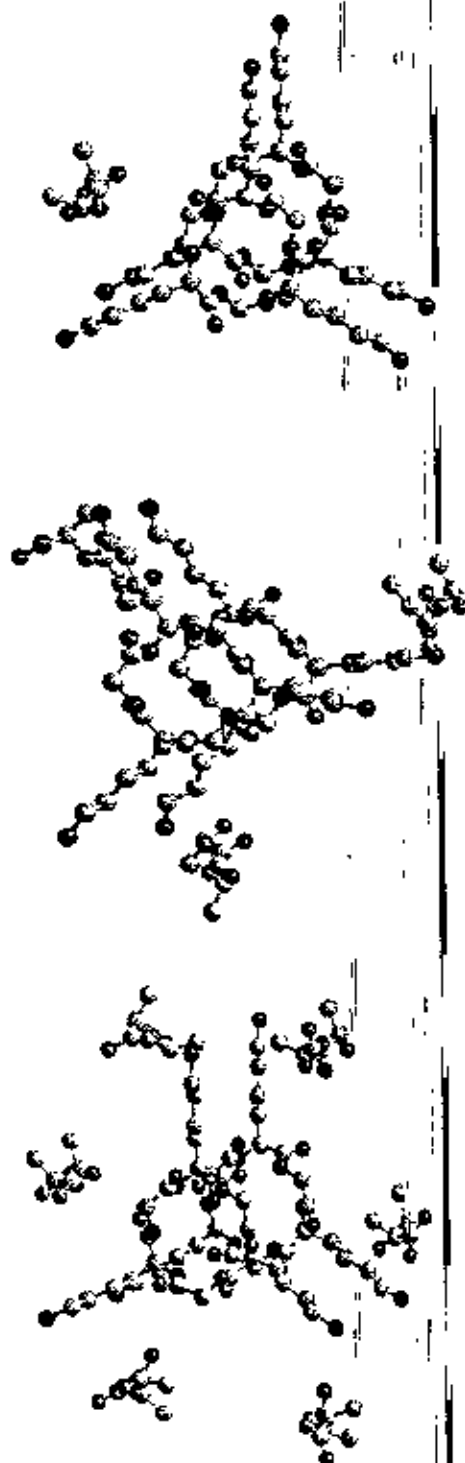


Fig. 2 Demonstration of geographical positions of 1, 3 and 6 polylactic acid support around the CC nano coupled ring system as an example. This system is supported with non-covalent interactions

DD-L-LA in the interval of 3-12 Å are more stable as well as CD-L-LA in the interval of 2-12 Å. The behavior of BD-L-LA is different nearby the PLA support. The distance of 1, 3, 5, 9, 11 and 12 Å are more stable than others. (Tab. 1)

Analyzing the dipole moment of system, and the effect of PLA support on it, it is revealed that AA-L-LA nano carrier system has a disturbance point in 11 Å as well as AB-L-LA system in 2, 4 and 6. The behavior of BB-L-LA is the same as both two others, as it has a not in harmony point in 2 Å. CD-L-LA presents the minimum dipole

moment at point of 3 Å, where DD-L-LA nano system, shows it at 12 Å. The trends of dipole moment harmony in CC-L-LA and AC-L-LA is complicated as well as AD-L-LA. In AC-L-LA, there is a maximum point in 5 Å and a minimum at 9 Å. Other points have to be analyzed separately. AD-L-LA, has a minimum at 3 Å, where the maximums are in the points of 10 and 11 Å. 5 Å and 11-12 Å are the points of maximum and minimum referred to CC-L-LA. (Tab. 2)

Table 1. Stability analysis of PLA heterocyclic nanoring systems, due to distance difference

Distance (Å)	Gibbs' free energy difference (Kcal/mol)									
	AA-L-LA	AB-L-LA	AC-L-LA	AD-L-LA	BD-L-LA	BC-L-LA	DD-L-LA	CC-L-LA	CD-L-LA	OD-L-LA
1	-2494070.524	-2489382.43	n.i.	-2690434.0	-2478152.642	n.i.	-2689088.022	-2697626.593	n.i.	-2900487.054
2	-2494961.031	-2489388.00	-2596494.116	-2696458.4	-2481065.162	n.i.	-2688449.127	-2694744.075	-2796279.60	-2900498.209
3	-2494968.847	-2489387.43	-2596462.747	2696433.2	-2481547.867	n.i.	-2689093.324	-2698099.51	-2799162.82	-2900501.040
4	-2444472.090	-2489387.67	-2596467.219	-2696490.5	-2481568.586	n.i.	-2688965.51	-2698512.508	-2799156.95	-2900500.918
5	-2494956.782	-2489387.67	-2596460.377	-2696446.1	-2481568.604	n.i.	-2689123.264	-2699577.654	-2799155.90	-2400501.644
6	-2494959.586	-2489384.56	-2596470.722	-2696465.7	-2481568.371	n.i.	-2688858.371	-2699635.068	-2799155.61	-2900501.054
7	-2494962.744	-2489381.65	-2596471.216	-2696467.9	-2481568.254	n.i.	-2688858.371	-2699616.785	-2799155.28	-2900501.229
8	-2494968.354	-2489383.71	-2596471.603	-2696483.9	-2481568.196	n.i.	-2688594.501	-2699717.146	-2799155.88	-2900500.857
9	-2494966.244	-2489383.81	-2596478.565	-2696487.6	-2481568.163	n.i.	-2689114.477	-2699695.355	-2794158.19	-2900501.253
10	-2494963.626	-2489383.75	-2596471.515	-2696410.6	-2481568.144	-2689960.759	-2689656.474	-2699672.326	-2794155.00	-2900501.241
11	-2494952.087	-2489383.76	-2301459.442	-2696410.4	-2481468.129	-2689659.342	-2689139.970	-2699664.956	-2794158.74	-2900501.228
12	-2494967.423	-2489383.65	-2301376.654	-2696497.7	-2481568.122	-2690082.916	-2689115.042	-2699750.316	-2799154.64	-2900501.188

n.i. = Not identified

Table 2. The effect of distance interval on dipole moment of a heterocyclic nano ring

Distance (Å)	Dipole moment (Debye)									
	AA-L-LA	AB-L-LA	AC-L-LA	AD-L-LA	BD-L-LA	BC-L-LA	DD-L-LA	CC-L-LA	CD-L-LA	OD-L-LA
1	21.9978	2.3077	n.i.	24.6886	9.8668	n.i.	n.i.	68.6771	n.i.	4.9752
2	22.5429	2.4184	85.4296	21.9649	11.7168	n.i.	n.i.	41.6577	65.5898	4.8667
3	23.3534	2.201	28.1477	18.5838	8.3609	n.i.	n.i.	92.1895	61.9222	4.6409
4	25.569	2.545	31.4813	27.0105	8.0944	n.i.	n.i.	39.7497	62.6993	4.2963
5	26.1594	2.545	40.5203	29.3474	8.0333	n.i.	n.i.	18.2832	63.7012	4.1613
6	26.095	2.1988	34.7136	21.9298	8.0111	n.i.	n.i.	88.8574	63.5888	4.1805
7	25.9548	2.1946	85.9761	24.4532	8.0045	n.i.	n.i.	101.3193	63.7509	4.4127
8	25.7003	2.2038	37.3799	32.0384	8.0044	n.i.	n.i.	86.3138	63.7720	4.3342
9	26.0726	2.1878	21.311	35.2659	8.0069	n.i.	n.i.	56.0881	63.7930	4.1984
10	26.7408	2.1649	88.7563	47.5408	8.0103	n.i.	n.i.	110.2719	63.7961	4.1426
11	71.3648	2.1783	38.3845	48.7782	8.0137	n.i.	n.i.	117.2082	63.8663	4.1779
12	27.0104	2.2008	38.1001	44.2720	8.0169	41.1361	8.7607	64.1206	63.8922	-4622.51

n.i. = Not identified

The behavior of nano rings are different near by the PLA in point of stability. DD nano system presents the best stability not only with one, but also with 3 and 6 PLA. CC, BD and AD couples stand the second rank. Where BC and AC get the third. The stability of AA, AB and BB are less in comparison to others. Increasing the number of supports can not affect the behavior of nano systems, but makes them more stable in general (Tab. 3).

Analyzing the dipole moment, it is revealed that the maximum dipole moment referred to system with just one PLA support and increasing to three ones makes the system to have less dipole moment. For AD, BC, CC, AA and AD couple rings the trend is the same. No significant changes is observed for AC system. The trend for DD and BD systems are analyzed vice versa. Although the changes in BB and AB are not very considerable but an increasable trend is observed (Fig. 4).

Table 3. The effect of merging of PLA support around the systems. The stability of systems is analyzed based on Gibbs free energy

	Gibbs free energy changes (kcal/mol)		
	n=1	n=3	n=6
AA-n(L) LA	-2494972.09	-3247449.79	-4376066.49
AB-n(L) LA	-2489388.00	-3241674.86	-4370106.90
AC-n(L) LA	-2596460.38	-3348792.39	-4477322.43
AD-n(L) LA	-2696497.69	-3449125.34	-4577166.21
BB-n(L) LA	-2481547.87	-3233913.92	-4362380.03
BC-n(L) LA	-2590088.92	-3342413.37	-4470846.99
BB-n(L) LA	-2689139.97	-3442125.14	-4570571.45
CC-n(L) LA	-2699717.15	-3451728.98	-4580133.80
DD-n(L) LA	-2900501.65	-3652820.38	-4781254.79

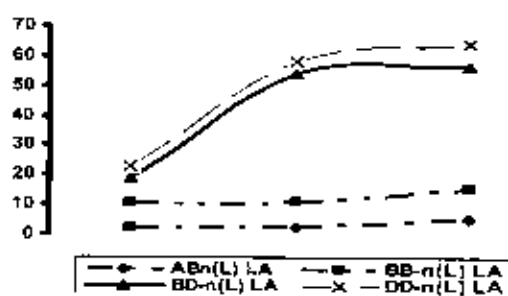


Fig. 3

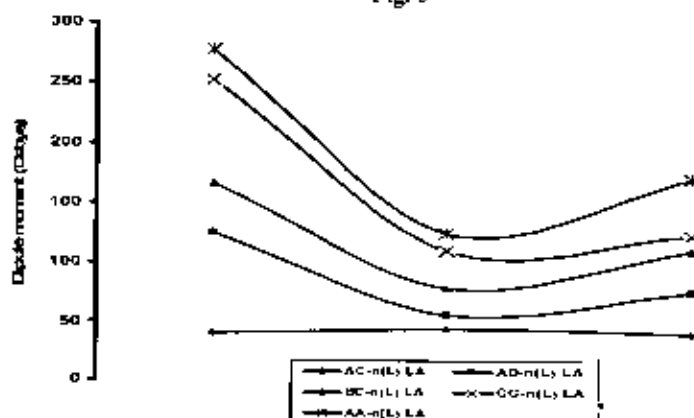


Fig. 4. Trend of dipole moment changes, during increasing the PLA support from 1, to 3 and 6 units.

## CONCLUSION

The computational methods allow the investigator to enter in the world of nano designs and present the new idea without any concern.

Design and introducing a tight biodegradable and biocompatible nano system to drug delivery, seems to be important in the world of nanomedicine today.

The main goal of such suggestion is to be far away of biohazards, such as remaining the residues in the cell. Peptides as the building blocks of natural proteins in biological world, give us this thought that utilization of such biomaterials may never make such risks such as sythetic materials. Because of the open ended and hollow fiber tube properties, the cyclo hexa peptide nan rings or tubes are interested in the field of nano delivery of drugs. Such rings or tubes have two useful sites to attach and delivery the drugs. One is internal, another is defined in external side. The changeable physicochemical properties of such rings, give this chance to manage the nano delivery system based on the drug characteristics and properties of target organelle or cell. It is tried to introduce some physicochemical properties of such nano systems in this investigation.

It is thought that when we put a drug into such systems the rings goes under a big pressure to leave each others. To prevent such phenomenon a biocompatible and biodegradable poly electrolyte, such as poly lactic acid is

investigated, to analyze the stability of nano vehicle with different concentration of this support

Analyzing the positional standing of one poly lactic acid chain, around the coupled nano system, PLA is preferred to stand to the distance of 4 Å of AA, such as 2-5 Å for AB and 12 Å for both BC and AD. The stability of some systems, could not be affected in the wide range of distances such as, AC in 1-10 Å, BB in 3-12 Å, CC in 4-12 Å and both CD and DD in the 2-12 Å (Tab. 1).

To choose a perfect nano carrier, dipole moment is a very important parameter. The data presented in Table 2, suggested various dipole moments in Debye. It is necessary for next investigations to choose the suitable dipole moment. Although it is revealed that increasing the PLA support concentration, makes the systems more stable, but the behavior of systems in this support is different as it presented in both Table and figure 3.

DD nano system presents the best, in all conditions where CC, BD and AD couples stand in the second rank. BC and AC stand after. The stability of AA, AB and BB are less, in comparison. Although no effect in behavior of nano systems are seen, increasing the number of supports make them more stable. Coming near and go far, the PLA affect the dipole moment of system, deeply, as it is illustrated in figure 4.

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